Approaches to parameter and variance estimation in generalized linear models

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Abstract

EUGENIO ANDRACA CARRERA: Approaches to parameter and variance estimation in generalized linear models.
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In many studies of clustered binary data, it is reasonable to consider models in which both response probability and cluster size are related to unobserved random effects. Two resampling methods have been recently proposed in the literature for mean parameter estimation in this setting: within-cluster resampling (WCR) and within-cluster paired resampling (WCPR). These procedures are believed to provide valid estimates in the presence of nonignorable cluster size. We identify the parameters estimated under WCR and under unweighted generalized estimating equations and elaborate on their differences and validity. We propose a simple weighted generalized estimating equations strategy that is asymptotically equivalent to WCPR but avoids the intensive computation involved in WCPR. We investigate the parameter estimated by WCPR for a generalized mixed model. We show that the parameter estimated by WCPR may be affected by factors other than the actual effects of exposure and propose an alternative strategy for the analysis of correlated binary data with cluster-specific intercepts based on simple generalized estimating equations for random intercept-matched pairs.

We study the problem of variance estimation in small samples using robust or sandwich variance estimators. Robust variance estimators are widely used in linear regression with heteroscedastic errors, generalized linear models with possibly misspecified variance model, and generalized estimating equations. In these settings, the robust variance estimator provides asymptotically consistent estimates of the covariance matrix of mean parameters. However, the robust variance estimator may severely underestimate the true variance in studies with small sample size. Bias-corrected versions of the robust variance estimator have been proposed to improve its small sample performance. We introduce a new class of corrected robust variance estimators with an emphasis on variance reduction and small sample performance. These estimators are applicable to linear regression, generalized linear models and generalized estimating equations. We show in simulations that the new estimators perform better in terms of variance and confidence interval coverage than many current estimators, while maintaining comparable average confidence interval width.

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List of Abbreviations

CWGEE	Cluster weighted generalized estimating equations
GEE	Generalized estimating equations
GLM	Generalized linear models
HCCME	Heteroscedasticity-consistent covariance estimators
OLS	Ordinary least squares
MINQUE	Minimum norm quadratic estimator
WCPR	Within-cluster resampling
WCR	Within-cluster paired resampling

Chapter 1

Introduction and literature review

1.1 Introduction

1.1.1 Cluster resampling methods

Studies involving correlated or clustered binary data arise often in medical applications. Statistical tools have been proposed to analyze clustered binary data for various study designs and parametrizations. Random-effect models and marginal models are commonly used by researchers depending on whether interest lies in subject-specific effects or population average effects. Within-cluster resampling (WCR) was suggested by Hoffman, Sen and Weinberg (2001) as a procedure for parameter estimation in marginal models where response probability and cluster size are related to unobserved random effects. A similar method, within-cluster paired resampling (WCPR), was suggested by Rieger and Weinberg (2002) for estimation of subject-specific effects in models resembling a matched-pairs setup. They proposed WCPR for the analysis of correlated binary data with cluster-specific intercepts and slopes.

Even though WCR and WCPR have gained popularity in the literature, it is not clear what parameters they estimate and how they differ from generalized estimating equations (GEE). Hoffman et al. (2001) claim that unweighted generalized estimating equations is not a valid estimating procedure when cluster size is related to response probability.

Similarly, Rieger and Weinberg (2003) suggest that conditional logistic regression (CLR) is not a valid estimating procedure in the presence of cluster-specific intercepts and slopes. WCR and WCPR are proposed as alternative estimating approaches in these settings. In §1.2 and §1.3 we review the available literature on WCR and WCPR. In Chapter 2 we investigate the parameters estimated by WCR, WCPR and unweighted generalized estimating equations in various models. We show that WCR and WCPR can be written in terms of specially weighted estimating equations. We study the parameters induced by WCR, WCPR and GEE and comment on the validity of each procedure.

1.1.2 Variance estimation

WCR and WCPR are methods of mean parameter estimation for correlated data. Statistical inference of these mean parameters requires estimates of their variance. The robust or 'sandwich' variance estimator, introduced by Liang and Zeger (1986), is widely used to estimate the covariance matrix of mean parameters in correlated data. One of the main advantages of the robust variance estimator is that it provides consistent estimates of the true covariance matrix of the parameters of interest, even if the variance model is misspecified. It is applicable in settings such as linear regression with heteroscedastic errors and generalized linear models. However, it has been shown that the robust variance estimator may lead to anti-conservative inference in small samples in many situations. Corrections to the robust variance estimator have been proposed to improve its small sample performance. Most corrections to the sandwich estimator available in the literature focus on reducing its bias. Kauermann and Carroll (2001) showed that the robust variance estimator has higher variance than parametric variance estimators when the parametric model is correct. They showed that the increased variance of the robust variance estimator results in a loss of efficiency.

In §1.4 we review the literature on robust variance estimation; we cover variance estimators for linear regression with heteroscedastic errors, as well as their bias, variance and performance. In section 1.4.4 we review variance estimation for correlated data. In Chapter 3 we introduce a new family of variance estimators for linear regression and generalized estimating equations that includes some of the estimators introduced in §1.4 as well as new estimators not previuosly considered in the literature. We show that some of the new estimators have smaller variance than currently available estimators and that this translates into improved confidence interval coverage. In Chapter 4 we extend the family of variance estimators to correlated data. We show that new estimators improve upon current estimators in terms of variance and coverage in simulations with correlated Gaussian data and correlated binary data. In Chapter 5 we summarize the results of the previous chapters and discuss future research.

1.2 Literature review: within cluster resampling

1.2.1 Random effects models

One common approach to account for within-cluster correlation in correlated data is through random effects models. We introduce one such model with a random intercept for binary data.

Consider a study with K clusters, indexed by $i = 1, \ldots, K$ and observations within cluster i indexed by $j = 1, \ldots, n_i$. Let the jth binary response in the ith cluster be denoted by Y_{ij}, and let it be related to a $(p \times 1)$ vector of covariates $\mathbf{x}_{ij}$ through

$$\operatorname{logit}(\mathrm{E}(Y_{ij})) = \alpha_i + \mathbf{x}_{ij}^{\top}\boldsymbol{\beta}. \tag{1.1}$$

If α_i in model (1.1) can be assumed to follow a probability distribution dependent on parameters $\boldsymbol{\theta}$ under some regularity conditions, then a random effects model eliminates α_i by estimating $\boldsymbol{\theta}$ and the fixed slope $\boldsymbol{\beta}$ through likelihood methods. Models with logit link and cluster-specific random effects were first proposed by Cox (1958) and Rasch (1961). Laird (1982) proposed the use of random effects models for the analysis of longitudinal data and Stiratelli et al. (1984) extended random effects models to correlated binary data. The interpretation of $\boldsymbol{\beta}$ may be marginal if random effects are integrated out or conditional within a cluster.

Neuhaus et al. (1992) showed that misspecification of the random effects distribution may lead to bias in regression coefficients, however this bias tends to be small. Neuhaus and McCulloch (2006) then showed that ignoring the correlation between covariates and random effects may also lead to biased regression coefficients.

An alternative to random effects models, marginal methods for the analysis of correlated binary data based on generalized estimating equations became available after the work of Liang and Zeger (1986) and Zeger and Liang (1986). The GEE approach assumes mean and variance models for the response and accounts for within-cluster association by using a working correlation matrix for each cluster's vector of responses $\mathbf{Y}_i$. We discuss generalized estimating equations in more detail later in this document in the context of sandwich variance estimators for correlated data.

1.2.2 Within cluster resampling

Hoffman et al. (2001) proposed WCR for the analysis of correlated binary data with nonignorable cluster size. They define nonignorable cluster size as any violation of the property $E(Y_{ij}|n_i, X_{ij}) = E(Y_{ij}|X_{ij})$. In particular, they consider a model where response probability and cluster size are related to an unobserved random effect. Hoffman et al. (2001) claim that unweighted generalized estimating equations is not a valid method of estimation when cluster sizes are nonignorable and propose WCR as a valid estimation alternative.

The WCR procedure is based on sampling one observation from each cluster at each of Q resampling steps. The q-th data set then consists of one independent observation from each cluster. A regression model for independent data is fit to the q-th resample and an estimate of mean parameters and their covariance matrix is obtained. The WCR estimate is obtained by pooling the estimators obtained at each resampling step. The WCR procedure is described in detail in Chapter 2.

Williamson, Datta and Satten (2003) and Benhin, Rao and Scott (2005) showed that the WCR procedure is equivalent to generalized estimating equations with independence working correlation structure and cluster weight equal to the inverse of cluster size.

Neuhaus and McCulloch (2006) discussed Hoffman et al.'s (2001) paper and suggested that nonignorable cluster size be considered as a misspecification of the random effects distribution. They argue that the bias of slope coefficients in the simulations of Hoffman et al. (2001) and Williamson et al. (2003) is small, and that only the intercept shows significant bias. Neuhaus and McCulloch (2006) claim that these results are consistent with their research on misspecified random effects distribution (Neuhaus et al., 1992).

Even though the simulations of Hoffman et al. (2001) and Williamson et al. (2003) show small bias in slope coefficients and small differences between estimates obtained by unweighted GEE and WCR, their data examples show large differences between estimates obtained by the two approaches. In Chapter 2 we explain the differences between unweighted GEE and WCR in these simulations and data examples.

Follmann, Proschan and Leiffer (2003) extended the use of within cluster resampling to applications including angular data, p-values and Bayesian inference. Cong, Yin and Shen (2007) and Williamson et al. (2008) used WCR to model correlated survival data where the outcome of interest is associated with cluster size. Datta and Satten (2005; 2007) extended WCR to rank-tests and signed-ranked tests in situations with 'informative cluster sizes'. Our work focuses on the application of WCR to correlated binary data.

Recent areas of application of WCR include cross-sectional surveys in epidemiology (Williamson, Kim and Warner, 2007), veterinary epidemiology (Faes et al., 2006) and genetic association in families (Shin et al., 2007). Faes et al. (2006) note that an alternative approach to WCR, with a different parameter interpretation, is to include cluster size as a covariate in the model. While this model may be useful in many scenarios, we do not explore it further.

1.3 Literature review: within-cluster paired resampling

Rieger and Weinberg (2003) proposed within cluster paired resampling for the analysis of correlated binary data for models with cluster-specific intercepts and slopes. The method is based on resampling two observations from each cluster such that one observation has response $y_{ij} = 1$ while the other has response $y_{ik} = 0$. Clusters with at least one y-discordant pair are called 'informative clusters'. The resulting resampled data set resembles data from a matched-pair design. Conditional logistic regression based on the resampled pairs is then used to estimate the parameter vector $\boldsymbol{\beta}$. The final estimate $\hat{\boldsymbol{\beta}}_{WCPR}$ is the mean of Q resamples.

Conditional logistic regression has been widely used in case-control studies (Breslow and Day, 1980). CLR assumes a cluster-specific intercept or random effect. Through conditioning, CLR eliminates random intercepts and estimates conditional or cluster-specific slope parameters. CLR makes no distributional assumptions about the random effects. It assumes independent outcomes within clusters conditional on the random effects and a conditional slope parameter $\boldsymbol{\beta}$ common to all clusters. These two assumptions are not required if all clusters have only two observations each and the data resemble a matched-pair design. This is the motivation of the WCPR method: the resampling procedure proposed by Rieger and Weinberg (2002) produces resampled data sets containing one pair of y-discordant observations from each informative cluster and resembles a matched-pair design. The WCPR is studied in more detail in Chapter 2.

Rieger, Kaplan and Weinberg (2001) proposed a less general version of WCPR based on sampling one affected and one unaffected sibling from each sibship in family studies to test for linkage and association between a disease and candidate genes. The authors named their method 'Within Sibship Paired Resampling' (WSPR). Both WCPR and WSPR have met limited discussion in the literature. Our research aims to improve the understanding of WCPR and offer alternative analysis tools for estimation of cluster level parameters for correlated binary data. The results on WCPR are easily extended to the special case of WSPR for use in family-based case-control studies.

1.4 Literature review: variance estimation

Consider the linear model $\mathrm{E}(\mathbf{Y}) = \mathbf{X}\boldsymbol{\beta}, \mathrm{Var}(\mathbf{Y}) = \boldsymbol{\Gamma}$ where $\mathbf{Y}$ is an $n \times 1$ vector of responses, $\mathbf{X}$ is a known $n \times p$ matrix of covariates of rank p, $\boldsymbol{\beta}$ is a $p \times 1$ vector of unknown parameters, and $\boldsymbol{\Gamma} = \mathrm{diag}(\gamma_1, \ldots, \gamma_n)$ is unknown.

The ordinary least squares estimator of $\boldsymbol{\beta}$, given by $\hat{\boldsymbol{\beta}} = (\mathbf{X^T X})^{-\mathbf{1}}\mathbf{X^T Y}$, is best linear unbiased under homoscedasticity, $\gamma_1 = \cdots = \gamma_n = \sigma^2$. It also remains unbiased under heteroscedasticity, but is no longer best unbiased. Asymptotically, for large n, $\hat{\boldsymbol{\beta}}$ is consistent under fairly general conditions (Eicker, 1963). The ordinary least squares estimator (OLS) of $\mathrm{cov}(\hat{\boldsymbol{\beta}})$,

$$(\mathbf{X^T X})^{-\mathbf{1}} \sum_{i=1}^{n} r_i^2/(n-p),$$

where $r_i = Y_i - \mathbf{x}_i^T\hat{\boldsymbol{\beta}}$, is based on the assumption of homoscedasticity. This estimator is the one typically printed out by most regression software. In general, the true covariance is given by

$$\mathrm{cov}(\hat{\boldsymbol{\beta}}) = (\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\boldsymbol{\Gamma}\mathbf{X}(\mathbf{X}^T\mathbf{X})^{-1}. \tag{1.2}$$

The OLS variance estimator is generally biased under heteroscedasticity and can lead to gross undercoverage of corresponding confidence intervals. This weakness of the OLS estimator has long been recognized and several alternative estimators exist.

The goal of this section is to review some of the most relevant approaches to estimate (1.2) under heteroscedasticity in the literature. It is organized as follows. In §1.4.1 we introduce some notation. In §1.4.2 we review variance estimators proposed for linear models with heteroscedasticity. In §1.4.3 we study issues of bias, variance and performance of some of these variance estimators in published simulation studies. §1.4.4 reviews variance estimators available for correlated data.

1.4.1 Notation

We will use the following notation throughout this dissertation. If $\mathbf{a} = (a_1, \cdots, a_n)^T$ is a vector, then diag($\mathbf{a}$) will denote a diagonal matrix with diagonal elements $a_1, \cdots, a_n$. Conversely, if $\mathbf{A}$ is a square matrix with elements a_{ij}, then diag($\mathbf{A}$) will denote the column vector $(a_{11}, \cdots, a_{nn})^T$.

For any two vectors or matrices $\mathbf{B} = (b_{ij})$ and $\mathbf{C} = (c_{ij})$ of the same dimensions, we denote their *Schur product* (Marcus and Minc, 1964, p.120) as $\mathbf{B} * \mathbf{C} := (b_{ij}c_{ij})$. Consequently, the k-th *Schur power* of $\mathbf{B}$ is denoted by $\mathbf{B}^{*k} = (b_{ij}^k)$.

The 'hat matrix' $\mathbf{H} = (h_{ij})$ is given by $\mathbf{H} = \mathbf{X}(\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T$. Its diagonal elements, h_{ii}, are called 'leverages'. Also, let the vector of squared residuals be denoted by $\mathbf{S}$, with elements r_i^2. Finally, let us define the matrix $\mathbf{P} := (\mathbf{I} - \mathbf{H})^{*2}$ where $\mathbf{I}$ is the identity matrix.

Estimators of the true covariance are generally obtained by replacing $\mathbf{\Gamma}$ in (1.2) by an estimator $\hat{\mathbf{\Gamma}} = \text{diag}(\hat{\boldsymbol{\gamma}})$. Since $\hat{\mathbf{\Gamma}}$ is diagonal, we may write it in full matrix form $\hat{\mathbf{\Gamma}}$ or, equivalently, in vector form $\hat{\boldsymbol{\gamma}}$. When talking about individual components of $\hat{\mathbf{\Gamma}}$ we write $\hat{\gamma}_i$, where it is understood that $\hat{\gamma}_i = \hat{\Gamma}_{ii}$.

1.4.2 Review of estimators

Early work on estimators of $\text{cov}(\hat{\boldsymbol{\beta}})$ and their properties can be traced to Eicker (1963) and Huber (1967). Eicker anticipated the results of White (1980) by studying conditions for the asymptotic normality of $(\hat{\boldsymbol{\beta}} - \boldsymbol{\beta})/\widehat{\text{cov}(\hat{\boldsymbol{\beta}})}$ where $\widehat{\text{cov}(\hat{\boldsymbol{\beta}})}$ is obtained by replacing $\boldsymbol{\Gamma}$ by $\text{cov}(r_i r_i^T)$ in (1.2). Huber (1967) further studied the asymptotic properties of $\widehat{\text{cov}(\hat{\boldsymbol{\beta}})}$ under maximum likelihood methodology.

Hartley et al. (1969) and Rao (1970) proposed the first variance estimators unbiased under heteroscedasticity for a wide range of linear models. Rao (1970) named this class of estimators MINQUE (minimum norm quadratic estimator). Estimators derived from MINQUE such as the almost unbiased estimator soon followed (Horn et al., 1975). In 1980, White proposed a heteroscedasticity-consistent covariance matrix estimator. His estimator, denoted HC0, is often used by researchers in fields such as economics and social sciences, and is commonly available in most software packages (Long and Ervin, 2000). Since White's (1980) seminal paper, modified White estimators such as HC1, HC2 and HC3 have appeared in the literature. The performance of these estimators in small samples has been studied extensively by MacKinnon and White (1985), Long and Ervin (2000), Flachaire (2005), and many more.

In the following sections we introduce some of these estimators as well as some others related to our work. Later, we discuss some of the literature available regarding their performance in small samples, as well as issues of bias and variance.

MINQUE

Hartley et al. (1969) proposed unbiased estimators for a linear model with a stratified design with one unit per stratum and unequal variances. Their estimator can be written as $\hat{\boldsymbol{\gamma}} = \mathbf{P}^{-1}\mathbf{S}$. The estimator of Hartley et al. (1969) is included in a larger class of estimators referred to as MINQUE by Rao (1970).

Consider a linear combination $\boldsymbol{\alpha}^T\boldsymbol{\gamma} = \sum \alpha_i \gamma_i$ to be estimated. A quadratic form

$\mathbf{Y}^T\mathbf{AY}$ is said to be MINQUE of $\boldsymbol{\alpha}^T\boldsymbol{\gamma}$ if $\mathbf{A} = (a_{ij})$ is such that $\|\mathbf{A}\|$ is minimized subject to

$$\mathbf{AX} = \mathbf{0} \quad \text{and} \quad \sum a_{ii}\gamma_i \equiv \sum \alpha_i\gamma_i.$$

These two conditions guarantee invariance to translation of $\boldsymbol{\beta}$ and unbiasedness of $\mathbf{Y}^T\mathbf{AY}$ as an estimator of $\boldsymbol{\alpha}^T\boldsymbol{\gamma}$.

MINQUE exist for more general linear models than the model of interest of this review. The model we consider is that of independent, unreplicated data with variances that are unknown and possibly all different. For this model the unreplicated MINQUE corresponds to the estimator of Hartley et al. (1969) (Horn et al. 1975).

Even though MINQUE are unbiased, they exhibit some undesirable properties. First, existence of MINQUE is not guaranteed; it is conditional on $\mathbf{P}$ being non-singular. Rao (1970) gives sufficient conditions for the existence of $\mathbf{P}^{-1}$, however these conditions are not simple. Second, even if MINQUE exist, it is possible to obtain negative estimators of some γ_i and $\text{Var}(\mathbf{z}^T\hat{\boldsymbol{\beta}})$ for some $p \times 1$ vector $\mathbf{z}$ in finite samples (Horn et al., 1975; Dorfman, 1991). Finally, MINQUE seems to exhibit large variance in many scenarios (Chesher and Jewitt, 1987; Bera, Suprayitno and Premaratne, 2002).

HC0. White's estimator

White's 1980 paper on a heteroscedasticity-consistent covariance matrix estimator is one of the most influential papers in the field. His HC0 estimator is simply obtained by replacing $\mathbf{\Gamma}$ in (1.2) by $\hat{\mathbf{\Gamma}}^{(0)} := \text{diag}(\mathbf{S})$.

Since the expected value of the vector of squared residuals is given by $\text{E}(\mathbf{S}) = \mathbf{P}\boldsymbol{\gamma}$ it follows that White's estimator is biased for finite samples. The extent of HC0's bias was studied by Chesher and Jewitt (1987). Issues of bias and performance are considered in the following section.

White's (1980) major contribution was showing that

$$(\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\hat{\mathbf{\Gamma}}^{(0)}\mathbf{X}(\mathbf{X}^T\mathbf{X})^{-1} \xrightarrow{p} (\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\mathbf{\Gamma}\mathbf{X}(\mathbf{X}^T\mathbf{X})^{-1}$$

under either homoscedasticity or heteroscedasticity under regularity conditions. It allows researchers to conduct adequate inference under unknown heteroscedasticity for large enough samples.

HC1, HC2 and HC3

Several finite sample corrections to White's estimator have been proposed in the literature. Perhaps the simplest one was given by Hinkley (1977). Hinkley's estimator HC1 is a degrees of freedom corrected version of HC0 given by

$$\text{HC1} := \frac{n}{n-p}\text{HC0}.$$

In 1975, Horn et al. proposed the almost unbiased estimator, also known as HC2. The HC2 estimator of $\mathbf{\Gamma}$ can be written componentwise as $\hat{\gamma}_i^{(1)} = r_i^2/(1-h_{ii})$ and in vector form as $\hat{\boldsymbol{\gamma}}^{(1)} = \mathbf{DS}$. The HC2 estimator of $\text{cov}(\hat{\boldsymbol{\beta}})$ is obtained by replacing $\hat{\mathbf{\Gamma}}^{(1)} = \text{diag}(\hat{\boldsymbol{\gamma}}^{(1)})$ in (1.2). Horn et al. (1975) proposed HC2 based on the fact that the expected value of the squared residuals $\text{E}(\mathbf{S}) = \mathbf{P}\boldsymbol{\gamma}$ depends on both $\mathbf{\Gamma}$ and the leverages h_{ii} through $\mathbf{P}$. This estimator is unbiased under homoscedasticity, but in general it is biased under heteroscedasticity.

The HC3 estimator closely approximates the jackknife estimator of Miller (1974). The HC3 is obtained by replacing $\hat{\mathbf{\Gamma}}^{(2)}$ in (1.2), where $\hat{\boldsymbol{\gamma}}^{(2)} = \mathbf{D}^2\mathbf{S}$. It be written componentwise as $\hat{\gamma}_i^{(2)} = r_i^2/(1-h_{ii})^2$. The HC3 estimator is biased upwards.

It is known that HC0, HC1, HC2 and HC3 are consistent for $\text{cov}(\hat{\boldsymbol{\beta}})$ under some regularity conditions. Dorfman (1991) proved that estimators obtained by replacing $\hat{\mathbf{\Gamma}}^{(\delta)}$ in (1.2) where $\hat{\gamma}_i^{(\delta)} = r_i^2/(1-h_{ii})^{\delta}$ are consistent for any fixed $\delta \geq 0$ as long as the leverages are bounded so that $\max_{1\leq i\leq n}(h_{ii}) \to 0$ as $n \to \infty$. HC0, HC2 and HC3 are special cases with $\delta = 0$, 1 and 2.

Other estimators

Other estimators have been proposed in the literature. We discuss two of them by Cribari-Neto et al. (2000) and Cribari-Neto (2004).

Cribari-Neto et al. (2000) proposed a sequence of modified White estimators of $\mathbf{\Gamma}$ with decreasing bias that is related to both HC0 and MINQUE. They argued that the k-th estimator in the sequence has bias of order $O(n^{-(k+2)})$. Their sequence of estimators $\hat{\boldsymbol{\gamma}}^{(0)}, \ldots, \hat{\boldsymbol{\gamma}}^{(k)}$ is defined in the following way:

1. Let $\hat{\boldsymbol{\gamma}}^{(0)} = \mathbf{S}$, White's estimator.
2. Let $B_{\hat{\boldsymbol{\gamma}}^{(k)}}(\boldsymbol{\gamma}) := \mathrm{E}(\hat{\boldsymbol{\gamma}}^{(k)}) - \boldsymbol{\gamma}$.
3. Obtain the k-th estimator in the sequence by subtracting the estimated bias from the $(k-1)$-th estimator evaluated at $\hat{\boldsymbol{\gamma}}^{(0)}$, that is $\hat{\boldsymbol{\gamma}}^{(k)} = \hat{\boldsymbol{\gamma}}^{(k-1)} - B_{\hat{\boldsymbol{\gamma}}^{(k-1)}}(\hat{\boldsymbol{\gamma}}^{(0)})$.

Cribari-Neto et al. (2000) showed that after k iterations

$$\hat{\boldsymbol{\gamma}}^{(k)} = \sum_{j=0}^{k} (-1)^j M^{(j)}(\hat{\boldsymbol{\gamma}}^{(0)})$$

where $M^{(j)} = (\mathbf{P} - \mathbf{I})^j \hat{\boldsymbol{\gamma}}^{(0)}$. Using this notation, their k-th estimator can be written as

$$\hat{\boldsymbol{\gamma}}^{(k)} = \left(\sum_{j=0}^{k} (\mathbf{I} - \mathbf{P})^j \right) \mathbf{S}.$$

As $k \to \infty$, $\hat{\boldsymbol{\gamma}}^{(k)}$ converges to $\mathbf{P}^{-1}\mathbf{S}$, the unreplicated MINQUE, if $\mathbf{P}^{-1}$ exists and diverges otherwise. This result follows from a generalization of the geometric series commonly known as the von Neumann series. This result was not explicitly noted by Cribari-Neto et al. (2000)

This sequence of estimators has some undesirable properties. First, if $\mathbf{P}$ is not invertible, then the sequence $\hat{\boldsymbol{\gamma}}^{(k)}$ is divergent. Second, even if $\mathbf{P}^{-1}$ exists, $\hat{\boldsymbol{\gamma}}^{(k)}$ may have some negative elements $\hat{\gamma}_i^{(k)} < 0$ for some $i \in \{1, \ldots, n\}$ for any $k \geq 1$.

Another estimator proposed recently in the literature is the HC4 estimator of Cribari-Neto (2004). Elementwise HC4 is defined by $\hat{\gamma}_i = r_i^2/(1 - h_{ii})^{\delta_i}$ where

$$\delta_i = \min\left(4, \frac{nh_{ii}}{\sum_{j=1}^{n} h_{ii}}\right).$$

The idea behind HC4 is to inflate the i-th residual by a larger factor than HC3 when h_{ii} is large relative to $\bar{h} = \sum_{j=1}^{n} h_{ii}/n$. Cribari-Neto (2004) found that HC4 performed better than HC3 and HC0 in terms of test size relative to nominal size in simulations. The HC4 estimator is a potentially useful alternative to HC3 when the design matrix $\mathbf{X}$ includes points of very high leverage. However, HC4 tends to be more biased than HC3 and usually leads to wider confidence intervals.

In the following sections we review results on bias, variance and performance in confidence intervals of the estimators introduced in this section. We find that most authors recommend the use of HC3 over competing estimators.

1.4.3 Bias, variance and performance

In many applications, interest lies in estimation and inference on the linear combination $\mathbf{z}^T\hat{\boldsymbol{\beta}}$ for some $p \times 1$ vector $\mathbf{z}$. Let $\mathbf{a}^T = \mathbf{z}^T(\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T$ and let us define $v := \mathrm{Var}(\mathbf{z}^T\hat{\boldsymbol{\beta}}) = \mathbf{a}^T\boldsymbol{\Gamma}\mathbf{a}$. The estimators discussed so far differ in terms of bias and variance of corresponding $\hat{v} = \mathbf{a}^T\hat{\boldsymbol{\Gamma}}\mathbf{a}$. These differences affect the way estimators $\hat{v}$ behave in terms of confidence interval coverage relative to nominal size, power and width of confidence intervals.

In this section we review the work of Chesher and Jewitt (1987) on limits on the bias of HC0, HC2 and the jackknife estimator, and the work of Kauermann and Carroll

(2001) on the role of variance on the efficiency of covariance matrix estimators. Finally, we discuss the performance of these estimators in simulations under heteroscedasticity.

Bias

Chesher and Jewitt (1987) studied the role of heteroscedasticity and design on the bias of HC0, HC2 and the jackknife estimator. They found bounds on the bias of these estimators in terms of the true $\mathbf{\Gamma}$ and the leverages h_{ii}. We present some of their results.

Let $\alpha = \max_i(\gamma_i)/\min_i(\gamma_i)$ be a measure of the level of heteroscedasticity present in the model. Chesher and Jewitt (1987) show that if heteroscedasticity is moderate, $\alpha < 2$, then the HC0 estimator $\hat{\upsilon}^{(0)} = \mathbf{a}^T\hat{\mathbf{\Gamma}}^{(0)}\mathbf{a}$ is biased downward for any $p \times 1$ vector $\mathbf{z}$. However, if $\alpha > 2$, it is possible for White's estimator to be biased upward.

Let $\text{pb}(\hat{\upsilon}^{(0)}) := \left(\text{E}(\hat{\upsilon}^{(0)}) - \upsilon\right)/\upsilon$ be the proportionate bias of $\hat{\upsilon}^{(0)}$. Under homoscedasticity Chesher and Jewitt (1987) show that

$$-\max(h_{ii}) \leq \text{pb}(\hat{\upsilon}^{(0)}) \leq -\min(h_{ii}).$$

Under heteroscedasticity, they derive the following results

$$\text{pb}(\hat{\upsilon}^{(0)}) \leq \max(\alpha h_{ii}(1 - h_{ii}) + h_{ii}(h_{ii} - 2))$$

and

$$-\max(h_{ii})(1/\alpha - 1) \leq \text{pb}(\hat{\upsilon}^{(1)}) \leq -\max(h_{ii})(\alpha + 1)$$

where $\hat{\upsilon}^{(1)}$ corresponds to the HC2 estimator. A similar result is derived for the jackknife estimator and therefore to a close approximation for HC3.

The importance of these results is twofold. First, they allow us to set bounds on the bias of HC0, HC1, HC2 and HC3 under known moderate heteroscedasticity in terms of $\mathbf{\Gamma}$ and under unknown heteroscedasticity in terms of the design. Second, Chesher and Jewitt (1987) show that the bias of HC0-HC3 is not dependent only on the level of heteroscedasticity, but that it can be strongly affected by the design, specially in the presence of high leverage points.

Variance

Kauermann and Carroll (2001) studied the variance of the robust or sandwich variance estimator in the linear model and in quasi-likelihood models and generalized estimating equations. They showed that the sandwich estimator has higher variability than parametric variance estimators when the parametric model is correct and that the extent of the extra variance depends on the design. Increased variance of the variance estimators translates into confidence intervals with subnominal coverage.

Let $p = 1 - \alpha$ be the quantile of the normal distribution for a given α. Kauermann and Carroll (2001) show that variance relates to coverage through the following theorem, we quote:

> *Theorem 2.* Let $\hat{\theta} \sim N(\theta, \sigma^2/n)$ and let $\hat{\sigma}^2$ be an unbiased estimator of σ^2 independent of $\hat{\theta}$. The coverage probability of the $1 - \alpha$ confidence interval $CI(\hat{\sigma}^2, \alpha)$ equals
>
> $$\Pr\{\theta \in CI(\hat{\sigma}^2, \alpha)\} = 1 - \alpha - c_p \frac{\mathrm{Var}(\hat{\sigma}^2)}{\sigma^4} + O(n^{-2})$$
>
> where $c_p = \phi(z_p)(z_p^3 + z_p)/8$, with $\phi(\cdot)$ the standard normal distribution density.

The authors then suggest a coverage adjustment to construct confidence intervals based on normal quantiles. This adjustment is based on homoscedastic errors. They show in simulations that their correction reduces undercoverage of sandwich estimators in the heteroscedastic case but may still result is subnominal coverage, particularly in the presence of points of high leverage.

Kauermann and Carroll (2001) state that: "...undercoverage is determined mainly by the variance of the variance estimator". Their work suggests that variance reduction of variance estimators is highly important when constructing confidence intervals of regression parameters in small samples.

Further work has focused on the issues of bias and variance of heteroscedasticity consistent variance estimators. Motivated by the work of Chesher and Jewitt (1987), Bera et al. (2002) studied the variance of MINQUE. They found that MINQUE may have very large variance particularly for highly unbalanced design matrices. Qian and Wang (2001) studied the influence of high leverage points on the bias of White's (1980) and Hinkley's (1977) estimators. They proposed bias-corrected versions of these estimators with a focus on reducing variance and MSE of $\hat{\upsilon}$. Our work focuses on a class of variance estimators with reduced variance.

Performance

There has been considerable research on the performance of HC0-HC3 estimators in terms of confidence interval coverage under heteroscedasticity. We comment on three influential papers on the problem by MacKinnon and White (1985), Long and Ervin (2000) and Cribari-Neto (2004).

MacKinnon and White (1985) compared HC1, HC2 and the jackknife estimator under different scenarios of heteroscedasticity in simulations with sample sizes 50, 100 and 200. The jackknife is closely approximated by the HC3 estimator (Dorfman, 1991; Long and Ervin, 2000); therefore conclusions regarding the jackknife should apply to HC3. Long and Ervin (2000) compared HC0-HC3 in simulations with sample sizes as small as 25. The conclusions of both articles are as follows:

- The OLS may lead to severely misleading inference under heteroscedasticity.
- Tests of heteroscedasticity lack power in small samples. When heteroscedasticity is suspect, the OLS should be replaced by HC3.

- HC3 performs better than HC0-HC2 in studies with sample size less than 250; for larger sample sizes the choice of variance estimator does not matter as much.
- White's estimator (HC0) underestimates the variance in small samples and leads to undercoverage of confidence intervals. The HC0 estimator should not be used in small samples, even though this seems to be common practice in research and software (Long and Ervin, 2000).

Cribari-Neto (2004) followed a different approach and studied the influence of high leverage points on confidence interval coverage of HC0, HC3 and HC4 estimators. He found that HC3 may perform poorly in the presence of points of high leverage and that HC4 is more robust to influential observations. The disadvantage of HC4 in relation to HC3 comes in the form of wider average confidence intervals and larger variance.

1.4.4 Correlated data

Correlated data are common in medical studies where each cluster contributes multiple observations to a study. The theory on the use of the robust variance estimator for correlated data can be traced back to the work of Huber (1967), Hartley et al. (1969) and White (1980), as discussed in previous sections. Liang and Zeger (1986) and Zeger and Liang (1986) extended the use of the robust variance estimator to generalized estimating equations. Since then, the robust variance estimator has gained popularity in the literature and is routinely used by researchers in many disciplines. We introduce some basic results on generalized estimating equations and robust variance estimation for correlated data.

Consider a clustered study with M total clusters. Let n_i denote the size of the i-th cluster and let observations within it be denoted by y_{ij}, $j = 1, \ldots, n_i$. The response of interest y_{ij} is related to a $p \times 1$ vector of covariates $\boldsymbol{x}_{ij}$ through $g(\mu_{ij}) = \boldsymbol{x}_{ij}^T\boldsymbol{\beta}$ where $\mu_{ij} = \mathrm{E}(y_{ij}|\boldsymbol{x}_{ij})$. Let $\boldsymbol{\mu_i} = \{\mu_{i1}, \ldots, \mu_{in_i}\}^T$ and let the vector of all responses be written as

$\mathbf{Y} = \{\mathbf{Y}_1^T, \ldots, \mathbf{Y}_M^T\}^T$. Also let $\text{cov}(\mathbf{Y}_i) = \mathbf{\Gamma}_i$ and the block-diagonal matrix $\text{cov}(\mathbf{Y}) = \mathbf{\Gamma}$. The generalized estimating equations methodology of Liang and Zeger (1986) estimate $\boldsymbol{\beta}$ by solving the equations

$$U_{\beta,GEE1} = \sum_{i=1}^{M} \mathbf{D}_i \mathbf{V}_i^{-1}(\mathbf{Y}_i - \boldsymbol{\mu}_i) = 0$$

where $\mathbf{D}_i := \partial\boldsymbol{\mu}_i/\partial\boldsymbol{\beta}^T$, $\mathbf{V}_i := \text{diag}(\sigma_{ijj}^{\frac{1}{2}})\mathbf{R}_i(\alpha)\text{diag}(\sigma_{ijj}^{\frac{1}{2}})$, $\mathbf{R}_i$ is a working correlation matrix for $\text{corr}(\mathbf{y}_i)$ and $\sigma_{ijj} = \mu_{ij}(1 - \mu_{ij})$.

Estimators of $\text{cov}(\hat{\boldsymbol{\beta}})$ are obtained by replacing estimators of $\mathbf{\Gamma}_i$ in

$$\left(\sum_{i=1}^{M} \mathbf{D}_i^T \mathbf{V}_i^{-1} \mathbf{D}_i\right)^{-1} \left(\sum_{i=1}^{M} \mathbf{D}_i^T \mathbf{V}_i^{-1} \mathbf{\Gamma}_i \mathbf{V}_i^{-1} \mathbf{D}_i\right) \left(\sum_{i=1}^{M} \mathbf{D}_i^T \mathbf{V}_i^{-1} \mathbf{D}_i\right)^{-1}. \tag{1.3}$$

The robust variance estimator of Liang and Zeger (1986), denoted here by BC0, is obtained by replacing $\mathbf{\Gamma}_i$ by $\hat{\mathbf{\Gamma}}_i := \mathbf{r}_i \mathbf{r}_i^T$ in (1.3) where $\mathbf{r}_i = (\mathbf{y}_i - \hat{\boldsymbol{\mu}}_i)$. Liang and Zeger (1986) showed that the robust variance estimator provides consistent estimates of regression parameters in correlated data even when the covariance of the responses is misspecified. However it has been shown that the robust variance estimator is usually biased downwards in small samples and leads to Wald tests that are too liberal (Mancl and DeRouen, 2001; Fray and Graubard, 2001; Lipsitz et al., 1994). This topic is discussed in more detail in Chapter 4.

Several approaches have been suggested to improve estimation of $\text{cov}(\hat{\boldsymbol{\beta}})$ and the performance of Wald tests in small samples. Two corrections to the sandwich variance estimator given by Kauermann and Carroll (2001) and Mancl and DeRouen (2001) are especially relevant to our work.

Kauermann and Carroll (2001) suggest using

$$\hat{\mathbf{\Gamma}}_i := (\mathbf{I}_{n_i} - \mathbf{H}_{ii})^{-1/2} \mathbf{r}_i \mathbf{r}_i^T (\mathbf{I}_{n_i} - \mathbf{H}_{ii})^{-1/2T}$$

in (1.3) where $\mathbf{H}_{ij} = \mathbf{D}_i \left(\sum_{l=1}^{K} \mathbf{D}_l^T \mathbf{V}_l^{-1} \mathbf{D}_l \right)^{-1} \mathbf{D}_j^T \mathbf{V}_j^{-1}$. This estimator will be referred to as BC1. The matrix $\mathbf{H}_{ii}$ is the leverage of the i-th subject (Preisser and Qaqish, 1996) and can be seen as a generalization of the univariate h_{ii}. The rationale behind Kauermann and Carroll's (2001) correction is that if $E((\mathbf{y}_i - \boldsymbol{\mu}_i)(\mathbf{y}_i - \boldsymbol{\mu}_i)^T) = \sigma^2 \mathbf{V}_i$ then $E(\mathbf{z}^T \mathrm{BC1} \mathbf{z}) = \mathrm{Var}(\mathbf{z}^T \hat{\boldsymbol{\beta}})\{1 + O(K^{-2})\}$ for any $p \times 1$ vector $\mathbf{z}$.

Mancl and DeRouen (2001) suggested the correction

$$\hat{\mathbf{\Gamma}}_i := (\mathbf{I}_{n_i} - \mathbf{H}_{ii})^{-1} \mathbf{r}_i \mathbf{r}_i^T (\mathbf{I}_{n_i} - \mathbf{H}_{ii})^{-1T}$$

in (1.3). Mancl and DeRouen's (2001) estimator will be referred to as BC2. Their derivation follows a different argument than Kauermann and Carroll (2001). They obtain the first order approximation

$$\mathrm{E}(\mathbf{r}_i \mathbf{r}_i^T) \approx (\mathbf{I}_i - \mathbf{H}_{ii}) \mathbf{\Gamma}_i (\mathbf{I}_i - \mathbf{H}_{ii})^T + \sum_{j \neq i} \mathbf{H}_{ij} \mathbf{\Gamma}_j \mathbf{H}_{ij}^T$$

and drop the summation in the expression above assuming its contribution is negligible.

Both corrected estimators improve upon the standard sandwich estimator in terms of confidence interval coverage. Lu et al. (2007) compared both estimators in a simulation study. They found that in general BC2 provides coverage closer to nominal than BC1 except in studies with small cluster sizes, where BC2 may lead to overcoverage. An interesting note is that the observed bias of BC2 is expected to be larger than the bias of BC1 in most situations even though BC2 provides coverage closer to nominal. An explanation for this behavior is that positive bias in variance estimators may compensate for their variability when constructing confidence intervals (Lu et al., 2007). Kauermann and Carroll (2001) results on the variance of the variance estimator discussed in the previous section extend to generalized estimating equations. They show that the variance of the sandwich estimator directly affects the coverage of confidence intervals. The research of Lu et al. (2007) and Kauermann and Carroll (2001) strongly suggests that both bias and variance of sandwich variance estimators should be taken into account when constructing confidence intervals of regression parameters with either independent or correlated data. In Chapter 4 we study variance estimation for correlated data in more detail. We introduce a class of variance estimators that includes BC0, BC1 and BC2 as well as some new estimators. We compare estimators in this class in simulation scenarios for correlated data. We show that newly proposed estimators perform better in terms of variance and confidence interval coverage than BC0, BC1 and BC2.

The literature includes other approaches to constructing sandwich variance estimators and corresponding Wald tests for studies with correlated data. We briefly name some of them. Fay and Graubard (2001) proposed a modification to the sandwich estimator based on the first order Taylor expansion of the expectation of the i-th squared residual. They also suggested evaluating corresponding Wald tests as an F ratio with degrees of freedom that are a function of the estimated variance of the sandwich estimator. Pan and Wall (2002) also suggested a correction to the degrees of freedom of t or F tests as a function of the variance of the variance estimator. Approaches based on degrees of freedom corrections have met limited success (Lu et al., 2007; Braun, 2007). McCaffrey and Bell (2006) introduced a bias-reduction correction to the sandwich estimator in the setting of correlated binary data along with a Satterthwaite correction to the degrees of freedom of corresponding t tests. However, their method may not work adequately in the presence of high intra-cluster correlation. Morel et al. (2003) suggest a correction to the sandwich estimator based on adding a fraction of the naive variance estimator. Braun (2007) studied the problem from the point of view of cluster randomized trials. He suggested combining GEE regression estimates with variance estimators based on penalized quasi-likelihood and corrected Wald tests. The methods of Morel (2003) and Braun (2007) seem to work adequately in terms of coverage of confidence intervals in many situations; however the correction of Mancl and DeRouen (2001) seems to perform better with a small number of clusters (Braun, 2007). Some of the approaches above are not exclusive: Pan and Wall (2003) and Braun (2007) discuss the possibility of using corrected estimators such as Mancl and DeRouen's (2001) together with a Wald test correction. Our work focuses on corrections to the sandwich variance estimator rather than degrees of freedom corrections of Wald tests. However, both are viable areas of research.

1.4.5 Summary

We introduced two methods for mean parameter estimation for correlated binary data: within cluster resampling and within-cluster paired resampling. WCR was proposed for marginal parameter estimation in situations where cluster size may be related to response probability. WCPR was proposed for conditional parameter estimation for models with cluster-specific intercepts and slopes. The literature on WCR and WCPR does not identify the parameters estimated by each approach clearly. A comparison of the parameters estimated by WCR, WCPR and unweighted GEE is needed to gain understanding of these procedures. Our work aims to compare these estimation approaches, clarify their differences and comment on their validity.

We reviewed the topics of robust variance estimation for linear models under heteroscedasticity and correlated data. The robust variance estimator is asymptotically consistent but usually anti-conservative in small samples. Several corrections improve the small sample performance of the robust variance estimator. Most corrections focus on the bias of the variance estimator. Kauermann and Carroll (2001) showed that the variance of the variance estimator is largely responsible for interval undercoverage in small samples. The goal of our work is to propose a new class of robust variance estimators with an emphasis on variances reduction and small sample performance.

Chapter 2

Random cluster size, within-cluster resampling and generalized estimating equations

2.1 Introduction

Correlated binary data are common in public health and biomedical applications. Several statistical tools have been developed to analyze this type of data, such as random-effect models (Laird and Ware, 1982) and generalized estimating equations (GEE) (Liang and Zeger, 1986). An interesting problem arises when both response and cluster size are associated with unobserved random effects. Hoffman, Sen and Weinberg (2001) proposed 'within cluster resampling' (WCR) for the analysis of correlated binary data with nonignorable cluster size, defined as any violation of the property $E(Y_{ij}|n_i, X_{ij}) = E(Y_{ij}|X_{ij})$. They use nonignorable cluster size in the context of a random effects model in which cluster size N_i is random and associated with an unobserved random effect P_i. Their method is based on resampling units within clusters. Williamson, Datta and Satten (2003) and Benhin, Rao and Scott (2005) showed that resampling in WCR can be avoided through the use of cluster-weighted generalized estimating equations. Rieger and Weinberg (2003) proposed within cluster resampling of pairs of discordant observations for estimation of conditional parameters.

In this chapter we investigate the parameters estimated by unit-resampling, pair-resampling and generalized estimating equations. We explore the validity of unit-resampling and generalized estimating equations in studies with non-ignorable cluster sizes and propose a new method of estimation for conditional parameters with correlated binary data. Our analysis extends the understanding of these models and the strengths and weaknesses of these estimation procedures.

This chapter is organized as follows. In §2.2 we describe the WCR procedure. In §2.3 we introduce the model used by Hoffman et al. (2001) and Williamson et al. (2003) and investigate the parameters estimated by WCR and GEE in their model and two other models. In §2.4 we describe within cluster paired resampling (WCPR). In §2.5 we introduce the model used by Rieger and Weinberg (2003), study the parameter estimated by WCPR and propose an alternative estimating method. §2.6 is a conclusion.

2.2 Within-cluster unit resampling

Consider a study with K clusters, indexed by $i = 1, \ldots, K$. Let observations within cluster i be indexed by $j = 1, \ldots, n_i$. Let the jth binary response in the ith cluster be denoted by Y_{ij} with corresponding $p \times 1$ vector of covariates $\mathbf{x}_{ij}$. Throughout this section we consider the logistic model

$$\text{logit} E(Y_{ij}; \mathbf{x}_{ij}) = \mathbf{x}_{ij}^{\top} \boldsymbol{\beta} \tag{2.1}$$

where $\boldsymbol{\beta}$ is a parameter vector to be estimated.

The WCR procedure can be summarized as follows: a data set is obtained by randomly selecting one observation from each cluster. Thus each resample consists of K independent observations. Then by fitting a regression model for independent data to the q-th resample, an estimate $\hat{\boldsymbol{\beta}}(q)$, and an estimate of its covariance matrix $\widehat{\boldsymbol{\Sigma}}(q)$, are obtained. The resampling procedure is repeated Q times. The final estimate is the mean of the Q estimates,

$$\hat{\boldsymbol{\beta}}_{WCR} = \frac{1}{Q}\sum_{q=1}^{Q}\hat{\boldsymbol{\beta}}(q), \tag{2.2}$$

and its covariance is estimated by

$$\widehat{\boldsymbol{\Sigma}} = \frac{1}{Q}\sum_{q=1}^{Q}\widehat{\boldsymbol{\Sigma}}(q) - \mathbf{S}_{\boldsymbol{\beta}}, \tag{2.3}$$

where $\mathbf{S}_{\boldsymbol{\beta}}$ is the sample covariance matrix of the Q estimates.

We analyze the WCR procedure to identify what parameters it estimates. The q-th resample is identified by the sampling vector

$$\mathbf{Z}(q) = (Z_1(q), \cdots, Z_K(q))^\top,$$

where the components of $\mathbf{Z}(q)$ are independent and $Z_i(q)$ is an integer drawn randomly from the set $\{1, \cdots, n_i\}$. The estimate $\hat{\boldsymbol{\beta}}(q)$ is the solution in $\boldsymbol{\beta}$ of the estimating equation

$$\mathbf{U}_q(\boldsymbol{\beta}; \mathbf{Z}(q)) := \sum_{i=1}^{K}\sum_{j=1}^{n_i} I(Z_i(q) = j)\mathbf{x}_{ij}(y_{ij} - \mu_{ij}) = \mathbf{0},$$

where $\mu_{ij} := E[Y_{ij}]$. We use E_c to denote expectations with respect to resampling, conditioned on the data. The expected value of $\mathbf{U}_q(\boldsymbol{\beta}; \mathbf{Z}(q))$ conditional on the data is

$$E_c[\mathbf{U}_q(\boldsymbol{\beta}; Z(q))] = \sum_{i=1}^{K}\frac{1}{n_i}\sum_{j=1}^{n_i}\mathbf{x}_{ij}(y_{ij} - \mu_{ij}). \tag{2.4}$$

Thus when both K and Q are large, and under standard regularity conditions, $\hat{\boldsymbol{\beta}}_{WCR}$

is equivalent to the solution of

$$\mathbf{U}_{WCR}(\boldsymbol{\beta}) := \sum_{i=1}^{K} \frac{1}{n_i} \sum_{j=1}^{n_i} \mathbf{x}_{ij}(y_{ij} - \mu_{ij}) = \mathbf{0}. \tag{2.5}$$

The above estimating equation is a weighted generalized estimating equations with independence working correlation structure and cluster weight $1/n_i$. This equivalence is useful for two purposes. First, the computational burden of the resampling procedure can be avoided and the same estimate obtained by using generalized estimating equations with independence working correlation structure and cluster weight $1/n_i$. This can be easily implemented in standard software for generalized estimating equations. The covariance matrix can be estimated by the sandwich variance estimator. This has been shown by Williamson et al. (2003).

Second, the parameter estimated by WCR can be found as the solution of $E[\mathbf{U}_{WCR}(\boldsymbol{\beta})] = \mathbf{0}$ where the expectation is taken under the model of interest.

2.3 A beta-binomial model and associated parameters

2.3.1 The model

The WCR procedure of Hoffman et al. (2001) was not derived in the context of a specific model. However, the model gleaned from their simulations is a mixed model of the beta-binomial type in which cluster size is random and is correlated with the cluster-specific random effect. Here we describe the model used in the simulation section of Williamson et al. (2003) which differs only in some minor numerical details from that of Hoffman et al. (2001). There is a single cluster-level binary covariate x_i. The random effect P_i is distributed as beta(a_0, b_0) if $x_i = 0$ and beta(a_1, b_1) if $x_i = 1$. The parameters (a_l, b_l) are chosen such that for $x_i = 0$ the mean of P_i, $a_0/(a_0 + b_0) = 0.25$ and the within-cluster correlation $1/(a_0 + b_0 + 1) = 0.15$. For $x_i = 1$ the mean of P_i is 0.35 and the within-cluster correlation is 0.25. This gives $a_0 = 17/12, b_0 = 4.25, a_1 = 1.05$ and $b_1 = 1.95$. Conditional on P_i, cluster size N_i follows a truncated binomial$(9, g(P_i))$ where values 0, 1, 8 and 9 are discarded. The binomial probability $g(P_i)$ is as follows: $g(P_i) = 0.25$ if $P_i > E[P_i]$ and $g(P_i) = 0.75$ if $P_i \leq E[P_i]$. Conditional on P_i and N_i, the response $T_i := \sum_{j=1}^{n_i} Y_{ij}$ follows a binomial(N_i, P_i) distribution.

2.3.2 Estimation by WCR

We now investigate the parameters estimated by WCR. Let $\boldsymbol{\beta} = (\beta_0, \beta_1)^\top$ and $\pi_i(\boldsymbol{\beta})$ be the function

$$\pi_i(\boldsymbol{\beta}) := \{1 + \exp(-\beta_0 - \beta_1 x_i)\}^{-1}.$$

In the context of the above model, (2.5) can be written as

$$\mathbf{U}_{WCR}(\boldsymbol{\beta}) = \sum_{i=1}^{K} \frac{1}{N_i}(1, x_i)^T \{T_i - N_i \pi_i(\boldsymbol{\beta})\} = \sum_{i=1}^{K} (1, x_i)^T \{\frac{T_i}{N_i} - \pi_i(\boldsymbol{\beta})\}.$$

We assume that $\Pr(N_i > 0) = 1$. This implies that $\boldsymbol{\beta}_{WCR}$ is the limit solution in $\boldsymbol{\beta}$ of

$$\sum_{i=1}^{K} (1, x_i)^T \left\{ E\left[\frac{T_i}{N_i}\right] - \pi_i(\boldsymbol{\beta}) \right\} = \mathbf{0}. \tag{2.6}$$

Under the model of section (2.3.1), $E[T_i | N_i, P_i] = N_i P_i$ which implies that

$$E\left[\frac{T_i}{N_i} | N_i, P_i\right] = P_i, \tag{2.7}$$

and by unconditioning

$$E\left[\frac{T_i}{N_i}\right] = E[P_i].$$

Thus if $E[P_i]$ follows a logistic regression on x_i with parameters $\boldsymbol{\beta}^*$, then $\boldsymbol{\beta}^*$ will be the limit solution of (2.6), that is $\boldsymbol{\beta}_{WCR} = \boldsymbol{\beta}^*$. That is certainly the case in the model given above, and the parameters are

$$\beta_0^* = \text{logit}(0.25) \approx -1.099, \qquad \beta_1^* = \text{logit}(0.35) - \text{logit}(0.25) \approx 0.48.$$

Note that in the above derivation the critical condition is (2.7); as long as

$$E[\frac{T_i}{N_i}|N_i, P_i] = P_i,$$

WCR estimates the same parameter regardless of the dependence, or lack thereof, between N_i and P_i.

On a technical note, we have assumed uniqueness of the limiting root of (2.6) which, strictly speaking, follows from other considerations. The required conditions are not restrictive and we assume that they hold. A similar assumption is made below.

2.3.3 Estimation by GEE

The estimating function for unweighted generalized estimating equations is

$$\mathbf{U}_{GEE}(\boldsymbol{\beta}) = \sum_{i=1}^{K} (1, x_i)^T \{T_i - N_i \pi_i(\boldsymbol{\beta})\}.$$

Its expected value with respect to both Y_i and N_i is

$$E[\mathbf{U}_{GEE}(\boldsymbol{\beta})] = \sum_{i=1}^{K} (1, x_i)^T \{E[T_i] - \pi_i(\boldsymbol{\beta}) E[N_i]\}.$$

So $\boldsymbol{\beta}_{GEE}$, the parameter estimated by unweighted generalized estimating equations is the limit solution in $\boldsymbol{\beta}$ of

$$\sum_{i=1}^{K} E[N_i]\,(1, x_i)^T \left\{ \frac{E[T_i]}{E[N_i]} - \pi_i(\boldsymbol{\beta}) \right\} = \mathbf{0}.$$

For the model given above,

$$E[N_i; x_i = 0] = 4.72, \qquad E[T_i; x_i = 0] = 0.957,$$

$$E[N_i; x_i = 1] = 4.66, \qquad E[T_i; x_i = 1] = 1.31,$$

with corresponding $\boldsymbol{\beta}_{GEE} = (-1.37, 0.43)^\top$. The mean parameter estimates reported by Williamson et al. (2003) from their simulation study, $(-1.382, 0.429)^\top$ for $K = 50$ and $(-1.366, 0.418)^\top$ for $K = 500$, are in close agreement with the theory.

Essentially, unweighted generalized estimating equations are valid for fitting the model

$$\text{logit}\ \frac{E[T_i]}{E[N_i]} = \beta_0 + \beta_1 x_i, \tag{2.8}$$

while weighted generalized estimating equations with cluster weight $1/N_i$ and, equivalently, WCR are valid for fitting the model

$$\text{logit}\ E[\frac{T_i}{N_i}] = \beta_0 + \beta_1 x_i. \tag{2.9}$$

Both methods are valid for their respective models, and the choice of estimation method should be based on whether the model of interest is (2.8) or (2.9). The two models coincide only if, for all i, $E[T_i]/E[N_i] = E[T_i/N_i]$, a condition equivalent to $\text{Cov}(T_i/N_i, N_i) = 0$.

2.3.4 Examples of nonignorable cluster size

The purpose of these examples is to show that the choice of estimation procedure should be based on examination of the model and its parameters.

A missing data model

Let Y_{ij} , $j = 1, \ldots, n_i^*$, be i.i.d. Bernoulli variables with mean p_i given by

$$\text{logit } p_i = \beta_0 + \beta_1 x_i,$$

where x_i is a cluster level binary covariate. Let $\{Z_{ij}, j = 1, \cdots, n_i^*\}$ be missingness indicators such that $Z_{ij} = 1$ if Y_{ij} is observed and $Z_{ij} = 0$ if Y_{ij} is missing, and suppose that

$$\gamma_s := \Pr(Z_{ij} = 1 | Y_{ij} = s), \quad s = 0, 1,$$

with $\gamma_0 \neq \gamma_1$.

Suppose we observe only $T_i = \sum_{j=1}^{n_i^*} Y_{ij} Z_{ij}$ and $N_i = \sum_{j=1}^{n_i^*} Z_{ij}$. Nonignorability of cluster size can be seen by comparing $E[Y_{ij}] = p_i$ to $E[Y_{ij} | N_i = n_i^*] = p_i \gamma_1 / \{p_i \gamma_1 + (1 - p_i)\gamma_0\}$. Unweighted GEE fit the model (2.8) given by

$$\text{logit} \frac{E[T_i]}{E[N_i]} = \text{logit} \frac{p_i \gamma_1}{p_i \gamma_1 + (1 - p_i)\gamma_0} = \beta_0^* + \beta_1 x_i, \tag{2.10}$$

where $\beta_0^* = \beta_0 + \log(\gamma_1 / \gamma_0)$. If the data are limited to clusters with $N_i > 0$ then (2.9) becomes

$$\text{logit} E[\frac{T_i}{N_i} | N_i > 0] = \text{logit} \frac{E[T_i | N_i > 0]}{E[N_i | N_i > 0]} = \beta_0^* + \beta_1 x_i$$

and both WCR and GEE fit (2.10). The proof is in the appendix. This example shows that it is possible for WCR and GEE to estimate the same parameters in the presence of nonignorable cluster sizes.

A model for developmental toxicity

Kuk (2003) developed a model for fetal response in developmental toxicity in which both the number of fetal implants as well as the death or malformation of implanted fetuses are dose dependent. The model produces ignorable cluster sizes according to the definition of Hoffman et al. (2001), but Kuk (2003) argues that failure to consider the association between dose and fetal implantation might underestimate the total effect of exposure.

Let N_0 be the unobserved cluster size that would have been observed in the absence of a toxic agent. Through the concept of thinning, the observed cluster size is assumed to have mean $\exp(\alpha_1 x_i)E(N_0)$ where x_i represents dose level of a toxic agent and $\alpha_1 \leq 0$.

Given that a fetus is implanted, the probability of death or malformation p_i is independent of cluster size and is modeled by

$$\text{logit} p_i = \beta_0 + \beta_1 x_i.$$

Under this model $E[T_i/N_i] = E[T_i]/E[N_i] = p_i$ and the parameters estimated under WCR and GEE will both asymptotically converge to β_0 and β_1.

Kuk (2003) argues that p_i itself is not the measure of risk of interest for developing a virtually safe dose, since it ignores the negative effect of the toxic agent on fetal implantation. He proposes a combined risk that takes into account the probability of failure to implant and the probability of successful implantation leading to malformation or death. This is the risk measure of interest in the model. In this case cluster size is associated with exposure in a way that leads to ignorable cluster size according to the definition by Hoffman et al. (2001). While WCR and GEE provide consistent estimates of β_0 and β_1, both underestimate the total risk associated with exposure.

2.4 Within cluster paired resampling

Rieger and Weinberg (2003) proposed within cluster paired resampling (WCPR) for the analysis of correlated binary data for models with cluster-specific intercepts and slopes. The method is based on resampling two observations from each cluster such that one observation has response $y_{ij} = 1$ and the other has response $y_{ik} = 0$. This can be done only in clusters with at least one $y_{ij} = 1$ and one $y_{ik} = 0$, that is, clusters for which $0 < t_i := \sum_{j=1}^{n_i} y_{ij} < n_i$. Such clusters are called informative clusters. The resulting resampled data set resembles data from a matched-pair design. The conditional likelihood based on the resampled pairs is then used for estimation. The resampling procedure is repeated Q times. The final estimate $\hat{\boldsymbol{\beta}}_{WCPR}$ and its estimated covariance matrix are calculated using (2.2) and (2.3). The parameter $\hat{\boldsymbol{\beta}}_{WCPR}$ can be interpreted as "the log odds per unit increase of exposure based on randomly sampling an affected-unaffected pair from a randomly sampled informative cluster" (Rieger and Weinberg, 2002).

We describe the procedure using the sampling-vector notation. For $i = 1, \cdots, K$ define the sets

$$A_i = \{j : y_{ij} = 1\}, \qquad B_i = \{j : y_{ij} = 0\}.$$

For the q-th resample, let $Z_{i1}(q)$ and $Z_{i0}(q)$, $i = 1, \cdots, K$, be independent random variables distributed uniformly over the sets A_i and B_i, respectively. We set $Z_{i1} = 0$ if A_i is empty and $Z_{i0} = 0$ if B_i is empty. Sampling one pair from each informative cluster and maximizing the conditional likelihood is equivalent to solving:

$$\mathbf{U}_q(\boldsymbol{\beta}; \mathbf{Z}(q)) = \sum_{i=1}^{K} \sum_{j=1}^{n_i} \sum_{k=1}^{n_i} I(Z_{i1}(q) = j) I(Z_{i0}(q) = k) \boldsymbol{\Delta}_{ijk} (y_{ij} - \gamma_{ijk}) = 0, \tag{2.11}$$

where $\boldsymbol{\Delta}_{ijk} := \mathbf{x}_{ij} - \mathbf{x}_{ik}$ and $\gamma_{ijk} = E[Y_{ij} | Y_{ij} + Y_{ik} = y_{ij} + y_{ik}; \boldsymbol{\Delta}_{ijk}]$.

For each $j \in A_i$ and $k \in B_i$, let

$$w_i = E_c[I(Z_{i1}(q) = j) I(Z_{i0}(q) = k)] = \begin{cases} \frac{1}{t_i(n_i - t_i)} & \text{if } 0 < t_i < n_i \\ 0 & \text{otherwise.} \end{cases}$$

Then the expected value of $\mathbf{U}_q(\boldsymbol{\beta}; \mathbf{Z}(q))$ conditional on the data is

$$E_c[\mathbf{U}_q(\boldsymbol{\beta}; \mathbf{Z}(q))] = \sum_{i=1}^{K} w_i \sum_{j \in A_i, k \in B_i} \boldsymbol{\Delta}_{ijk}(y_{ij} - \gamma_{ijk}). \tag{2.12}$$

Empty sums are taken to be zero.

We propose solving $\mathbf{U}_{WCPR} := E_c[\mathbf{U}_q(\boldsymbol{\beta}; \mathbf{Z}(q))] = \mathbf{0}$ to estimate $\boldsymbol{\beta}$. We will refer to this strategy as 'cluster weighted generalized estimating equation' (CWGEE). This can be implemented in standard software by converting each informative cluster to a pseudo-cluster consisting of $t_i(n_i - t_i)$ observations with responses $y_{ij} = 1$, $y_{ik} = 0$, associated covariate vectors $\boldsymbol{\Delta}_{ijk}$ and cluster weight w_i. A standard logistic regression model with no intercept is fitted using y_{ij} as response, and with an independence working correlation structure. For large K and Q, the weighted CWGEE estimator is equivalent to the WCPR estimator. This follows from arguments similar to those of Williamson et al. (2003).

The CWGEE approach offers advantages over WCPR. First, CWGEE avoids the intensive computation involved in WCPR. Second, in a resampled data set in WCPR, some elements of $\boldsymbol{\Delta} ijk$ can be 0 for most or every sampled pair, resulting in infinite or undefined parameter estimates. This may happen in studies with small number of clusters or where the exposure of interest is rare. The instability of the resampling-based estimates, especially with small K, has been noted by Hoffman et al. (2001) and Williamson et al. (2003). In contrast, CWGEE does not suffer from this problem unless it is a global issue affecting the whole data set.

2.5 A mixed model and associated parameters

2.5.1 The model

In this section we investigate the nature of the parameter estimated by WCPR, to be denoted β_{WCPR}, in a generalized mixed model used in Rieger and Weinberg (2002). We consider K clusters of equal size and a single binary covariate X_{ij} that may vary within a cluster. Covariates X_{ij}'s are mutually independent. Several values of the prevalence of exposure, $\Pr(X_{ij} = 1)$, will be investigated.

The intercept parameter is fixed at $\alpha = \text{logit}(0.25)$. The cluster-specifc random slope β_i takes two possible values with probability 1/2 each. Given this structure, β_{WCPR} is the root of the expected value of (2.12), that is, the solution of

$$\sum_{i=1}^{K} \sum_{\mathbf{y}_i, \mathbf{x}_i, b_i} \Pr(\mathbf{Y}_i = \mathbf{y}_i, \mathbf{X}_i = \mathbf{x}_i, \beta_i = b_i) \cdot w_i \sum_{j \in A_i, k \in B_i} \Delta_{ijk}(Y_{ij} - \gamma_{ijk}) = 0, \qquad (2.13)$$

where $\Pr(\mathbf{Y}_i, \mathbf{X}_i, \beta_i)$ is computed under the model as $\Pr(\mathbf{Y}_i, \mathbf{X}_i, \beta_i) = \Pr(\mathbf{X}_i = \mathbf{x}_i) \cdot \Pr(\beta_i = b_i) \cdot \Pr(\mathbf{Y}_i = \mathbf{y}_i | \mathbf{x}_i, b_i)$.

We calculate β_{WCPR} for each simulation setup of Rieger and Weinberg (2002).

Table 2.1 summarizes the results for the case $n_i = 4$ and $\Pr(X_{ij} = 1) = 0.5$. It can be seen that, in general, $\beta_{WCPR} \neq E[\beta_i]$. The table also shows the probability that a random cluster contributes an XY-informative pair, a pair that is discordant with respect to both Y and X. This is important because in the resampling scheme, only XY-informative pairs contribute to the conditional likelihood. The table shows that, for the setups considered, only about 34-42% of the clusters are expected to provide informative pairs. This implies that the resample estimates will be highly unstable when K is small, and thus a very large Q may be needed.

The parameter β_{WCPR} is a function not only of the distribution of β_i, but also of the intercept parameter, cluster size and exposure prevalence. This property is illustrated in Figure 2.1. In this setup the intercept and the distribution of β_i are held fixed. The plot shows that cluster size and exposure probability have a large impact on the value of β_{WCPR}. The impact of exposure prevalence is especially large for large cluster sizes. For example, when the common cluster size is 3 and the probability of exposure is 0.1, $\beta_{WCPR} = 0.1650$, which may suggest that exposure is a risk factor. When the common cluster size is 8 and the probability of exposure is 0.9, $\beta_{WCPR} = -0.2270$, which may now suggest that the exposure has a protective effect. The attractiveness of WCPR is that it is simple to describe. However, this comes at the high cost of β_{WCPR} being affected by factors other than the actual effects of exposure. When applying or using WCPR, this feature must be kept in mind.

2.5.2 An alternative GEE estimator

Alternative estimating methods for the analysis of correlated binary data for models with cluster-specific intercepts and slopes can be obtained by applying different weights than CWGEE in (2.12). We propose solving

$$\mathbf{U}_{UWGEE} := \sum_{i=1}^{K} \sum_{j \in A_i, k \in B_i} \boldsymbol{\Delta}_{ijk}(y_{ij} - \gamma_{ijk}) = \mathbf{0}. \tag{2.14}$$

We will refer to this approach as UWGEE. The parameter β_{WCPR} obtained by either WCPR or CWGEE can be interpreted as “the log odds per unit increase of exposure based on randomly sampling an affected-unaffected pair from a randomly sampled informative cluster” (Rieger and Weinberg, 2002). The parameter β_{UWGEE} that solves (2.14) is interpreted as “the log odds per unit increase of exposure based on randomly sampling an affected-unaffected matched pair from the population of all such matched pairs”.

The advantage of β_{UWGEE} over β_{WCPR} is that β_{UWGEE} is not affected by cluster size and exposure prevalence. For example, the value of β_{UWGEE} is 0.165 for all combinations of cluster size and exposure probability shown in Figure 2.1.

2.5.3 Example

We analyzed data from the Intergenerational Epidemiologic Study of Adult Periodontitis known as Multi-Pied (Gansky et. al, 1998; 1999). The study included 467 subjects. The number of teeth per person ranged between 2 and 32 with a mean of 21. For each person in the study the investigators recorded the mean clinical attachment level, in mm, by type of tooth. The binary outcome of interest is whether the mean clinical attachment exceeded 3 mm. We consider one binary covariate: whether a tooth is categorized as posterior (molar or premolar) or anterior (cuspid or incisor) and fit the logistic model

$$\text{logit}E(Y_{ij}|\alpha_i, \beta, MOLAR_{ij}) = \alpha_i + \beta(MOLAR_{ij}), \tag{2.15}$$

where MOLAR$_{ij}$ is an indicator of whether the jth tooth in the ith subject is posterior. This is the same model used by Rieger and Weinberg (2003) but with a different data set. The parameter of interest β is interpreted as the log odds of mean clinical attachment exceeding 3 mm of a molar tooth compared to an anterior tooth based on randomly sampling a pair of affected-unaffected teeth from a randomly sampled person with at least one such pair of teeth.

We fit the model using WCPR with 1000, 5000 and 10000 resamples and with the CWGEE and UWGEE approaches. Our analysis used only the 167 subjects with at least one affected-unaffected pair of teeth. Table 2.2 shows estimates of β and corresponding standard errors. Results under CWGEE and WCPR with a large number of resamples were very similar. Under CWGEE we obtained $\widehat{\beta} = 0.1064$ with estimated standard error 0.1339. Under WCPR with 10,000 resamples we obtained $\widehat{\beta} = 0.1070$ (0.1354). The close agreement between the two methods was expected due to the asymptotic equivalence of the WCPR and the CWGEE estimators. The UWGEE method obtains $\widehat{\beta} = 0.0925$ (0.1449).

2.6 Discussion

We investigated two within-cluster resampling procedures. The difference between unit resampling and unweighted generalized estimating equations is that they estimate different models and have different target parameters. With that in mind, both WCR and unweighted generalized estimating equations are robust to dependence between N_i and P_i. The choice of procedure should be based on whether the model of interest is (2.8) or (2.9).

For the paired resampling procedure, the computational cost can be avoided by using a special version of weighted generalized estimating equations that is easily implemented in standard software. The attractiveness of WCPR is that it is simple to describe and implement. However, its target parameter is unduely sensitive to cluster size and exposure prevalence. An alternative version of generalized estimating equations with unit weights estimates a target parameter that is not affected by cluster size distribution and exposure prevalence. Since cluster size and, more importantly, exposure distribution are not intrinsically related to exposure risk, the alternative procedure is preferable.

Table 2.1: Parameters estimated by WCPR and expected proportion of XY-informative clusters

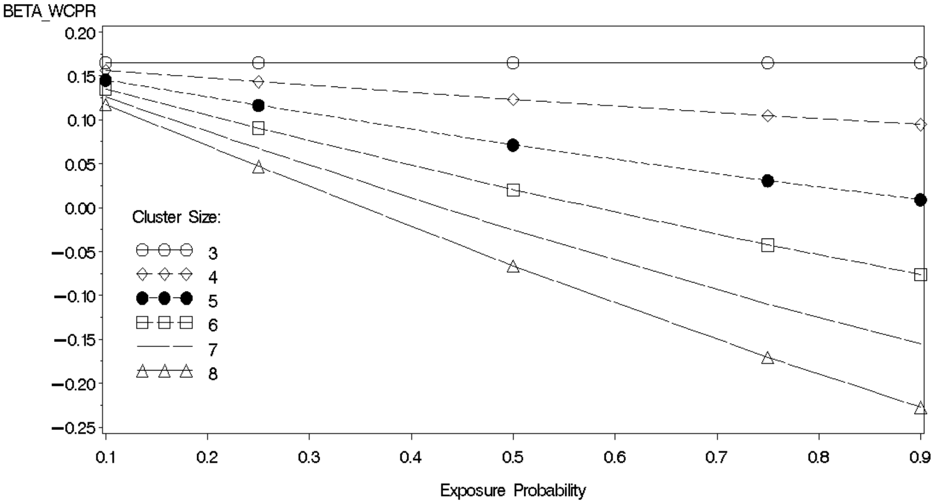
β_i values	$E(\beta_i)$	β_{WCPR}	% XY-informative
0.3/-0.3	0	0.01990	34.2
1.5/-0.3	0.6	0.67050	40.0
2.0/-0.3	0.85	0.89470	42.4
1.2/-1.2	0	0.26340	36.3
2.0/-2.0	0	0.54799	39.2
0.992/-2.5	-0.754	-0.03677	33.9
1.026/-2.9	-0.937	-0.04004	33.9
0.934/-1.8	-0.433	-0.00017	34.2
1.046/-2.5	-0.727	-0.00223	34.2

β_i values assigned with probability 1/2, cluster size = 4, $\alpha = \text{logit}(0.25)$, exposure prevalence = 0.5 .

Table 2.2: Analysis of dental data

	$\widehat{\beta}$	(SE)
UWGEE	0.0925	(0.1449)
CWGEE	0.1064	(0.1339)
WCPR		
1,000 resamples	0.0986	(0.1360)
5,000 resamples	0.1109	(0.1392)
10,000 resamples	0.1070	(0.1354)

Figure 2.1: True β_{WCPR} by cluster size and exposure probability



Clusters assigned $\beta_i = -2.5$ or $\beta_i = 1.25$ with probability 1/2.
Common intercept $\alpha = \text{logit}(0.25)$.

Chapter 3

Variance estimation in regression models

3.1 Introduction

Consider again the linear model introduced in Chapter 1: $E\mathbf{Y} = \mathbf{X}\boldsymbol{\beta}, \mathrm{Var}(\mathbf{Y}) = \boldsymbol{\Gamma}$ where $\mathbf{Y}$ is an $n \times 1$ vector of responses, $\mathbf{X}$ is a known $n \times p$ matrix of covariates of rank p, $\boldsymbol{\beta}$ is a $p \times 1$ vector of unknown parameters, and $\boldsymbol{\Gamma} = \mathrm{diag}(\gamma_1, \ldots, \gamma_n)$ is unknown.

In Chapter 1 we stated that the ordinary least squares (OLS) estimator of $\boldsymbol{\beta}$ is best linear unbiased only under homoscedasticity and that the OLS estimator of $\mathrm{cov}(\hat{\boldsymbol{\beta}})$ is biased and leads to improper inference under heteroscedasticity. We introduced variance estimators that are robust to heteroscedasticity. The goal of this chapter is to introduce a class of robust variance estimators for independent data that includes some currently available estimators as well as some new estimators. We evaluate estimators in this class in terms of confidence interval coverage under homoscedasticity and some scenarios of heteroscedasticity.

Throughout this chapter, we use the notation introduced in 1.4.1. If $\mathbf{a} = (a_1, \cdots, a_n)^T$ is a vector, we write diag($\mathbf{a}$) to denote a diagonal matrix with diagonal elements $a_1, \cdots, a_n$. Conversely, if $\mathbf{A}$ is a square matrix with elements a_{ij}, then diag($\mathbf{A}$) will denote the column vector $(a_{11}, \cdots, a_{nn})^T$. $\mathbf{H}$ denotes the hat matrix $\mathbf{H} = \mathbf{X}(\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T$, and $\mathbf{S}$ is the vector of squared residuals with elements r_i^2, where $r_i = Y_i - \mathbf{x}_i^T\hat{\boldsymbol{\beta}}$.

Heteroscedasticity-consistent covariance estimators (HCCME) of the true covariance,

$$\mathrm{cov}(\hat{\boldsymbol{\beta}}) = (\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\boldsymbol{\Gamma}\mathbf{X}(\mathbf{X}^T\mathbf{X})^{-1}, \tag{3.1}$$

are generally obtained by replacing $\boldsymbol{\Gamma}$ in (3.1) by an estimator. The most commonly used HCCME, the ‘sandwich’, ‘empirical’ or ‘robust’ variance estimator, was proposed by White in 1980. White’s estimator, $\hat{\gamma}_i = r_i^2$, is biased in finite samples (Chesher and Jewitt, 1987) and can lead to inadequate coverage of confidence intervals. Several corrections to White’s estimator have been proposed to reduce its bias or improve its coverage. A well known class of HCCMEs is given by $\hat{\gamma}_i = r_i^2/(1 - h_{ii})^{\delta}$ (Dorfman, 1991), where h_{ii} are the diagonal elements of $\mathbf{H}$ and $\delta \geq 0$. White’s estimator is obtained with $\delta = 0$, the ‘almost unbiased’ estimators of Horn et al. (1975) and Wu (1986) with $\delta = 1$ and the jackknife estimator of Miller (1974) with $\delta = 2$ to a close approximation. These three estimators are referred to as HC0, HC2 and HC3 respectively (Long and Ervin, 2000). Cribari-Neto (2004) proposed HC4, given by $\hat{\gamma}_i = r_i^2/(1 - h_{ii})^{\delta_i}$ with $\delta_i = \max(4, h_{ii}/\bar{h})$, for designs with high leverage points. Estimators HC0-HC3 have been evaluated by MacKinnon and White (1985) and Flachaire (2005), among others.

The HC2 estimator is unbiased only under homoscedasticity. The HC3 and HC4 are generally biased upwards. However, bias is not the only concern with the sandwich estimator. In fact, bias can be removed completely; since $E[\mathbf{S}] = \mathbf{P}\boldsymbol{\gamma}$, where $\mathbf{P}$ has elements that are the squares of the corresponding elements of $(\mathbf{I} - \mathbf{H})$, the estimator $\hat{\gamma} = \mathbf{P}^{-1}\mathbf{S}$ is exactly unbiased for $\boldsymbol{\gamma} = \text{diag}(\boldsymbol{\Gamma})$. Horn et al. (1975) show that this estimator is the (unreplicated) MINQUE (minimum norm quadratic estimator) with uncorrelated and heteroscedastic errors of Rao (1970). Even though the MINQUE is unbiased, it has large variance (Bera et al., 2002) and can have negative components. Kauermann and Carroll (2001) identified high variability of the sandwich estimator as a source of poor coverage of confidence intervals. We show that reducing the variance of covariance estimators results in improved coverage of confidence intervals. This chapter is organized as follows. In §3.2 we describe the new class of estimators; in §3.3 we present simulation studies; in §3.4 we show data analysis examples; §3.5 is a conclusion.

3.2 Heteroscedasticity-consistent covariance estimators

3.2.1 A class of variance estimators

We consider estimators of the true covariance of $\text{cov}(\hat{\boldsymbol{\beta}})$ obtained by replacing $\boldsymbol{\Gamma}$ in (3.1) by an estimator. Since $\boldsymbol{\Gamma}$ is a diagonal matrix, we limit our attention to the vector of its diagonal elements $\boldsymbol{\gamma} = \text{diag}(\boldsymbol{\Gamma})$. We define the class of estimators of $\boldsymbol{\gamma}$:

$$\hat{\gamma}_{\delta}^{(k)} = \mathbf{D}^{\delta-1}(\mathbf{D}\mathbf{P})^{k}\mathbf{D}\mathbf{S}, \tag{3.2}$$

where $\mathbf{D} = \mathrm{diag}\{1/(1-h_{ii})\}$, k is an integer and $\delta \geq 0$. The diagonal $\mathbf{D}^{\delta-1}$ will be called the scale matrix and $(\mathbf{DP})^k\mathbf{D}$ will be called the weight matrix. Several well known estimators are obtained by replacing $\hat{\mathbf{\Gamma}}_\delta^{(k)} := \mathrm{diag}(\hat{\boldsymbol{\gamma}}_\delta^{(k)})$ in (3.1):

- The case $k = -1$ and $\delta = 1$, $\hat{\boldsymbol{\gamma}}_1^{(-1)} = \mathbf{P}^{-1}\mathbf{S}$, yields the unreplicated MINQUE.
- The case $k = 0$ and $\delta = 0$, $\hat{\boldsymbol{\gamma}}_0^{(0)} = \mathbf{S}$, yields HC0.
- The case $k = 0$ and $\delta = 1$, $\hat{\boldsymbol{\gamma}}_1^{(0)} = \mathbf{DS}$, yields HC2.
- The case $k = 0$ and $\delta = 2$, $\hat{\boldsymbol{\gamma}}_2^{(0)} = \mathbf{D}^2\mathbf{S}$, yields HC3.
- The case $k \to \infty$ and $\delta = 1$ yields the OLS estimator. Here $\hat{\boldsymbol{\gamma}}_1^{(\infty)} := \lim_{k\to\infty}\hat{\boldsymbol{\gamma}}_1^{(k)} = \frac{1}{n-p}\mathbf{JS}$, where $\mathbf{J}$ is the $n \times n$ matrix with all elements equal to 1. The proof is in the appendix.

The HC4 estimator does not belong to class (3.2). It uses $\hat{\boldsymbol{\gamma}}_{\delta_*}^{(0)} = \mathbf{D}_*\mathbf{S}$ where $\mathbf{D}_* = \mathrm{diag}(1/(1-h_{ii})^{\delta_i})$, $\delta_i = \max(4, h_{ii}/\bar{h})$ and $\bar{h} = \sum h_{ii}/n$.

Estimators $\hat{\boldsymbol{\gamma}}_\delta^{(k)}$ corresponding to values of k other than -1, 0 and $k \to \infty$ have not previously appeared in the literature. In this chapter we study estimators $\hat{\boldsymbol{\gamma}}_\delta^{(1)}$ with $k = 1$. Componentwise, they can be written as:

$$(\hat{\boldsymbol{\gamma}}_\delta^{(1)})_i = \frac{1}{(1-h_{ii})^{\delta-1}}\left(r_i^2 + \sum_{j\neq i}\frac{h_{ij}^2}{(1-h_{ii})(1-h_{jj})}r_j^2\right). \tag{3.3}$$

We define new estimators HC3$^{(1)}$ with $\delta = 2, k = 1$ and HC4$^{(1)}$ with $\hat{\boldsymbol{\gamma}}_{\delta_*}^{(1)} = \mathbf{D}_*(\mathbf{DP})\mathbf{S}$. Under homoscedasticity, the most efficient estimator, the OLS, assigns equal weight to each squared residual r_i^2 to estimate σ^2. When heteroscedasticity is suspect, estimators such as HC0, HC2 and HC3 of the form $(\hat{\boldsymbol{\gamma}}_\delta^{(0)})_i = r_i^2/(1-h_{ii})^\delta$ assign full weight to each observation's squared residual when estimating γ_i. Estimators $\hat{\boldsymbol{\gamma}}_\delta^{(1)}$ assign a positive weight to every squared residual when estimating each γ_i. As such, $\hat{\boldsymbol{\gamma}}_\delta^{(1)}$ offers a weight matrix that falls between $(\hat{\boldsymbol{\gamma}}_\delta^{(0)})_i = r_i^2/(1-h_{ii})^\delta$ and the weight matrix for OLS.

3.2.2 Generalized linear models (GLM)

GLM generalizes the linear model introduced earlier and allows the study of non-linear models under a unified framework. Robust covariance estimation in GLM is obtained by replacing an estimator of $\boldsymbol{\Gamma}$ in the generalized version of (3.1). In this section, we show how to generalize the class of estimators $\hat{\boldsymbol{\gamma}}_\delta^{(k)}$ to GLM. For a complete treatment of GLM see McCullagh and Nelder (1989).

In GLM, $E\mathbf{Y} = \boldsymbol{\mu}$ is related to a known matrix of predictors $\mathbf{X}$ and an unknown parameter $\boldsymbol{\beta}$ through a link function $g(\cdot)$ by

$$g(\mu_i) = \eta_i = \sum_j x_{ij}\beta_j.$$

Typically, a working model for $\mathrm{Var}(y_i)$ dependent on μ_i is also used, usually denoted by $V_i = V_i(\mu_i)$. Maximum likelihood estimates of $\boldsymbol{\beta}$ are obtained by solving

$$\mathbf{X}^T\mathbf{W}\mathbf{X}\hat{\boldsymbol{\beta}} = \mathbf{X}^T\mathbf{W}\mathbf{Z}$$

iteratively where $\mathbf{Z}$ is the adjusted dependent variable

$$z_i = \hat{\eta}_i + (y_i - \mu_i)\left(\frac{\partial \eta_i}{\partial \mu_i}\right)$$

and $\mathbf{W}$ is a diagonal matrix given by $\mathbf{W}^{-1} = \text{diag}\left(V_i\left(\frac{\partial \eta_i}{\partial \mu_i}\right)^2\right)$.

After solving for $\hat{\boldsymbol{\beta}}$ in the last iteration, let $\mathbf{Y}^* = \sqrt{\mathbf{W}}\mathbf{Z}$ and $\mathbf{X}^* = \sqrt{\mathbf{W}}\mathbf{X}$. It follows that $\hat{\boldsymbol{\beta}} = (\mathbf{X}^{*T}\mathbf{X}^*)^{-1}\mathbf{X}^{*T}\mathbf{Y}^*$. Therefore we can use $\mathbf{Y}^*$ and $\mathbf{X}^*$ with correspondingly defined $\mathbf{D}^*$, $\mathbf{P}^*$ and $\mathbf{S}^*$ to obtain a class of variance estimators for GLM given by

$$\hat{\boldsymbol{\gamma}}_\delta^{*(k)} = \mathbf{D}^{*\delta-1}(\mathbf{D}^*\mathbf{P}^*)^k\mathbf{D}^*\mathbf{S}^*.$$

The corresponding estimate of $\text{Cov}(\hat{\boldsymbol{\beta}})$ is obtained by replacing $\hat{\boldsymbol{\gamma}}_\delta^{*(k)}$ in the generalized version of (3.1).

3.2.3 Properties

We derive some properties of the class of covariance estimators in (3.2).

1. Estimators $\hat{\boldsymbol{\gamma}}_1^{(k)}$ are unbiased under homoscedasticity for any integer k.

2. **Theorem 3.1**. If $\mathbf{P}$ is invertible and $\text{Var}(\mathbf{S}) \propto \mathbf{P}$, then $\text{Var}(\mathbf{z}^{\mathbf{T}}\hat{\boldsymbol{\Gamma}}_\delta^{(k+1)}\mathbf{z}) \leq \text{Var}(\mathbf{z}^{\mathbf{T}}\hat{\boldsymbol{\Gamma}}_\delta^{(k)}\mathbf{z})$ for any $p \times 1$ real vector $\mathbf{z}$, any $\delta \geq 0$ and any integer k.

3. For any $p \times 1$ real vector $\mathbf{z}$, and fixed integers k and $\delta \geq 0$, $\mathbf{z}^{\mathbf{T}}\hat{\boldsymbol{\Gamma}}_\delta^{(k)}\mathbf{z} \xrightarrow{p} \mathbf{z}^{\mathbf{T}}\boldsymbol{\Gamma}\mathbf{z}$ as $n \to \infty$.

4. **Theorem 3.2**. If $k = 1$, the corresponding weight matrix $(\mathbf{DP})\mathbf{D}$ is equal to the

correlation matrix of $\mathbf{S}$ under normality and homoscedasticity.

Proofs are given in the appendix.

Property 1 implies that the MINQUE, HC2 and OLS estimators are unbiased under homoscedasticity. A direct consequence of Property 1 is that $E(\hat{\boldsymbol{\gamma}}_\delta^{(k_1)}) = E(\hat{\boldsymbol{\gamma}}_\delta^{(k_2)})$ for any integers k_1 and k_2 and any δ under homoscedasticity.

Property 2 implies that if $\text{Var}(\mathbf{S}) \propto \mathbf{P}$ then for fixed δ we can rank $\mathbf{z}^{\mathbf{T}}\hat{\boldsymbol{\Gamma}}_\delta^{(k)}\mathbf{z}$ in terms of their variances by means of k. In particular, the condition $\text{Var}(\mathbf{S}) \propto \mathbf{P}$ is satisfied if $\mathbf{Y} \sim N_n(\mathbf{X}\boldsymbol{\beta}, \sigma^2\mathbf{I})$ (normality and homoscedasticity), but is slightly more general. Kauermann and Carroll (2001) proved that under normality and homoscedasticity, linear combinations of the OLS estimator have smaller variance than linear combinations of the HC2 estimator. Theorem 3.1 is a generalization of Kauermann and Carroll's (2001) result. A direct corollary is that, under homoscedasticity and normality, linear combinations of the unreplicated MINQUE have higher variance than the HC2 estimator, and the HC2 higher variance than the OLS.

Property 3 assures consistency of this class of estimators for fixed δ and k. Property 4 allows for an interpretation of the weight matrix in $\hat{\boldsymbol{\gamma}}_\delta^{(1)}$ as the correlation matrix of the vector of squared residuals under normality and homoscedasticity.

The properties above do not apply to finite samples under heteroscedasticity. In the following section, we compare estimators of the class $\hat{\boldsymbol{\gamma}}_\delta^{(k)}$ with $k = 0$ and $k = 1$ in simulations with small sample sizes under heteroscedasticity. We show that in many scenarios of heteroscedasticity, linear combinations of $\hat{\boldsymbol{\gamma}}_\delta^{(1)}$ have smaller variance than those of $\hat{\boldsymbol{\gamma}}_\delta^{(0)}$. The smaller variance of $\hat{\boldsymbol{\gamma}}_\delta^{(1)}$ translates into good performance of confidence intervals in small samples.

3.3 Simulations

MacKinnon and White (1985) compared several versions of the variance estimators of Hinkley (1977) and White (1980). They concluded that among the estimators considered in their chapter, the jackknife estimator performed best in terms of coverage of confidence intervals in small samples. Recent work in the literature of inference in the heteroscedastic linear model has used the jackknife estimator as a benchmark in simulations (Dorfman, 1991; Mancl and DeRouen, 2001; Kauermann and Carroll, 2001). The HC3 estimator is equivalent to the jackknife estimator to close approximation (Dorfman, 1991) and will be used throughout our simulations.

We compare the performance of sandwich estimators of $\mathrm{Var}(\mathbf{z}^T\hat{\boldsymbol{\beta}})$ of the form $\mathbf{a}^T\hat{\boldsymbol{\Gamma}}_{\delta}^{(k)}\mathbf{a}$, where $\mathbf{a^T} = \mathbf{z^T}(\mathbf{X^T}\mathbf{X})^{-\mathbf{1}}\mathbf{X^T}$, in a linear model with heteroscedasticity. We compare the estimators OLS ($\delta = 1, k \to \infty$), HC3 ($\delta = 2, k = 0$), HC3$^{(1)}$ ($\delta = 2, k = 1$), HC4 and HC4$^{(1)}$ in terms of bias, variance, confidence interval width and confidence interval coverage. The HC4 estimator is expected to improve upon HC3 in terms of coverage in scenarios with high leverage points (Cribari-Neto, 2004). Estimators HC3 and HC3$^{(1)}$ share the same scale matrix and therefore the same expected value under homoscedasticity. The same holds true for HC4 and HC4$^{(1)}$.

In GLM we study beta-binomial and gamma-Poisson examples of overdispersion. Liang and McCullagh (1993) conducted case studies of overdispersion in the binary case. They found that misspecification of the dispersion model may strongly affect inference. They also state that the use of the robust variance estimator of Liang and Zeger (1986) may be inadequate in small samples. In each case, our simulations compare the model based estimator of $\mathrm{Var}(\mathbf{z}^T\hat{\boldsymbol{\beta}})$, the robust variance estimator HC0* given by $\mathbf{a}^{*T}\hat{\boldsymbol{\Gamma}}_0^{(0)*}\mathbf{a}^*$ as defined in Section 3.2.2, and similarly defined HC3$^*(\delta = 2, k = 0)$ and HC3$^{(1)*}(\delta = 2, k = 1)$ in terms of bias, variance, confidence interval width and coverage. We show that HC3* and HC3$^{(1)*}$ lead to confidence intervals with adequate coverage even in moderately small samples.

Simulation 1. Linear model. The following simulation setup is taken from example 3 of Kauermann and Carroll (2001). Let $y_i = \beta_0 + x_i\beta_1 + \epsilon_i$ with $\beta_0 = 0$, $\beta_1 = 1$ and $\epsilon_i \sim N(0, \gamma_i)$. The errors are drawn from three different models: (1) homoscedastic with $\gamma_i^{1/2} = 0.2$, (2) $\gamma_i^{1/2} = 0.2 + \exp(x_i/2)/2$ and (3) $\gamma_i^{1/2} = \sqrt{(0.1 + x_i^2)}$. The covariates x_i are chosen to correspond to fixed quantiles of: (a) uniform distribution in (-0.5,0.5), (b) standard normal, (c) standard Laplace, (d) exponential($\lambda = 1$) centered around 0. Simulation results are based on 1000 replicates. Table 3.1 shows nominal 95% confidence intervals for β_1 using estimators OLS, HC3, HC3$^{(1)}$, HC4 and HC4$^{(1)}$ with sample sizes 15 and 30 based on quantiles of the t distribution with $n - 2$ degrees of freedom, and the ratio of average widths of confidence intervals and simulation variances of estimators HC3 and HC3$^{(1)}$. Table 3.2 shows the average simulation bias of the OLS, HC3, HC3$^{(1)}$, HC4 and HC4$^{(1)}$ and the ratio of average interval widths and simulation variances of HC4 and HC4$^{(1)}$.

The results on Table 3.1 show that the OLS estimator obtained subnominal coverage under heteroscedasticity. In most scenarios HC3$^{(1)}$ provided comparable coverage to HC3, and HC4$^{(1)}$ provided similar or higher coverage than HC4. The newly proposed HC3$^{(1)}$ lead to slightly wider confidence intervals on average than HC3 under homoscedasticity, the ratio of average widths ranged from 1.00 to 1.04, but the new estimator produced shorter intervals on average under heteroscedasticity, with average width ratios between 0.91 and 1.00. Table 3.2 shows that HC4$^{(1)}$ also obtained wider confidence intervals under homoscedasticity than HC4, with ratios between 1.00 and 1.10, but shorter intervals under heteroscedasticity, and average width ratios between 0.91 and 1.00.

The new estimators HC3$^{(1)}$ and HC4$^{(1)}$ obtained smaller simulation variance than HC3 and HC4 respectively in every scenario. Table 3.1 shows that the simulation variance of HC3$^{(1)}$ was only between 0.42 and 0.86 times the simulation variance of HC3 in scenarios with sample size 15 and between 0.51 and 0.94 times the simulation variance of HC3 in scenarios with sample size 30. Table 3.2 shows that the simulation variance of HC4$^{(1)}$ was between 0.36 and 0.85 times that of HC4 in scenarios with sample size 15 and between 0.45 and 0.91 in scenarios with sample size 30. The smaller variance of the new estimators explains why they were competitive in terms of coverage with HC3 and HC4 in these scenarios while obtaining intervals of shorter average width under heteroscedasticity.

Table 3.2 shows simulation bias of these estimators. It is known that HC3, HC3$^{(1)}$, HC4 and HC4$^{(1)}$ are biased in these scenarios. Positive bias of covariance estimators often increases confidence interval coverage and counteracts the effect of the estimators' high variability (Kauermann and Carroll, 2001; Lu et al. 2007). Therefore, it may be desirable to use biased variance estimators when constructing confidence intervals. However, given two or more variance estimators with comparable coverage, it is reasonable to prefer estimators with smaller bias and variance. Table 3.2 shows that HC3 and

HC3$^{(1)}$, and HC4 and HC4$^{(1)}$ had similar simulation biases under homoscedasticity. This is consistent with theoretical results since HC3 and HC3$^{(1)}$, and HC4 and HC4$^{(1)}$ have equal expectations under homoscedasticity. The new estimators HC3$^{(1)}$ and HC4$^{(1)}$ had smaller bias than HC3 and HC4 respectively in every scenario of heteroscedasticity.

We repeated the simulations above with sample size 50. The coverage of HC3$^{(1)}$ was very similar to that of HC3, but HC3$^{(1)}$'s width was 0.94 to 1.00 times the width of HC3 and the simulation variance of HC3$^{(1)}$ was only 0.60 to 0.96 times the variance of HC3 throughout all scenarios. These results were repeated for HC4$^{(1)}$ and HC4: the new estimator obtained similar coverage but smaller average confidence interval width (ratios from 0.92 to 1.00) and reduced simulation variance (ratios from 0.56 to 0.97). These results are not shown in tables.

We also evaluated the performance of HC3$^{(2)}$ with $\hat{\gamma}_2^{(2)} = \mathbf{D}(\mathbf{DP})^2\mathbf{DS}$ in the above scenarios. HC3$^{(2)}$ obtained slightly higher coverage (0.1% to 0.5%) than HC3$^{(1)}$ under homoscedasticity in scenarios with sample sizes 15 and 30, but lower coverage (up to 1% lower) in scenarios of heteroscedasticity. We do not study the HC3$^{(2)}$ estimator further in this paper.

Simulation 2. Beta-binomial data. Let $Y_i|x_i$, $i = 1, \ldots, n$, be independent, beta-binomial random variables with mean and variance given by $\mathrm{E}(Y_i|x_i) = m_i\pi_i$ and $\mathrm{Var}(Y_i|x_i) = m_i\pi_i(1-\pi_i)\{1+\rho(m_i-1)\}$, where $\pi_i = \pi(x_i) = \mathrm{logit}^{-1}(\beta_0 + x_i\beta_1)$. We fit a logistic model for binomial data ignoring the overdispersion term $\{1+\rho(m_i-1)\}$ and compare the coverage of nominal 95% confidence intervals for β_1 based on standard normal quantiles using the model-based variance estimator, the robust variance estimator HC0* of Liang and Zeger (1986), the approximately jackknife HC3* and the newly proposed HC3$^{(1)*}$ after 1000 simulations. We let $\boldsymbol{\beta} = \{0, 1\}^T$ and choose the covariate x_i to be: (1) equally spaced in [-0.5, 0.5] so that π_i is in (0.37, 0.63) and (2) equally spaced in [-2, -1] so that π_i is in (0.11, 0.27). The binomial denominators m_i range from 2 to 12 and are randomly selected from a truncated negative binomial distribution with mean 3.12 and variance 4.12 similar to the U.S. sibship size distribution in 1950 (Brass, 1958; Donner and Koval, 1987). We explore the combinations of $n = 25, 50$ and $\rho = 0.1, 0.2, 0.3, 0.5$. Results are shown in Table 3.3. It is clear that the binomial model-based variance estimator loses coverage quickly for increasing values of ρ. The robust variance estimator HC0* leads to undercoverage with $n = 25$. Both HC3* and HC3$^{(1)*}$ maintain appropriate coverage for every scenario. Even though HC3* and HC3$^{(1)*}$ are derived from the binomial model, they seem to implicitly account for the overdispersion of the data. The difference in width between HC3* and HC3$^{(1)*}$ was less than 0.5% in every scenario and is not shown in tables. The main difference between HC3* and HC3$^{(1)*}$ was a smaller observed variance of HC3$^{(1)*}$: the ratio of simulation variance of HC3$^{(1)*}$ to HC3* ranged from 0.65 to 0.91 in every scenario.

Simulation 3. Poisson data with extra-Poisson variation. Let $Y_i|x_i$, $i = 1, \ldots, n$ be independent random variables from a gamma-Poisson mixture with mean and variance given by $\mathrm{E}(Y_i|x_i) = \lambda_i$ and $\mathrm{Var}(Y_i|x_i) = \lambda_i(1 + b)$, where $\lambda_i = \lambda(x_i) = \exp(\beta_0 + x_i\beta_1)$. We fit a log-linear model for Poisson data ignoring the extra-Poisson variation term $(1 + b)$ and compare the coverage of nominal 95% confidence intervals for β_1 based on standard normal quantiles using the model-based variance estimator, the robust variance estimator HC0* of Liang and Zeger (1986), the approximately jackknife HC3* and the newly proposed HC3$^{(1)*}$ after 1000 simulations. We let $\boldsymbol{\beta} = \{0, 1\}^T$ and choose the covariate x_i to be equally spaced in [1/5, 5] in the log-scale so that λ_i is equally spaced in [1/5, 5]. We study the combinations of $n = 10, 25, 50$ and $b = 0.5, 1, 3, 5$. Results are shown in Table 3.4. It is clear again that the Poisson model-based variance estimator loses coverage quickly when extra-Poisson variation increases. The observed coverage of the model-based variance estimator did not improve with larger sample sizes and was as low as 60%. The robust variance estimator HC0* showed undercoverage, 81.7% to 91.7%, in scenarios with sample sizes 10 and 25 and moderate undercoverage, 91% to 92.7%, with sample size 50. The new HC3$^{(1)*}$ showed slightly higher coverage than HC3* in most scenarios, but both estimators maintained appropriate coverage throughout. Again, a desirable property of both HC3$^{(1)*}$ and HC3* is that they appear robust to the extra-Poisson variation of the data that is ignored when fitting the model. The difference in average confidence interval width between HC3$^{(1)*}$ and HC3* is less than 2% in every scenario and is not shown in tables, however HC3$^{(1)*}$ showed consistently smaller variance than HC3, a ratio ranging from 0.74 to 0.99.

3.4 Examples

First, we compare estimators OLS, HC0, HC3, HC3$^{(1)}$, HC4 and HC4$^{(1)}$ in a linear model for data on per capital spending on public schools and per capita income by state in the United States in 1979.

We then compare estimates and standard errors using different estimators in three data sets discussed by Liang and McCullagh (1993). These examples involve binary data with overdispersion.

Example 1. This example is taken from Cribari-Neto (2004). The data appear in Greene (1997, Table 12.1, p. 541). The response of interest y_i is per capita spending in dollars on public schools per state in 1979 in the United States. The covariate x_i is per capita income in dollars times 10^{-4}. The state of Wisconsin is dropped from all analyses due to missing response and Washington, DC is included. The state of Alaska has very large recorded values for both income (1.0851) and spending (821) and shows as a probable outlier in Figure 3.1. This results in very high leverage for Alaska, $h_{ii} = 0.651 \approx 10p/n = 0.180$. Interest lies on whether per capita income has a linear or quadratic effect on spending. We follow the analysis of Cribari-Neto (2004) and fit the model

$$y_i = \beta_0 + \beta_1 x_i + \beta_2 x_i^2 + \epsilon_i$$

with and without Alaska. The parameter of interest is β_2.

Table 3.7 shows estimates of $\hat{\beta}_2$ and corresponding standard errors using OLS, HC0, HC3, HC3$^{(1)}$, HC4 and HC4$^{(1)}$. Table 3.7 shows that the OLS and HC0 estimators' standard errors are noticeably smaller than those obtained with the other estimators. Even though HC3 and HC3$^{(1)}$ have the same expected value under homoscedasticity, this example shows that they can differ significantly in data analysis. The same holds true for HC4 and HC4$^{(1)}$. The interpretation and statistical significance of β_2 depends on the choice of standard error and on whether Alaska is included in the analysis or not. In both analyses with and without Alaska, HC3 appears to overcorrect the HC0 standard error when compared to HC3$^{(1)}$: corresponding standard errors for HC0, HC3 and HC3$^{(1)}$ are 829.99, 1995.24 and 1715.85 when including Alaska, and 626.68, 1103.03

and 1008.20 without Alaska. A similar situation arises with HC4 and the new HC4$^{(1)}$; the HC4 estimator appears to overcorrect the HC0 standard error. The results in Simulation 1 lead us to prefer HC3$^{(1)}$ and HC4$^{(1)}$ over HC3 and HC4 respectively. Standard errors obtained with HC4$^{(1)}$ are larger than HC3$^{(1)}$'s but account for points of high leverage. If the data have no points of high leverage, then HC3$^{(1)}$ is usually preferable to HC4$^{(1)}$. This example shows the possible effect of a high influence point on parameter estimates and standard errors. The estimators HC3$^{(1)}$ and HC4$^{(1)}$ appear less prone to overcorrect the HC0 standard errors than HC3 and HC4 in these data.

Example 2. Liang and McCullagh (1993) studied the applicability of two models for overdispersion in five data sets with binary responses from the literature. We revisit three of their data sets applying their two models for overdispersion, robust variance estimators based on their residuals, and a naive variance model.

The naive model is given by

$$\mathrm{Var}(\mathbf{Y}_i) = m_i \pi_i (1 - \pi_i)$$

where m_i is the binomial denominator for $\mathbf{Y}_i$ and π_i is the probability of success. We will refer to the naive model as Model 1.

Model 2 corresponds to a constant dispersion factor and is given by

$$\mathrm{Var}(\mathbf{Y}_i) = m_i \pi_i (1 - \pi_i) \sigma^2.$$

Model 3 comes from the beta-binomial distribution and is given by

$$\mathrm{Var}(\mathbf{Y}_i) = m_i\pi_i(1-\pi_i)\{1+(m_i-1)\rho\}$$

where ρ is the intra-class correlation parameter.

Table 3.5 shows parameter estimates and standard errors for three of the data sets analyzed by Liang and McCullagh (1993). The first data set corresponds to a toxicology study by Weil (1970) comparing two treatment groups, each with 16 observations. The second data set is taken from Crowder (1978, Table 3). Crowder's data address the growth of 831 seeds divided into 21 batches. The third data set comes from a teratological dietary study by Shepard, Mackler and Finch (1980) on 58 rats divided into 4 groups. Liang and McCullagh (1993) present a full description of these data sets. We show standard errors based on the robust variance estimator HC0* and the newly proposed HC3$^{(1)*}$ under the naive, constant dispersion and beta-binomial models. Note that sandwich estimators obtained from the residuals of the naive model or residuals of the constant dispersion model are equivalent.

Table 3.5 shows smaller standard errors obtained under the robust variance estimator HC0* than the model based estimator in the three data sets. The HC3$^{(1)*}$ estimator helps correct this behavior. However it is not clear which standard errors are 'correct' in any given case.

To gain understanding of this problem we simulated beta-binomial data with the same cluster setup and estimated parameters as those of Crowder's data in Table 3.5.

The correlation ρ was set at its estimated valued $\hat{\rho} = 0.19$. We fit the incorrect constant dispersion model and corresponding HC0* and HC3$^{(1)*}$. Coverage of nominal 95% confidence intervals based on these three estimators and normal quantiles after 10000 simulations is shown in Table 3.6. The new HC3$^{(1)*}$ shows coverage closer to nominal than the constant correlation model and much closer than the robust variance estimator HC0*.

Table 3.5 shows that standard errors based on models for overdispersion and the proposed HC3$^{(1)*}$ may differ significantly. In general, no one variance estimation method works adequately for every scenario of binary data with overdispersion. It is possible to devise situations where any of the estimators considered performs poorly. However, the proposed HC3$^{(1)*}$ has been shown to be a competitive approach to model-based overdispersion. It performs better than the commonly used robust variance estimator HC0* in most scenarios and should be preferred to it, especially in small to medium samples. It can help assess the appropriateness of an assumed dispersion model and offers a viable alternative when no dispersion assumptions are made.

3.5 Discussion

We described a new class of variance estimators for regression models, and focused on one member, HC3$^{(1)}$. The main motivation behind this estimator is that it has the same expected value than HC3 under homoscedasticity, yet it has smaller variance. Based on the new class of estimators, we defined HC4$^{(1)}$ as an alternative to the HC4 estimator of

Cribari-Neto (2004) for designs with high leverage points. The newly proposed estimators differ from previously described estimators in that the estimate of the variance of each observation is a linear combination of all the squared residuals, not only that observation's squared residual. They thus seem to reduce variability by borrowing strength across observations. We showed how the new class of estimators extends to generalized linear models. The generalized HC3$^{(1)*}$ provides adequate inference in many situations without the need for assumptions about the variance model. Our simulations show that HC3$^{(1)*}$ provides intervals with coverage close to the nominal level in all but the most extreme scenarios. Even when its coverage is similar to that of competing estimators like HC3* , it shows consistently smaller variance and sometimes smaller average interval width.

Table 3.1: Coverage of estimators OLS, HC3, $HC3^{(1)}$, HC4 and $HC4^{(1)}$

n=15

Model	Distribution	%Cover	%Cover	%Cover	%Cover	%Cover		
		OLS	HC3	$HC3^{(1)}$	HC4	$HC4^{(1)}$	C8	C9
1	Exponential	98.00	94.70	96.50	96.80	99.50	1.04	0.50
1	Laplace	97.80	93.70	95.80	95.20	96.80	1.02	0.69
1	Normal	97.00	94.00	95.20	93.50	94.90	1.01	0.77
1	Uniform	97.00	95.80	96.00	94.70	95.20	1.00	0.86
2	Exponential	87.90	88.20	91.40	93.80	98.70	0.94	0.42
2	Laplace	91.70	95.20	96.50	96.70	97.70	0.96	0.63
2	Normal	94.80	94.90	95.80	94.90	95.80	0.98	0.71
2	Uniform	96.30	95.60	95.80	94.50	95.10	1.00	0.86
3	Exponential	80.70	90.40	90.60	95.00	98.90	0.91	0.42
3	Laplace	79.60	90.20	90.10	92.80	93.20	0.93	0.61
3	Normal	86.30	93.10	92.20	93.30	92.70	0.95	0.67
3	Uniform	93.20	94.40	94.30	93.20	93.30	0.99	0.84

n=30

Model	Distribution	%Cover	%Cover	%Cover	%Cover	%Cover		
		OLS	HC3	$HC3^{(1)}$	HC4	$HC4^{(1)}$	C8	C9
1	Exponential	95.60	93.30	94.30	95.20	97.30	1.02	0.62
1	Laplace	97.40	93.60	94.70	95.20	96.80	1.01	0.79
1	Normal	96.70	95.00	95.30	94.90	95.20	1.00	0.86
1	Uniform	96.60	95.80	96.00	95.60	95.80	1.00	0.95
2	Exponential	77.20	89.10	89.20	93.90	96.70	0.93	0.52
2	Laplace	84.40	95.40	95.00	97.10	97.70	0.96	0.72
2	Normal	92.50	93.50	93.60	93.40	93.90	0.99	0.82
2	Uniform	96.00	95.50	95.50	94.90	95.10	1.00	0.94
3	Exponential	73.40	90.90	89.80	95.40	96.60	0.92	0.51
3	Laplace	76.20	91.50	90.60	94.70	94.10	0.95	0.72
3	Normal	83.50	93.00	92.40	93.70	93.30	0.97	0.79
3	Uniform	94.00	95.50	95.60	95.30	95.20	0.99	0.92

* C8 = Width($HC3^{(1)}$)/Width(HC3),   C9 = Var($HC3^{(1)}$)/Var(HC3)

Coverage, ratio of average widths and ratio of simulation variances refer to nominal 95% confidence intervals of β_1 after 1000 simulations. Model (1) is homoscedastic, and Models (2) and (3) are heteroscedastic as described in the text.

Table 3.2: Bias of estimators OLS, HC3, $HC3^{(1)}$, HC4 and $HC4^{(1)}$

n=15

Model	Distribution	%Bias	%Bias	%Bias	%Bias	%Bias		
		OLS	HC3	$HC3^{(1)}$	HC4	$HC4^{(1)}$	C8	C9
1	Exponential	70.23	72.58	72.08	485.79	483.58	1.10	0.40
1	Laplace	41.37	44.72	43.88	81.60	80.40	1.02	0.64
1	Normal	33.77	30.94	31.65	32.53	33.35	1.02	0.73
1	Uniform	24.30	24.11	24.08	12.44	12.40	1.00	0.85
2	Exponential	-43.22	41.24	11.01	483.62	334.73	0.94	0.36
2	Laplace	-35.68	27.37	11.94	69.07	46.42	0.96	0.60
2	Normal	-6.58	30.12	22.46	35.25	26.47	0.98	0.69
2	Uniform	19.77	22.51	22.13	11.00	10.65	1.00	0.85
3	Exponential	-59.81	20.12	-8.67	391.92	251.72	0.91	0.36
3	Laplace	-59.95	21.84	2.90	63.78	36.18	0.93	0.58
3	Normal	-45.97	22.56	8.87	29.91	14.26	0.95	0.65
3	Uniform	-10.89	17.61	13.66	7.01	3.31	0.99	0.84

n=30

Model	Distribution	%Bias	%Bias	%Bias	%Bias	%Bias		
		OLS	HC3	$HC3^{(1)}$	HC4	$HC4^{(1)}$	C8	C9
1	Exponential	27.89	26.22	26.51	123.79	124.57	1.05	0.50
1	Laplace	18.96	17.15	17.40	51.77	52.20	1.01	0.74
1	Normal	13.86	13.75	13.69	18.19	18.10	1.00	0.83
1	Uniform	11.38	10.44	10.51	5.32	5.40	1.00	0.94
2	Exponential	-60.00	15.51	-5.54	164.64	105.94	0.92	0.46
2	Laplace	-51.56	20.10	8.27	78.31	57.83	0.96	0.69
2	Normal	-21.00	7.23	3.92	14.30	10.34	0.99	0.80
2	Uniform	8.34	10.45	10.27	5.41	5.23	1.00	0.93
3	Exponential	-65.50	24.28	-0.64	187.50	118.22	0.91	0.45
3	Laplace	-62.32	17.39	5.35	73.71	53.28	0.95	0.68
3	Normal	-49.37	10.24	3.22	20.92	12.46	0.97	0.77
3	Uniform	-13.75	11.46	9.50	6.74	4.83	0.99	0.91

* C8 = Width($HC4^{(1)}$)/Width(HC4), C9 = Var($HC4^{(1)}$)/Var(HC4)

Bias, ratio of average widths and ratio of simulation variances refer to nominal 95% confidence intervals of β_1 after 1000 simulations. Model (1) is homoscedastic, and Models (2) and (3) are heteroscedastic as described in the text.

Table 3.3: Confidence intervals fitting a logistic model for binomial data to beta-binomial data

n=25

Model	ρ	%Cover	%Cover	%Cover	%Cover	$\frac{\mathrm{Var}(\mathrm{HC3}^{(1)})}{\mathrm{Var}(\mathrm{HC3})}$
		Model	HC0*	HC3*	HC3$^{(1)*}$	
1	0.1	92.4	92.4	96.2	96.6	0.78
1	0.2	85.1	89.8	94.5	94.9	0.81
1	0.3	85.1	92.5	96.1	96.4	0.78
1	0.5	73.1	90.4	94.5	94.5	0.74
2	0.1	91.3	90.9	94.1	94.4	0.65
2	0.2	89.8	93.1	95.8	96.4	0.86
2	0.3	86.2	90.9	94.5	94.8	0.80
2	0.5	79.1	91.2	95.9	96.3	0.90

n=50

Model	ρ	%Cover	%Cover	%Cover	%Cover	$\frac{\mathrm{Var}(\mathrm{HC3}^{(1)})}{\mathrm{Var}(\mathrm{HC3})}$
		Model	HC0*	HC3*	HC3$^{(1)*}$	
1	0.1	91.1	93.6	95.5	95.5	0.91
1	0.2	84.8	93.5	95.2	95.1	0.88
1	0.3	81.7	92.3	94.4	94.2	0.87
1	0.5	76.2	93.6	95.2	95.0	0.88
2	0.1	91.5	93.4	94.5	94.4	0.91
2	0.2	87.5	92.9	94.7	94.4	0.91
2	0.3	82.5	93.1	94.4	94.6	0.87
2	0.5	76.2	92.7	94.0	94.3	0.89

Nominal 95% confidence intervals of β_1 after 1000 simulations. Estimators compared are the binomial model-based variance estimator, the robust variance estimator HC0*, the approximately jackknife HC3* and the newly proposed HC3$^{(1)*}$.

Table 3.4: Confidence intervals fitting a Poisson model to gamma-Poisson data

n	b	%Cover Model	%Cover HC0*	%Cover HC3*	%Cover HC3$^{(1)*}$	$\frac{\text{Var}(\text{HC3}^{(1)})}{\text{Var}(\text{HC3})}$
10	0.5	91.5	86.6	94.1	96.0	0.95
10	1	85.8	85.4	95.1	96.1	0.86
10	3	76.1	85.2	95.9	97.0	0.79
10	5	68.5	81.7	93.9	96.6	0.62
25	0.5	90.3	90.7	94.7	94.9	0.95
25	1	86.1	90.3	94.1	94.1	0.95
25	3	71.5	89.8	93.7	94.4	0.91
25	5	64.1	87.6	91.9	93.1	0.85
50	0.5	88.9	92.4	93.7	93.7	0.98
50	1	84.3	92.7	94.0	94.2	0.97
50	3	71.1	91.9	93.6	93.6	0.96
50	5	60.0	91.0	93.1	93.2	0.97

Nominal 95% confidence intervals of β_1 after 1000 simulations. Estimators compared are the Poisson model-based variance estimator, the robust variance estimator HC0*, the approximately jackknife HC3* and the newly proposed HC3$^{(1)*}$.

Table 3.5: Analysis of overdispersed binary data

Weil-Williams' Toxicology Data

Dispersion	Estimate		Standard Error						
Model :	1&2	3	1	2			3		
			Model	Model	HC0*	HC3$^{(1)*}$	Model	HC0*	HC3$^{(1)*}$
Intercept	2.183	2.144	0.264	0.432	0.283	0.303	0.437	0.284	0.303
Treatment	-0.961	-1.021	0.330	0.541	0.475	0.508	0.539	0.471	0.502

Crowder's Germination Data

Dispersion	Estimate		Standard Error						
Model :	1&2	3	1	2			3		
			Model	Model	HC0*	HC3$^{(1)*}$	Model	HC0*	HC3$^{(1)*}$
Intercept	-0.558	-0.535	0.126	0.172	0.176	0.226	0.194	0.178	0.223
Root	1.318	1.330	0.178	0.242	0.242	0.313	0.278	0.238	0.298
Seed	0.146	0.070	0.223	0.305	0.287	0.384	0.312	0.289	0.373
Root*Seed	-0.778	-0.819	0.306	0.418	0.374	0.501	0.435	0.382	0.492

Shepard-Mackler-Finch's Teratology Data

Dispersion	Estimate		Standard Error						
Model :	1&2	3	1	2			3		
			Model	Model	HC0*	HC3$^{(1)*}$	Model	HC0*	HC3$^{(1)*}$
Intercept	1.144	1.212	0.129	0.219	0.276	0.286	0.223	0.269	0.279
Group 2	-3.323	-3.370	0.331	0.560	0.440	0.477	0.563	0.430	0.462
Group 3	-4.476	-4.585	0.731	1.238	0.610	0.746	1.303	0.624	0.757
Group 4	-4.13	-4.250	0.476	0.806	0.576	0.646	0.848	0.605	0.668

Estimates and standard errors are obtained using Model 1: naive, Model 2: constant dispersion, and Model 3: beta-binomial, and corresponding robust variance estimators HC0* and HC3$^{(1)*}$.

Table 3.6: Beta-binomial simulations based on Crowder's data

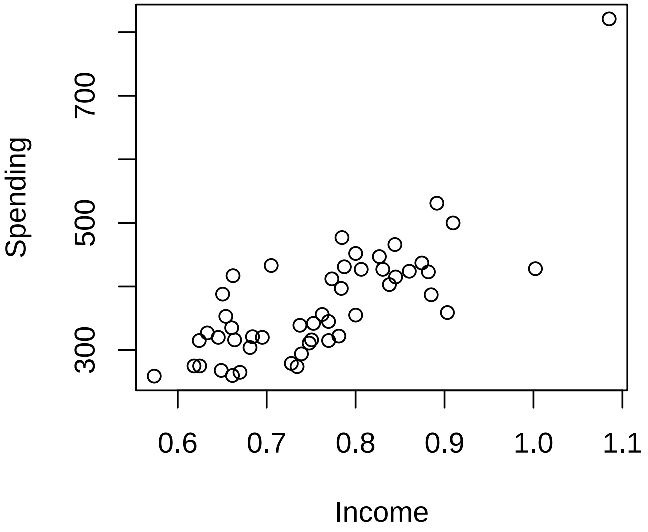
	%Coverage		
Parameter	Model	HC0*	HC3$^{(1)*}$
Intercept	90.71	84.06	90.94
Root	89.85	87.39	93.84
Seed	93.23	86.16	93.84
Root*Seed	92.30	88.02	95.73

Nominal 95% confidence intervals using the constant dispersion model, HC0* and HC3$^{(1)*}$ after 1000 simulations.

Table 3.7: Analysis of Greene's data

With Alaska, n=50		Without Alaska, n=49	
$\hat{\beta}_2 = 1587.04$		$\hat{\beta}_2 = -314.14$	
	SE		SE
OLS	716.38	OLS	872.60
HC0	829.99	HC0	626.68
HC3	1995.24	HC3	1103.03
HC3$^{(1)}$	1715.85	HC3$^{(1)}$	1008.20
HC4	5488.93	HC4	2320.83
HC4$^{(1)}$	4649.77	HC4$^{(1)}$	2065.17

Figure 3.1: Per capita income and per capita spending in public schools



Chapter 4

Variance estimation for correlated data

4.1 Introduction

The generalized estimating equations (GEE) methodology (Liang and Zeger, 1986) facilitates the analysis of correlated and longitudinal data. GEE accounts for correlation within subjects or clusters by specifying a working correlation model for observations within a subject. The robust covariance estimator for GEE provides consistent estimation of the true covariance matrix of the parameters of interest even if the working correlation model is misspecified. However, it is known that the robust covariance estimator may lead to anti-conservative inference when the number of independent subjects or clusters is small (Mancl and DeRouen, 2001; Fay and Graubard, 2001; Lipsitz et al., 1994).

Two main types of corrections have been proposed to improve the small sample properties of inferential methods based on the robust variance estimator: bias-corrections to the estimator itself and corrections to the degrees of freedom of the test statistic. Corrections to the degrees of freedom of test statistics have met limited success (Fay and Graubard, 2001; Lu et al., 2007; Braun, 2007). In this chapter we consider the bias corrected robust variance estimators of Kauermann and Carroll (2001) and Mancl and DeRouen (2001). These corrections obtain confidence intervals closer to nominal size in small samples than the uncorrected robust variance estimator.

In Chapter 3, we proposed a class of robust variance estimators for independent data that includes some currently available estimators and introduced new estimators with reduced variance and improved confidence interval coverage. In this chapter, we extend the class of variance estimators of Chapter 3 to generalized estimating equations. The new class includes the estimators of Kauermann and Carroll (2001) and Mancl and DeRouen (2001) as well as some new estimators. We follow a similar approach to Chapter 3 and show in simulations for correlated data that the newly proposed estimators have smaller variance and better coverage than current estimators. This chapter is organized as follows. In §4.2 we define the class of variance estimators in Chapter 3 in a recursive manner. In §4.3 we define a class of variance estimators for GEE based on similar recursive arguments. In §4.4 we present simulation studies; in §4.5 we show a data analysis example. §4.6 is a conclusion.

4.1.1 Notation

Some of the notation used in this chapter was introduced in Chapter 1 and Chapter 3. We require the following additional notation in this chapter: the matrix $\mathbf{B} = \{\mathbf{A}\}_{diag}$ will denote the square matrix with diagonal elements $b_{ii} = a_{ii}$ and $b_{ij} = 0$ if $i \neq j$. Let

$\mathbf{C}$ be a block matrix with block elements $\mathbf{C_{ij}}$, then blockdiag($\mathbf{C}$) will denote the block diagonal matrix with block elements $\mathbf{C_{ii}}$.

4.2 Independent Data

Consider the linear model $E\mathbf{Y} = \mathbf{X}\boldsymbol{\beta}, \text{Var}(\mathbf{Y}) = \boldsymbol{\Gamma}$ where $\mathbf{Y}$ is an $n \times 1$ vector of responses, $\mathbf{X}$ is a known $n \times p$ matrix of covariates of rank p, $\boldsymbol{\beta}$ is a $p \times 1$ vector of unknown parameters, and $\boldsymbol{\Gamma} = \text{diag}(\gamma_1, \dots, \gamma_n)$ is unknown. In Chapter 3, we proposed a class of estimators of $\text{cov}(\hat{\boldsymbol{\beta}})$ for independent data obtained by replacing $\boldsymbol{\Gamma}$ by $\hat{\boldsymbol{\Gamma}}_\delta^{(k)}$ in

$$\text{cov}(\hat{\boldsymbol{\beta}}) = (\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\boldsymbol{\Gamma}\mathbf{X}(\mathbf{X}^T\mathbf{X})^{-1}.$$

We defined $\hat{\boldsymbol{\Gamma}}_\delta^{(k)} = \text{diag}(\hat{\boldsymbol{\gamma}}_\delta^{(k)})$ in vector form as

$$\hat{\boldsymbol{\gamma}}_\delta^{(k)} = \mathbf{D}^{\delta-1}(\mathbf{D}\mathbf{P})^k\mathbf{D}\mathbf{r}^{*2} \tag{4.1}$$

where $\mathbf{D} = \text{diag}\{1/(1-h_{ii})\}$, $\mathbf{P} = (\mathbf{I}-\mathbf{H})^{*2}$, $\mathbf{r} = \mathbf{Y} - \hat{\mathbf{Y}}$, k is an integer, $\delta \geq 0$, $\mathbf{H} = \mathbf{X}(\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T$ and the operator $\mathbf{A}^{*b}$ denotes the b-th *Schur power* of $\mathbf{A}$. Estimators in this class are consistent for $\text{cov}(\hat{\boldsymbol{\beta}})$ for any fixed integer k and $\delta \geq 0$. The class in (4.1) includes White's estimator HC0 with $\hat{\boldsymbol{\Gamma}}_0^{(0)}$, HC2 with $\hat{\boldsymbol{\Gamma}}_1^{(0)}$ and HC3 with $\hat{\boldsymbol{\Gamma}}_2^{(0)}$. We also discussed the HC4 estimator of Cribari-Neto (2004) for data sets with high leverage points. The HC4 estimator does not belong to the class in (4.1), but it is closely related. We proposed new estimators HC3$^{(1)}$ and HC4$^{(1)}$ and showed that they improve upon HC3 and HC4 respectively in terms of confidence interval coverage and variance of the variance estimators in many scenarios for linear models and generalized linear models in small samples.

Variance estimators in (4.1) follow a recursive structure that allows a generalization to correlated data. The result follows from the fact that $E\mathbf{r}^{*2} = \mathbf{P}\boldsymbol{\gamma}$ and therefore $E\hat{\boldsymbol{\gamma}}_{\delta}^{(k-1)} = \mathbf{D}^{\delta-1}(\mathbf{DP})^{k-1}\mathbf{DP}\boldsymbol{\gamma}$. This allows us to write estimators in (4.1) as:

$$\hat{\boldsymbol{\gamma}}_{\delta}^{(k)} = E\hat{\gamma}_{\delta}^{(k-1)}|_{\boldsymbol{\gamma}=\hat{\boldsymbol{\gamma}}_{1}^{(0)}} = \mathbf{D}^{\delta-1}(\mathbf{DP})^{k-1}\mathbf{DP}\boldsymbol{\gamma}|_{\boldsymbol{\gamma}=\hat{\boldsymbol{\gamma}}_{1}^{(0)}} = \mathbf{D}^{\delta-1}(\mathbf{DP})^{k}\mathbf{Dr}^{*2},$$

and in matrix form as

$$\hat{\boldsymbol{\Gamma}}_{\delta}^{(k)} = \mathrm{E}(\hat{\boldsymbol{\Gamma}}_{\delta}^{(k-1)})|_{\boldsymbol{\Gamma}=\hat{\boldsymbol{\Gamma}}_{1}^{(0)}} = \mathrm{diag}(\mathbf{D}^{\delta-1}(\mathbf{DP})^{k}\mathbf{Dr}^{*2}). \tag{4.2}$$

Thus (4.2) defines $\hat{\boldsymbol{\Gamma}}_{\delta}^{(k)}$ in terms of $\hat{\boldsymbol{\Gamma}}_{\delta}^{(k-1)}$ and the HC2 variance estimator $\hat{\boldsymbol{\Gamma}}_{1}^{(0)}$, and therefore the class of estimators in (4.1) is defined recursively. In the following sections, the recursive property of $\hat{\boldsymbol{\Gamma}}_{\delta}^{(k)}$ is extended to new variance estimators for generalized estimating equations.

Finally, before discussing GEE, we write estimators $\hat{\boldsymbol{\Gamma}}_{\delta}^{(k)}$, with $k \geq 0$, in a form that is easily generalizable to correlated data:

$$\hat{\boldsymbol{\Gamma}}_{\delta}^{(k)} = \{(\mathbf{D}^{\delta-1}(\mathbf{DP})^{k}\mathbf{D})^{*1/2}\mathrm{diag}(\mathbf{r}^{*2})(\mathbf{D}^{T}(\mathbf{P}^{T}\mathbf{D}^{T})^{k}\mathbf{D}^{(\delta-1)T})^{*1/2}\}_{diag}$$

$$= \{(\mathbf{D}^{\delta-1}(\mathbf{DP})^{k}\mathbf{D})^{*1/2}\{\mathbf{rr}^{T}\}_{diag}(\mathbf{D}(\mathbf{PD})^{k}\mathbf{D}^{\delta-1})^{*1/2}\}_{diag}.$$

In particular, the case $k = 0$ simplifies to

$$\hat{\mathbf{\Gamma}}_{\delta}^{(0)} = \{\mathbf{D}^{\delta/2}\{\mathbf{r}\mathbf{r}^T\}_{diag}\mathbf{D}^{\delta/2}\}_{diag} = \{\mathbf{D}^{\delta/2}\mathbf{r}\mathbf{r}^T\mathbf{D}^{\delta/2}\}_{diag}. \tag{4.3}$$

4.3 Correlated Data

We revisit some concepts of variance estimation for correlated data discussed in §1.4.4. Consider a study with M total clusters and n_i observations in the i-th cluster. Observations in the i-th cluster are indexed by y_{ij}, $j = 1, \ldots, n_i$. The response y_{ij} is related to a $p \times 1$ vector of covariates $\boldsymbol{x}_{ij}$ through $g(\mu_{ij}) = \boldsymbol{x}_{ij}^T\boldsymbol{\beta}$ where $\mu_{ij} = \mathrm{E}(y_{ij}|\boldsymbol{x}_{ij})$. Let $\boldsymbol{\mu_i} = \{\mu_{i1}, \ldots, \mu_{in_i}\}^T$ and let the vector of all responses be written as $\mathbf{Y} = \{\mathbf{Y}_1^T, \ldots, \mathbf{Y}_M^T\}^T$. We define $\mathrm{cov}(\mathbf{Y}_i) = \mathbf{\Gamma}_i$ and the block-diagonal matrix $\mathrm{cov}(\mathbf{Y}) = \mathbf{\Gamma}$. GEE estimates of $\boldsymbol{\beta}$ are obtained by solving

$$U_{\beta,GEE1} = \sum_{i=1}^{M} \mathbf{D}_i^T\mathbf{V}_i^{-1}(\mathbf{Y}_i - \boldsymbol{\mu}_i) = 0$$

where $\mathbf{D}_i = \partial\boldsymbol{\mu}_i/\partial\boldsymbol{\beta}^T$, $\mathbf{V}_i = \mathrm{diag}(\sigma_{ijj}^{\frac{1}{2}})\mathbf{R}_i(\alpha)\mathrm{diag}(\sigma_{ijj}^{\frac{1}{2}})$, $\mathbf{R}_i$ is a working correlation matrix for $\mathrm{corr}(\mathbf{Y}_i)$ and $\sigma_{ijj} = \mathrm{Var}(Y_{ij})$. We stated that estimators of $\mathrm{cov}(\hat{\boldsymbol{\beta}})$ are obtained by replacing $\mathbf{\Gamma}_i$ by an estimator in

$$\mathrm{cov}(\hat{\boldsymbol{\beta}}) = \left(\sum_{i=1}^{M} \mathbf{D}_i^T\mathbf{V}_i^{-1}\mathbf{D}_i\right)^{-1} \left(\sum_{i=1}^{M} \mathbf{D}_i^T\mathbf{V}_i^{-1}\mathbf{\Gamma}_i\mathbf{V}_i^{-1}\mathbf{D}_i\right) \left(\sum_{i=1}^{M} \mathbf{D}_i^T\mathbf{V}_i^{-1}\mathbf{D}_i\right)^{-1}. \tag{4.4}$$

The BC0, or robust variance estimator of $\mathrm{cov}(\hat{\boldsymbol{\beta}})$, is obtained by replacing $\mathbf{\Gamma}_i$ by $(\hat{\mathbf{\Gamma}}_0^{(0)})_i := \mathbf{r}_i\mathbf{r}_i^T$ in (4.4) where $\mathbf{r}_i = (\mathbf{y}_i - \hat{\boldsymbol{\mu}}_i)$. Kauermann and Carroll (2001) and Mancl and DeRouen (2001) introduced corrections to the BC0 estimator. The BC1 estimator of Kauermann and Carroll (2001) is obtained by replacing

$$(\hat{\mathbf{\Gamma}}_1^{(0)})_i := (\mathbf{I}_{n_i} - \mathbf{H}_{ii})^{-1/2}\mathbf{r}_i\mathbf{r}_i^T(\mathbf{I}_{n_i} - \mathbf{H}_{ii})^{-T/2}$$

in (4.4). The BC2 estimator of Mancl and DeRouen (2001) is obtained by replacing

$$(\hat{\mathbf{\Gamma}}_2^{(0)})_i := (\mathbf{I}_{n_i} - \mathbf{H}_{ii})^{-1}\mathbf{r}_i\mathbf{r}_i^T(\mathbf{I}_{n_i} - \mathbf{H}_{ii})^{-T}.$$

The BC1 and BC2 estimators were proposed to improve the small sample properties of the BC0 estimator. For correlated binary data, Lu et al. (2007) generally recommend the use of BC2 over BC1 and BC0 in the construction of confidence intervals based on standard normal quantiles.

The poor performance of BC0 in terms of confidence interval coverage in small samples can be attributed to its downward bias and its large variance compared to parametric estimators. Kauermann and Carroll (2001) show that the large variance of the robust or sandwich variance estimator causes undercoverage of confidence intervals in small samples. In Chapter 3, we showed that sandwich estimators with $\hat{\mathbf{\Gamma}}_\delta^{(1)}$ defined in (4.1) improve upon HC2 and HC3 estimators in terms of variance and confidence interval coverage for independent data. In the following section, we use the results of §4.2 to extend the family of variance estimators in (4.1) to correlated data.

4.3.1 A class of variance estimators for correlated data

Let $\boldsymbol{D} = \text{blockdiag}((\mathbf{I}_i - \mathbf{H}_{ii})^{-1})$ where $\mathbf{H}_{ij} = \mathbf{D}_i\mathbf{S}^{-1}\mathbf{D}_j^T\mathbf{V}_j^{-1}$ and $\mathbf{S} = \sum_{l=1}^{M}\mathbf{D}_l\mathbf{V}_l^{-1}\mathbf{D}_l^T$. Note that $\mathbf{D}_i$ are not components of $\boldsymbol{D}$.

For any $\delta \geq 0$, we define a class of variance estimators for correlated data obtained by replacing $\boldsymbol{\Gamma}_i$ in (4.4) by

$$\hat{\boldsymbol{\Gamma}}_\delta^{(0)} := \text{blockdiag}(\boldsymbol{D}^{\frac{\delta-1}{2}}\boldsymbol{D}^{\frac{1}{2}}\text{blockdiag}(\mathbf{r}\mathbf{r}^T)\boldsymbol{D}^{\frac{1}{2}T}\boldsymbol{D}^{\frac{\delta-1}{2}T}) = \text{blockdiag}(\boldsymbol{D}^{\frac{\delta}{2}}\mathbf{r}\mathbf{r}^T\boldsymbol{D}^{\frac{\delta}{2}T}).$$

These estimators are a generalization of the independent data variance estimators $\hat{\boldsymbol{\Gamma}}_\delta^{(0)}$ defined in (4.1) and written in form (4.3). In particular, if $\delta = 0$ we obtain BC0, if $\delta = 1$ we obtain Kauermann and Carroll's estimator BC1 with

$$\hat{\boldsymbol{\Gamma}}_1^{(0)} = \text{blockdiag}(\mathbf{D}^{\frac{1}{2}}\mathbf{r}\mathbf{r}^T\mathbf{D}^{\frac{1}{2}T}).$$

If $\delta = 2$ we obtain Mancl and DeRouen's estimator BC2 with

$$\hat{\boldsymbol{\Gamma}}_2^{(0)} = \text{blockdiag}(\mathbf{D}\mathbf{r}\mathbf{r}^T\mathbf{D}^T).$$

In order to construct estimators $\hat{\boldsymbol{\Gamma}}_\delta^{(k)}$ with $k > 0$ for correlated data we propose a recursive procedure analogous to the one described in §4.2. If k is a positive integer and $\delta \geq 0$, we define:

$$\hat{\boldsymbol{\Gamma}}_\delta^{(k)} = E(\hat{\boldsymbol{\Gamma}}_\delta^{(k-1)})|_{\boldsymbol{\Gamma}=\hat{\boldsymbol{\Gamma}}_1^{(0)}}. \tag{4.5}$$

The expectation $E(\hat{\mathbf{\Gamma}}_\delta^{(k-1)})$ is evaluated using the approximation

$$E(\mathbf{r}_i\mathbf{r}_i^T) \approx (\mathbf{I}_i - \mathbf{H}_{ii})\mathbf{\Gamma}_i(\mathbf{I}_i - \mathbf{H}_{ii})^T + \sum_{j\neq i}\mathbf{H}_{ij}\mathbf{\Gamma}_j\mathbf{H}_{ij}^T \tag{4.6}$$

given by Mancl and DeRouen (2001). This approximation allows a componentwise definition of the recursive procedure in (4.5). Consider $(\hat{\mathbf{\Gamma}}_\delta^{(k)})_i$, the estimator of $\text{cov}(\mathbf{Y}_i)$ given by the i-th block-diagonal element of $\hat{\mathbf{\Gamma}}_\delta^{(k)}$. If $k=0$ and $\delta=1$, we obtain the BC1 estimator with

$$(\hat{\mathbf{\Gamma}}_1^{(0)})_i = (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{1}{2}}\mathbf{r}_i\mathbf{r}_i^T(\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{1}{2}T}.$$

We use (4.6) to obtain its approximate expectation

$$E(\hat{\mathbf{\Gamma}}_1^{(0)})_i \approx (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{1}{2}}\left((\mathbf{I}_i - \mathbf{H}_{ii})\mathbf{\Gamma}_i(\mathbf{I}_i - \mathbf{H}_{ii})^T + \sum_{j\neq i}\mathbf{H}_{ij}\mathbf{\Gamma}_j\mathbf{H}_{ij}^T\right)(\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{1}{2}T},$$

and the recursive structure in (4.5) to define

$$(\hat{\mathbf{\Gamma}}_1^{(1)})_i = E(\hat{\mathbf{\Gamma}}_1^{(0)})_i|_{\mathbf{\Gamma}_j=(\hat{\mathbf{\Gamma}}_1^{(0)})_j \quad \forall j=1,\ldots,M}$$

$$\approx (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{1}{2}}\left((\mathbf{I}_i - \mathbf{H}_{ii})(\hat{\mathbf{\Gamma}}_1^{(0)})_i(\mathbf{I}_i - \mathbf{H}_{ii})^T + \sum_{j\neq i}\mathbf{H}_{ij}(\hat{\mathbf{\Gamma}}_1^{(0)})_j\mathbf{H}_{ij}^T\right)(\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{1}{2}T}$$

$$= \mathbf{r}_i\mathbf{r}_i^T + (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{1}{2}}\left(\sum_{j\neq i}\mathbf{H}_{ij}(\mathbf{I}_j - \mathbf{H}_{jj})^{-\frac{1}{2}}\mathbf{r}_j\mathbf{r}_j^T(\mathbf{I}_j - \mathbf{H}_{jj})^{-\frac{1}{2}T}\mathbf{H}_{ij}^T\right)(\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{1}{2}T}.$$

The estimator $(\hat{\mathbf{\Gamma}}_1^{(1)})_i$ defined above is a generalization of the independent data

$$(\hat{\boldsymbol{\gamma}}_1^{(1)})_i = r_i^2 + \sum_{j\neq i}\frac{h_{ij}^2}{(1-h_{ii})(1-h_{jj})}r_j^2$$

introduced in Chapter 3.

In general, estimators $(\hat{\mathbf{\Gamma}}_\delta^{(1)})_i$ can be written as

$$\begin{aligned}(\hat{\mathbf{\Gamma}}_\delta^{(1)})_i &= (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{\delta-1}{2}}\mathbf{r}_i\mathbf{r}_i^T(\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{\delta-1}{2}T} \\ &+ (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{\delta}{2}}\left(\sum_{j\neq i}\mathbf{H}_{ij}(\mathbf{I}_j - \mathbf{H}_{jj})^{-\frac{1}{2}}\mathbf{r}_j\mathbf{r}_j^T(\mathbf{I}_j - \mathbf{H}_{jj})^{-\frac{1}{2}T}\mathbf{H}_{ij}^T\right)(\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{\delta}{2}T}.\end{aligned}$$

Variance estimators BC1 and BC2 are obtained by replacing $\mathbf{\Gamma}$ by $\hat{\mathbf{\Gamma}}_1^{(0)}$ and $\hat{\mathbf{\Gamma}}_2^{(0)}$ in (4.4). We define two new variance estimators: BC1$^{(1)}$ and BC2$^{(1)}$, obtained by replacing $\mathbf{\Gamma}$ by $\hat{\mathbf{\Gamma}}_1^{(1)}$ and $\hat{\mathbf{\Gamma}}_2^{(1)}$ in (4.4) respectively. In the following sections we compare the performance of BC1 and BC2 to that of BC1$^{(1)}$ and BC2$^{(1)}$ in simulations. We show that the newly proposed estimators perform better in many scenarios in terms of variance and coverage of confidence intervals.

The focus of this chapter is improved performance of variance estimators for correlated data in small samples. However, it can be shown that the newly proposed variance estimators BC1$^{(1)}$ and BC2$^{(1)}$ share the same large sample properties as BC1 and BC2. A proof of consistency of BC1$^{(1)}$ and BC2$^{(1)}$ is shown in the appendix.

4.3.2 Computational issues

Let $\mathbf{A}$ be a $n \times n$ positive semidefinite matrix. We use the notation $\mathbf{A}^{\frac{1}{2}}$ to denote the specific square root matrix defined via diagonalization as follows. Let $\mathbf{A} = \mathbf{V}\mathbf{D}\mathbf{V}^T$ be the eigen-decomposition of $\mathbf{A}$ where $\mathbf{V}$ is the matrix of eigenvectors of $\mathbf{A}$ and $\mathbf{D}$ is the diagonal matrix $\mathbf{D} = \mathbf{V}^T\mathbf{A}\mathbf{V}$. Then $\mathbf{A}^{\frac{1}{2}} = \mathbf{V}\mathbf{D}^{\frac{1}{2}}\mathbf{V}^T$.

It would appear that for any $\delta \geq 0$, computation of estimators in the class $\hat{\mathbf{\Gamma}}_\delta^{(1)}$

requires much more computational effort than $\hat{\mathbf{\Gamma}}_\delta^{(0)}$ since the new estimators involve cross terms $\mathbf{H}_{ij}$, $i \neq j$. However, the terms $\mathbf{H}_{ij}$ need not be calculated in estimators like $\hat{\mathbf{\Gamma}}_1^{(0)}$ and $\hat{\mathbf{\Gamma}}_2^{(0)}$. In this section we show that the expression of $\hat{\mathbf{\Gamma}}_\delta^{(1)}$ can be manipulated so that its computation does not involve terms $\mathbf{H}_{ij}$, $i \neq j$. We use the fact that $\mathbf{H}_{ij} = \mathbf{D}_i \mathbf{S}^{-1} \mathbf{D}_j^T \mathbf{V}_j^{-1}$ where $\mathbf{S} = \sum_{l=1}^M \mathbf{D}_l \mathbf{V}_l^{-1} \mathbf{D}_l^T$.

In order to simplify $\hat{\mathbf{\Gamma}}_\delta^{(1)}$, we use its componentwise form:

$$\begin{aligned}(\hat{\mathbf{\Gamma}}_\delta^{(1)})_i &= (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{\delta-1}{2}} \mathbf{r}_i \mathbf{r}_i^T (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{\delta-1}{2}T} \\ &+ (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{\delta}{2}} \left(\sum_{j \neq i} \mathbf{H}_{ij} (\mathbf{I}_j - \mathbf{H}_{jj})^{-\frac{1}{2}} \mathbf{r}_j \mathbf{r}_j^T (\mathbf{I}_j - \mathbf{H}_{jj})^{-\frac{1}{2}T} \mathbf{H}_{ij}^T \right) (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{\delta}{2}T}.\end{aligned}$$

The first term of $(\hat{\mathbf{\Gamma}}_\delta^{(1)})_i$ does not allow further simplification. The second term of the sum can be written as

$$\begin{aligned}&(\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{\delta}{2}} \left(\sum_{j \neq i} \mathbf{D}_i \mathbf{S}^{-1} \mathbf{D}_j^T \mathbf{V}_j^{-1} (\mathbf{I}_j - \mathbf{H}_{jj})^{-\frac{1}{2}} \mathbf{r}_j \mathbf{r}_j^T (\mathbf{I}_j - \mathbf{H}_{jj})^{-\frac{1}{2}T} \mathbf{V}_j^{-1} \mathbf{D}_j \mathbf{S}^{-1} \mathbf{D}_i^T \right) \times \\ &(\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{\delta}{2}T} \\ = \; &(\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{\delta}{2}} \mathbf{D}_i \mathbf{S}^{-1} \left(\sum_{j \neq i} \mathbf{D}_j^T \mathbf{V}_j^{-1} (\mathbf{I}_j - \mathbf{H}_{jj})^{-\frac{1}{2}} \mathbf{r}_j \mathbf{r}_j^T (\mathbf{I}_j - \mathbf{H}_{jj})^{-\frac{1}{2}T} \mathbf{V}_j^{-1} \mathbf{D}_j \right) \times \\ &\mathbf{S}^{-1} \mathbf{D}_i^T (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{\delta}{2}T}. \qquad (4.7)\end{aligned}$$

Now let $\mathbf{U} := \left(\sum_{l=1}^M \mathbf{D}_l^T \mathbf{V}_l^{-1} (\mathbf{I}_l - \mathbf{H}_{ll})^{-\frac{1}{2}} \mathbf{r}_l \mathbf{r}_l^T (\mathbf{I}_l - \mathbf{H}_{ll})^{-\frac{1}{2}T} \mathbf{V}_l^{-1} \mathbf{D}_l \right)$. It follows that (4.7) can be written as

$$\begin{aligned}&(\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{\delta}{2}} \mathbf{D}_i \mathbf{S}^{-1} \left(\mathbf{U} - \mathbf{D}_i^T \mathbf{V}_i^{-1} (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{1}{2}} \mathbf{r}_i \mathbf{r}_i^T (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{1}{2}T} \mathbf{V}_i^{-1} \mathbf{D}_i \right) \times \\ &\mathbf{S}^{-1} \mathbf{D}_i^T (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{\delta}{2}T},\end{aligned}$$

and therefore we can write

$$
\begin{aligned}
(\hat{\mathbf{\Gamma}}_{\delta}^{(1)})_i &= (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{\delta-1}{2}} \mathbf{r}_i \mathbf{r}_i^T (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{\delta-1}{2}T} \\
&+ (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{\delta}{2}} \mathbf{D}_i \mathbf{S}^{-1} \left(\mathbf{U} - \mathbf{D}_i^T \mathbf{V}_i^{-1} (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{1}{2}} \mathbf{r}_i \mathbf{r}_i^T (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{1}{2}T} \mathbf{V}_i^{-1} \mathbf{D}_i \right) \times \\
& \mathbf{S}^{-1} \mathbf{D}_i^T (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{\delta}{2}T}.
\end{aligned}
$$

This last form of $(\hat{\mathbf{\Gamma}}_{\delta}^{(1)})_i$ is computationally simpler since it does not involve any cross terms $\mathbf{H}_{ij}$, $i \neq j$.

4.4 Simulations

We compare the performance of sandwich estimators of $\mathrm{Var}(\mathbf{z}^T \hat{\boldsymbol{\beta}})$ of the form $\mathbf{z}^T \widehat{(\mathrm{cov}\hat{\beta})} \mathbf{z}$ in simulations for correlated data.

The first example concerns multivariate normal data with possibly misspecified working correlation structure. The second example deals with correlated binary data. For each set of simulations we compare the newly proposed BC1$^{(1)}$ and BC2$^{(1)}$ with the estimators BC1 of Kauermann and Carroll (2001), BC2 of Mancl and DeRouen (2001), the uncorrected estimator BC0 and the naive or model-based variance estimator in terms of interval coverage and variance.

Simulation 1. Multivariate normal data. We simulate $\mathbf{y}_i$ from a multivariate normal distribution with element-wise expected value $Ey_{ij} = \beta_0 + x_{1i}\beta_1 + x_{2ij}\beta_2$ with $\beta_0 = 0$, $\beta_1 = 1$ and $\beta_2 = 1$ where x_1 is a cluster level covariate generated from a standard normal distribution and x_2 varies within-cluster and is generated as (a) exponential with mean

1, (b) standard Laplace, (c) standard normal. We consider simulations with $M = 10$ and $M = 20$ independent clusters and common cluster size $n_i = 4$. The cluster-level correlation matrix is either exchangeable (XCH) with $\sigma^2 = 1$ and $\rho = 0.2$ or has an independence structure (I) with $\sigma^2 = 1$. The working correlation matrix is independent (I), exchangeable with ρ estimated from the data (XCH), or exchangeable with $\rho = 0.2$ fixed (True). Confidence intervals were constructed using quantiles of a t-distribution with $\sum n_i - 3$ degrees of freedom. Simulation results are based on 2000 replicates. Table 4.1 shows nominal 95% confidence intervals for β_1 using the naive or model-based variance estimator, the uncorrected BC0, BC1 of Kauermann and Carroll (2001), BC2 of Mancl and DeRouen (2001), BC1$^{(1)}$ and BC2$^{(1)}$. Table 4.2 shows corresponding 95% confidence intervals for β_2.

Table 4.1 and Table 4.2 show that the naive or model based variance estimator provided adequate coverage for both β_1 and β_2 only when both the true correlation and the working correlation had an independence structure, or both the true correlation and the working correlation structures were exchangeable and ρ was fixed at its true value. The scenarios with true independence or exchangeable structure and exchangeable working correlation structure have a correctly specified correlation structure. These scenarios show that in small samples, underestimation of association parameters can affect the coverage of confidence intervals of mean parameters obtained by the model based variance estimator even when the model is correct. Lu et al. (2007) suggest a bias correction for estimated association parameters that improves the confidence coverage of mean parameters based on the model, BC0 and BC1 variance estimators, and may result in slight overcoverage of the BC2 estimator. Our simulation results show coverage based on uncorrected mean and association parameter estimates.

The uncorrected robust variance estimator BC0, the BC1 estimator and BC1$^{(1)}$ produced varying levels of undercoverage of confidence intervals in every scenario, often falling bellow 90%. The BC2 estimator improved upon BC0 and BC1 in terms of coverage but still slightly undercovered the parameters of interest, with coverage close to 93% and 94% in most scenarios. The newly proposed BC2$^{(1)}$ obtained coverage closer to nominal than any other estimator considered. The newly proposed BC2$^{(1)}$ and BC1$^{(1)}$ led to equal or higher coverage than BC2 and BC1 respectively in every situation, while maintaining comparable average interval width: the difference in average interval width between BC2$^{(1)}$ and BC2 was less than 1% in most scenarios with a maximum difference of 4%. Differences in width are not shown in tables. The main difference between the new estimators and BC2 and BC1 was the smaller observed variance of the new estimators.

We repeated these simulations using autoregressive(1) (AR1) and moving average(1) (MA1) true correlation structures and AR1, MA1, exchangeable and independence working correlation structures. The results were comparable to the ones presented in Table 4.1 and Table 4.2 in terms of coverage, width and variance of the estimators. These results suggest that BC2 and BC2$^{(1)}$ may protect against misspecification of the working correlation structure in scenarios with a small number of clusters. Overall, the new BC2$^{(1)}$ performed better than BC2 in terms of coverage and variance, and was comparable in terms of average width. We also repeated these simulations with $M = 50$ independent clusters. Results were qualitatively similar to the case $M = 20$, but the difference in coverage and variance between estimators was smaller. The BC2$^{(1)}$ still obtained coverage closer to nominal overall and smaller variance than BC2.

Simulation 2. Correlated binary data. We conducted a simulation study to evaluate the performance of the newly proposed BC1$^{(1)}$ and BC2$^{(1)}$ with the estimators BC1 of Kauermann and Carroll (2001) and BC2 of Mancl and DeRouen (2001) in a setting with variable cluster sizes. Let us define $\mu_{ijk} = \text{pr}(Y_{ij} = Y_{ik} = 1)$. The association between Y_{ij} and Y_{ik} is represented by the odds ratio

$$\psi_{ijk} = \frac{\mu_{ijk}(1 - \mu_{ij} - \mu_{ik} + \mu_{ijk})}{(\mu_{ij} - \mu_{ijk})(\mu_{ik} - \mu_{ijk})}.$$

We generated correlated binary data from the models

$$\text{logit}(\mu_{ij}) = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2ij}$$

and

$$\log(\psi_{ijk}) = \alpha_0 + \alpha_1 |x_{1i}| + \alpha_2 |x_{2ij} - x_{2ik}|$$

using the conditional linear family of Qaqish (2003). The covariate x_1 is a cluster level covariate generated from the standard normal distribution and x_2 varies within-cluster and is generated as (a) exponential with mean 1, (b) standard Laplace, (c) standard normal.

Estimation was done using GEE1 for $\boldsymbol{\beta}$ with independence working correlation structure $\mathbf{R}_i(\boldsymbol{\alpha}) = \mathbf{I}$. The residuals $\mathbf{r}_i$ obtained from these estimating equations were used to construct variance estimators of β_1 and β_2 of the form $\mathbf{a}^T \text{BC}_\delta^{(k)} \mathbf{a}$ with $\mathbf{a}^T = \{0, 1, 0\}$ and $\{0, 0, 1\}$ respectively.

We fixed $\boldsymbol{\beta} = \{-1, 0.4, 0.1\}^T$ and $\boldsymbol{\alpha} = \{0.1, 0.3, -0.2\}^T$. This setup results in ψ_{ijk} between 0.4 and 2.7 for most realizations of x_{1i}, x_{2ij} and x_{2ik}. Number of clusters was evaluated at $M = 10, 20$ or 25. Cluster sizes were set to either common size $n_i = 4$ or a 50/50 mixture of clusters sizes 4 and 14. Corresponding 95% nominal confidence intervals were constructed using a t-distribution with $\sum n_i - 3$ degrees of freedom. Simulation results are based on 1000 replicates and are summarized in Table 4.3.

Our conclusions are as follows. Simulations results show that confidence intervals based on the naive variance estimator BC0, BC1 and BC1$^{(1)}$ may undercover the parameters of interest. This behavior is clearest in confidence intervals for β_1 where the number of clusters was 10 or 20 and cluster sizes were a 50/50 mixture of clusters sizes 4 and 14. The BC2 estimator of Mancl and DeRouen and the new BC2$^{(1)}$ provided coverage closer to nominal in most scenarios. Confidence intervals obtained using the new estimators BC1$^{(1)}$ and BC2$^{(1)}$ had approximately the same average width as BC1 and BC2 respectively in every scenario: the maximum difference in average width between BC2$^{(1)}$ and BC2 was less than 1.5%. The difference in widths between estimators is not shown in tables. The new estimators showed smaller variance in every scenario and consistently higher coverage overall. In these simulations, it appears that BC2$^{(1)}$ outperforms all other estimators considered in terms of coverage and also outperforms BC2 in terms of variance while maintaining comparable average width.

4.5 Example

We analyze data from a clinical trial of 59 epileptic patients carried out by Leppik et al. (1985). The data appear in Thall and Vail (1990). An 8-week baseline seizure rate was recorded for each patient in the trial. Patients were randomized to either the antiepileptic drug progabide or a placebo and the number of seizures in two weeks periods of time was recorded at four successive clinic visits.

We fit a model for clustered Poisson data with GEE to analyze the number of seizures at the four visits after randomization. We use the same covariates as Thall and Vail (1990): baseline seizure rate, calculated as the logarithm of $\frac{1}{4}$ times the baseline seizure rate, logarithm of age in years, indicators Trt for the progabide group and Visit_4 for the fourth clinic visit. Table 4.4 shows mean parameter estimates and standard errors assuming (1) an exchangeable correlation structure and (2) an independence correlation structure. Standard errors are calculated using the model-based variance estimator (MB), the model-based variance estimator corrected for overdispersion using the deviance of the model (MB*), the robust variance estimator BC0, the BC1 estimator of Kauermann and Carroll (2001), the BC2 estimator of Mancl and DeRouen (2001) and the newly introduced BC1$^{(1)}$ and BC2$^{(1)}$. Thall and Vail (1990) fit models with several variance-covariance structures to these data; we present parameter estimates and standard errors for their model "11" using the robust variance estimator BC0. If we let Y_{it} be the number of seizures for patient i at time t then model "11" assumes $\text{Var}(Y_{it}) = \alpha_t EY_{it}$ and $\text{cov}(Y_{it}, Y_{iu}) = 0$.

Table 4.4 shows that parameter estimates and standard errors calculated with the robust variance estimator BC0 were similar for the exchangeable correlation model and the independence model. In this example, the corrected variance estimators BC1, BC1$^{(1)}$, BC2 and BC2$^{(1)}$ led to larger standard errors than BC0 under both the exchangeable and independence correlation models and the standard errors reported by Thall and Vail (1990) under model 11. This result suggests that BC0 standard errors might be too small for these data. In particular, standard errors for the covariates Trt and Base.Trt increased significantly when estimated under BC1, BC1$^{(1)}$, BC2 or BC2$^{(1)}$. Inference on the effect of progabide on seizures and its interaction with the baseline seizure rate may be anti-conservative if based on BC0 standard errors; use of corrected variance estimators seems warranted. Table 4.4 shows large discrepancies between the standard errors for Trt and Base.Trt estimated under BC1 and BC1$^{(1)}$ and under BC2 and BC2$^{(2)}$ respectively. Based on our simulation results on variance and coverage, we suspect that BC1 and BC2 might overinflate the standard errors of Trt and Base.Trt and that BC1$^{(1)}$ and BC2$^{(2)}$ may be more reliable. The reverse situation occurs with the effect of the covariate Baseline: the new estimators BC1$^{(1)}$ and BC2$^{(1)}$ suggest larger standard errors than BC1 and BC2. Standard errors calculated under BC0, BC1, BC1$^{(1)}$, BC2 and BC2$^{(1)}$ are not necessarily different even in small or medium samples: the standard errors for covariate Visit$_4$ were almost unchanged by the choice of variance estimator. The difference in standard errors across sandwich variance estimators would be expected to decrease with larger sample sizes. Based on the results of Lu et al. (2007) and the results in this chapter, we believe BC2$^{(1)}$ standard errors are most appropriate for analysis of these data.

The progabide data show strong evidence of heteroscedasticity and extra-Poisson variation. The sandwich estimators BC0, BC1, BC2, BC1$^{(1)}$ and BC2$^{(1)}$ are robust to misspecification of the variance model and offer some protection against heteroscedasticity and over-dispersion. However, these data also include at least one highly influential subject, identified by id 207 in Thall and Vail (1990). Deletion of this subject changes parameter estimates and standard errors. The goal of this example is to show differences between the various sandwich variance estimators in real data. A more detailed discussion of the progabide data and influential subjects can be found in Thall and Vail (1990).

4.6 Discussion

We introduced a new class of variance estimators for generalized estimating equations, and focused on two estimators not previously mentioned in the literature, $\text{BC1}^{(1)}$ and $\text{BC2}^{(1)}$. We showed in simulations that $\text{BC1}^{(1)}$ and $\text{BC2}^{(1)}$ are comparable in terms of average width to BC1 and BC2 respectively, but that $\text{BC1}^{(1)}$ and $\text{BC2}^{(1)}$ show smaller variance in most scenarios with a small number of clusters. The smaller variance of $\text{BC1}^{(1)}$ and $\text{BC2}^{(1)}$ translates into higher confidence interval coverage than BC1 and BC2 respectively. These results are consistent with the theory developed by Kauermann and Carroll (2001) on the variance of sandwich estimators and with similar results for variance estimators for independent data in Chapter 3. They show that increased variance of sandwich variance estimators often translates into loss of coverage.

In our simulations for correlated normal data, $\text{BC2}^{(1)}$ obtained higher coverage than BC2 in every scenario due to $\text{BC2}^{(1)}$'s smaller simulation variance and comparable average width. In every scenario, $\text{BC2}^{(1)}$ showed larger simulation variance and larger average interval width than $\text{BC1}^{(1)}$ and BC0 respectively. The difference in confidence interval coverage between BC2$^{(1)}$ and BC1$^{(1)}$ can therefore be attributed to the larger width of intervals obtained by BC2$^{(1)}$. Lu et al. (2007) note that intervals based on the BC2 estimator may be too conservative in small samples for clustered binary data. In our simulation study for correlated normal data, intervals constructed using a t distribution and $M - p$ degrees of freedom, instead of our choice of $\sum_i^M n_i - p$, produce slight subnominal coverage with BC1$^{(1)}$ and slight overcoverage with BC2$^{(1)}$. The use of $M - p$ degrees of freedom is common in the literature. Our work suggests that BC2$^{(1)}$ is preferable to BC2, and BC1$^{(1)}$ to BC1 in most situations. We believe that BC2$^{(1)}$ is preferable to BC1$^{(1)}$ in our simulation scenarios with intervals based on a t distribution with $\sum_i^M n_i - p$ degrees of freedom. More work is necessary to discriminate between BC2$^{(1)}$ and BC1$^{(1)}$ in more general settings. The distribution of test statistics and the choice of degrees of freedom for different corrections of the sandwich estimator are topics of interest in the literature, see for example Fay and Graubard (2001) and Pan and Wall (2002).

We observed in our simulations for correlated normal data that it is possible for a confidence interval based on BC0 to be wider than an interval based on BC1, and an interval based on BC1 to be wider than one based on BC2. This occurred in fewer than 0.5% of the simulated data sets with $M = 10$ clusters, and even less frequently in simulations with $M = 20$. The widths of intervals in every simulated data set were ordered as follows: BC2$^{(1)}$ $>$ BC1$^{(1)}$ $>$ BC0.

Our work shows that use of the standard robust variance estimator BC0 results in anti-conservative standard errors in studies with a small number of independent clusters. Even though this result is well known in the literature, the use of BC0 in studies with small sample size is still common in many fields. We recommend the use of corrected variance estimators for the analysis of clustered data with small or moderate number of clusters; in particular, the BC2$^{(1)}$ estimator obtains adequate coverage in the scenarios considered in this chapter. Further comparison of BC1$^{(1)}$ and BC2$^{(1)}$ might justify their use in other settings.

Table 4.1: Multivariate normal data with common cluster size $n_i = 4$. Variance estimation of cluster-level parameter.

M = 10

Correlation		Dist.		%Coverage							
True	Work	X_2	$\hat{\rho}$	Naive	BC0	BC1	BC1$^{(1)}$	BC2	BC2$^{(1)}$	C8	C9
I	I	expo	0	95.7	82.7	89.2	91.3	93.8	95.5	0.76	0.62
I	I	laplace	0	95.9	82.0	87.9	90.3	93.1	95.4	0.89	0.73
I	I	normal	0	94.3	81.6	88.2	90.2	93.5	95.7	0.81	0.52
I	XCH	expo	-0.048	90.7	83.3	90.2	91.2	94.2	95.7	0.72	0.39
I	XCH	laplace	-0.050	89.7	81.6	87.1	89.3	92.5	95.0	0.79	0.66
I	XCH	normal	-0.050	90.7	82.7	88.6	90.7	93.8	95.7	0.84	0.80
XCH	I	expo	0	87.9	82.5	88.4	90.0	92.7	94.7	0.76	0.65
XCH	I	laplace	0	87.6	81.6	88.0	89.7	93.1	95.0	0.76	0.64
XCH	I	normal	0	86.5	80.9	87.9	89.8	92.9	95.2	0.76	0.67
XCH	XCH	expo	0.112	90.0	82.4	88.6	91.0	93.2	95.4	0.75	0.62
XCH	XCH	laplace	0.114	90.0	81.5	88.4	90.0	93.2	95.7	0.82	0.82
XCH	XCH	normal	0.110	89.6	82.5	88.2	89.4	92.9	95.0	0.93	0.91
XCH	True	expo	0.2	97.3	84.9	90.3	92.8	94.8	97.4	0.71	0.46
XCH	True	laplace	0.2	97.7	88.1	92.8	94.5	95.6	97.5	0.79	0.60
XCH	True	normal	0.2	97.4	87.8	92.1	94.1	95.5	96.8	0.84	0.78

M = 20

Correlation		Dist.		%Coverage							
True	Work	X_2	$\hat{\rho}$	Naive	BC0	BC1	BC1$^{(1)}$	BC2	BC2$^{(1)}$	C8	C9
I	I	expo	0	95.0	89.0	91.5	92.4	94.3	94.8	0.85	0.81
I	I	laplace	0	95.6	89.5	91.7	92.7	93.9	94.7	0.86	0.80
I	I	normal	0	95.5	87.9	91.3	92.3	93.7	95.0	0.84	0.79
I	XCH	expo	-0.025	93.1	89.7	92.4	93.2	94.5	95.5	0.87	0.79
I	XCH	laplace	-0.021	92.9	89.1	91.7	92.1	93.8	94.1	0.83	0.76
I	XCH	normal	-0.026	92.9	89.1	91.4	92.0	94.1	94.8	0.84	0.79
XCH	I	expo	0	88.4	88.8	91.3	91.9	93.6	94.0	0.85	0.80
XCH	I	laplace	0	89.1	88.7	91.4	92.5	94.0	94.7	0.86	0.83
XCH	I	normal	0	87.3	88.7	91.8	92.5	94.3	95.0	0.84	0.80
XCH	XCH	expo	0.156	92.5	88.0	91.1	91.8	93.2	94.2	0.82	0.71
XCH	XCH	laplace	0.154	92.7	89.3	92.2	92.6	94.7	95.2	0.84	0.77
XCH	XCH	normal	0.154	92.1	88.4	91.2	92.1	93.4	94.1	0.82	0.70
XCH	True	expo	0.2	95.6	90.2	92.4	93.4	94.5	95.2	0.82	0.72
XCH	True	laplace	0.2	95.4	91.2	93.5	94.1	95.1	95.9	0.88	0.85
XCH	True	normal	0.2	95.5	90.8	93.1	93.8	95.0	95.7	0.85	0.79

* C8 = Var(BC1$^{(1)}$)/Var(BC1), C9 = Var(BC2$^{(1)}$)/Var(BC2)

Nominal 95% confidence intervals of β_1 after 2000 simulations using the naive variance estimator, BC0, BC1, BC1$^{(1)}$, BC2 and BC2$^{(1)}$.

Table 4.2: Multivariate normal data with common cluster size $n_i = 4$. Variance estimation of subject-level parameter

M = 10

Correlation		Dist.		%Coverage							
True	Work	X_2	$\hat{\rho}$	Naive	BC0	BC1	BC1$^{(1)}$	BC2	BC2$^{(1)}$	C8	C9
I	I	expo	0	95.4	86.6	90.2	91.2	93.2	94.9	0.86	0.72
I	I	laplace	0	95.6	82.6	88.6	91.2	93.1	96.2	0.82	0.61
I	I	normal	0	94.6	88.7	91.6	92.1	93.5	94.2	0.87	0.84
I	XCH	expo	-0.048	93.1	85.0	89.1	90.3	92.6	94.7	0.83	0.63
I	XCH	laplace	-0.052	93.5	80.2	86.0	88.6	91.0	94.7	0.80	0.48
I	XCH	normal	-0.049	93.3	86.6	89.6	90.0	92.2	93.1	0.86	0.81
XCH	I	expo	0	95.2	87.0	90.6	92.2	94.1	95.6	0.85	0.76
XCH	I	laplace	0	94.6	82.5	88.9	90.7	93.4	95.8	0.86	0.64
XCH	I	normal	0	94.9	88.8	91.1	91.8	93.7	94.8	0.84	0.78
XCH	XCH	expo	0.112	93.2	85.0	88.6	89.7	91.7	93.5	0.83	0.65
XCH	XCH	laplace	0.113	94.2	80.7	88.0	90.1	92.7	95.1	0.79	0.61
XCH	XCH	normal	0.110	95.2	88.3	90.8	91.4	93.3	94.1	0.89	0.85
XCH	True	expo	0.2	97.8	90.4	93.1	94.2	95.8	96.7	0.84	0.61
XCH	True	laplace	0.2	97.5	86.4	91.0	93.1	94.9	96.7	0.83	0.52
XCH	True	normal	0.2	97.0	92.9	94.3	94.7	95.8	96.2	0.88	0.84

M = 20

Correlation		Dist.		%Coverage							
True	Work	X_2	$\hat{\rho}$	Naive	BC0	BC1	BC1$^{(1)}$	BC2	BC2$^{(1)}$	C8	C9
I	I	expo	0	95.2	90.2	92.0	92.9	93.8	94.6	0.86	0.74
I	I	laplace	0	95.6	86.8	90.7	92.6	93.9	95.8	0.82	0.65
I	I	normal	0	95.4	92.2	93.4	93.6	94.5	94.7	0.93	0.92
I	XCH	expo	-0.023	93.7	88.8	90.7	91.3	92.4	92.8	0.82	0.71
I	XCH	laplace	-0.021	94.0	84.6	88.5	90.6	92.3	94.6	0.83	0.66
I	XCH	normal	-0.027	94.5	91.8	93.4	93.5	94.3	94.3	0.92	0.91
XCH	I	expo	0	95.3	90.5	92.1	92.8	94.0	95.0	0.84	0.78
XCH	I	laplace	0	95.4	87.2	90.7	92.2	93.6	95.0	0.85	0.67
XCH	I	normal	0	95.1	92.1	93.4	93.8	94.9	95.2	0.91	0.90
XCH	XCH	expo	0.152	94.4	89.2	91.4	91.9	93.0	93.5	0.85	0.75
XCH	XCH	laplace	0.156	95.0	86.6	89.4	91.7	92.6	95.2	0.80	0.55
XCH	XCH	normal	0.149	93.9	90.9	91.7	91.8	92.7	92.9	0.94	0.92
XCH	True	expo	0.2	96.8	93.5	94.8	95.2	96.0	96.5	0.88	0.78
XCH	True	laplace	0.2	95.6	88.0	90.9	92.9	93.5	95.3	0.77	0.57
XCH	True	normal	0.2	95.6	93.5	94.3	94.5	95.2	95.4	0.94	0.93

* C8 = Var(BC1$^{(1)}$)/Var(BC1), C9 = Var(BC2$^{(1)}$)/Var(BC2)

Nominal 95% confidence intervals of β_2 after 2000 simulations using the naive variance estimator, BC0, BC1, BC1$^{(1)}$, BC2 and BC2$^{(1)}$.

Table 4.3: Variance estimation for correlated binary data

95% nominal confidence intervals for cluster-level parameter β_1

		Dist.	%Coverage					$\frac{\text{Var(BC1}^{(1)})}{\text{Var(BC1)}}$	$\frac{\text{Var(BC2}^{(1)})}{\text{Var(BC2)}}$
M	n_i	X_2	Naive	BC1	BC1$^{(1)}$	BC2	BC2$^{(1)}$		
10	4/14	expo	87.3	86.5	87.4	92.7	94.7	77.0	64.4
	4/14	laplace	89.1	88.7	90.2	93.0	95.5	75.2	58.6
	4/14	normal	89.0	87.0	89.1	92.8	94.8	71.3	41.3
20	4/14	expo	85.8	89.4	89.5	92.5	92.9	73.9	63.1
	4/14	laplace	89.8	92.3	92.6	94.8	95.7	73.2	66.6
	4/14	normal	88.3	89.5	89.6	92.4	93.1	77.1	71.3
25	4	expo	92.6	93.0	93.3	94.9	95.7	80.2	71.3
	4	laplace	93.4	92.4	92.9	94.1	94.8	84.6	79.0
	4	normal	94.8	94.1	94.4	95.1	95.4	83.7	79.1

95% nominal confidence intervals for subject-level parameter β_2

		Dist.	%Coverage					$\frac{\text{Var(BC1}^{(1)})}{\text{Var(BC1)}}$	$\frac{\text{Var(BC2}^{(1)})}{\text{Var(BC2)}}$
M	n_i	X_2	Naive	BC1	BC1$^{(1)}$	BC2	BC2$^{(1)}$		
10	4/14	expo	94.4	92.6	92.8	94.2	94.9	87.6	79.0
	4/14	laplace	92.3	91.4	91.7	93.8	93.8	87.0	82.0
	4/14	normal	93.9	92.4	92.8	95.2	95.4	86.9	80.1
20	4/14	expo	93.1	93.2	93.6	94.5	94.8	91.4	88.2
	4/14	laplace	92.6	93.7	93.7	94.1	94.3	93.9	92.6
	4/14	normal	93.1	94.4	94.6	95.7	96.0	91.5	87.1
25	4	expo	96.0	95.4	95.5	96.3	96.5	90.7	83.9
	4	laplace	94.9	95.1	95.0	95.7	96.0	94.1	93.0
	4	normal	95.7	94.8	94.9	95.7	95.9	91.9	86.3

Coverage and ratio of simulation variances refer to nominal 95% confidence intervals after 1000 simulations.

Table 4.4: Analysis of progabide data

Correlation model: Thall and Vail (1990) model 11

		SE
Variable	Estimate	BC0
Int	-2.695	0.902
Base	0.933	0.087
Trt	-1.439	0.418
Base.Trt	0.595	0.171
Age	0.895	0.264
Visit$_4$	-0.168	0.065

Correlation model: exchangeable

		SE						
Variable	Estimate	MB	MB*	BC0	BC1	BC1$^{(1)}$	BC2	BC2$^{(1)}$
Int	-2.770	0.584	1.138	0.956	1.034	1.072	1.181	1.178
Base	0.950	0.063	0.122	0.099	0.103	0.116	0.108	0.127
Trt	-1.332	0.225	0.438	0.432	0.581	0.490	0.956	0.706
Base.Trt	0.559	0.091	0.177	0.177	0.262	0.210	0.463	0.331
Age	0.900	0.167	0.325	0.277	0.301	0.310	0.346	0.342
Visit$_4$	-0.157	0.044	0.085	0.066	0.067	0.067	0.068	0.068

Correlation model: independence

		SE						
Variable	Estimate	MB	MB*	BC0	BC1	BC1$^{(1)}$	BC2	BC2$^{(1)}$
Int	-2.732	0.407	0.793	0.944	1.022	1.060	1.168	1.165
Base	0.949	0.044	0.085	0.096	0.101	0.114	0.106	0.125
Trt	-1.333	0.157	0.305	0.429	0.578	0.486	0.955	0.703
Base.Trt	0.558	0.063	0.124	0.176	0.262	0.209	0.462	0.330
Age	0.890	0.116	0.227	0.275	0.299	0.308	0.343	0.339
Visit$_4$	-0.157	0.054	0.106	0.066	0.067	0.067	0.068	0.068

Standard errors are calculated using the model-based variance estimator (MB), the model-based variance estimator corrected for overdispersion (MB*) and estimators BC0, BC1, BC1$^{(1)}$, BC2 and BC2$^{(2)}$.

Chapter 5

Summary and future research

5.1 Summary of accomplishments

5.1.1 Chapter 2: Random cluster size, within-cluster resampling and generalized estimating equations

In Chapter 2 we discussed WCR for estimation of marginal parameters in correlated binary data and WCPR for estimation of conditional parameters. We showed that both WCR and WCPR can be thought of as specially weighted versions of generalized estimating equations. We elaborated on the differences between WCR and unweighted GEE in several models. We showed that the validity of WCR and unweighted GEE is not dependent on cluster size ignorability, as had been previously claimed in the literature, but rather that WCR and unweighted GEE estimate different parameters. The validity of WCR and unweighted GEE depend on the model and the parameters of interest of the study. We showed that the parameters estimated under WCPR have some undesirable properties, such as being affected by the distribution of cluster sizes in the sample and the exposure prevalence in the population. We proposed an alternative estimating procedure based on generalized estimating equations with unit weights that avoids some of the problems of WCPR, while having a similar interpretation.

5.1.2 Chapter 3: Variance estimation in regression models

We considered the problem of linear regression with heteroscedastic errors. The OLS variance estimator is biased in this setting and the use of heteroscedasticity consistent variance estimators is necessary. We reviewed robust variance estimators such as the MINQUE, White's HC0 (1980), HC1-HC3, and the HC4 estimator of Cribari-Neto (1994). We proposed a new class of variance estimators that includes the MINQUE, HC0, HC2, HC3 and the OLS as a limiting case. We showed that new robust variance estimators in this class have smaller variance under homoscedasticity and many scenarios of heteroscedasticity than HC0, HC2 and HC3. The new estimators show higher confidence interval coverage in simulations in small samples while while maintaining average interval width comparable to that of previously available estimators. We also proposed a corrected version of the HC4 estimator with improved properties and extended the new class of variance estimators to generalized linear models. In every case the newly proposed variance estimators had smaller variance in simulations and improved confidence interval coverage.

5.1.3 Chapter 4: Variance estimation for correlated data

We considered the problem of variance estimation for generalized estimating equations and correlated data. The robust variance estimator BC0 of Liang and Zeger (1986) is too liberal in studies with a small number of clusters. Corrected robust variance estimators such as the BC1 and BC2 estimators of Mancl and DeRouen (2001) and Kauermann and Carroll (2001) have been proposed to improve coverage in small samples. We generalized the family of variance estimators introduced in Chapter 3 to GEE and correlated data. We showed that the new family of variance estimators includes BC1 and BC2 as well as new estimators. We showed that two new estimators in this family outperform BC1 and BC2 in terms of confidence interval coverage and variance in simulations with correlated binary data and multivariate normal data and showed an application to the progabide data discussed by Thall and Vail (1990).

5.2 Future research

5.2.1 Robust variance estimation in other settings

Cox proportional-hazards model

The Cox proportional-hazards regression model (Cox, 1972) is widely used in survival analysis. It is a popular tool to relate covariates with the distribution of survival times. The proportional hazards assumption states a multiplicative relationship between the hazard function and the log-linear function of the covariates. If the assumption of proportional hazards holds, then the covariance matrix of the mean parameters can be consistently estimated by the model-based variance estimator. Therneau (1999) identified three kinds of diagnostics for Cox regression: violation of the assumption of proportional-hazards, effect of influential data points, and nonlinearity in the model. Lin and Wei

(1989) proposed a variance estimator for the Cox proportional-hazards model that is robust against misspecification of the proportional-hazards assumption. The robust variance estimator of Lin and Wei (1989) shares the sandwich structure of the robust variance estimator of Liang and Zeger (1986). In both types of variance estimators each subject's score function is added individually to obtain a sandwich-type variance estimator. We believe it may be possible to extend the class of variance estimators in Chapter 3 and Chapter 4 to Cox proportional-hazard models. The variance estimators derived in this dissertation assign weights to each subject's residual in a different way than the usual robust variance estimator. We have shown that this strategy leads to reduced variance and improved interval coverage in small samples in linear regression, generalized linear models and GEE. We believe that a similar approach may improve the small sample properties of sandwich estimators in proportional-hazard models when the assumption of proportional-hazards is violated.

Finite population sampling

Robust variance estimation has been developed for linear regression in finite population sampling by Royal and Cumberland (1978). Given a random sample from a finite population, Royal and Cumberland (1978) developed a variance estimator that is asymptotically equivalent to the jackknife and is robust to misspecification of the sample's variance model. Their variance estimator has a sandwich structure similar to that of the HC0 estimator. We believe that the variance estimators proposed in Chapter 3 may be extended to finite population sampling.

Association parameters

This dissertation has focused on variance estimation for mean parameters in various models. Sometimes interest lies in estimation of association parameters, such as intra-cluster correlations in clustered binary data. Preisser, Lu and Qaqish (in preparation) compared the BC0, BC1 and BC2 estimators for confidence interval coverage of intra-cluster correlations in simulations. A natural extension of our work is to evaluate the performance of new variance estimators for inference of association parameters for correlated binary data.

5.2.2 Other topics

Degrees of freedom corrections

We mentioned in Chapter 4 that two main types of corrections aim to improve the performance of robust variance estimators in small samples in correlated data in the literature: corrections to the robust variance estimator itself and corrections to the degrees of freedom of test statistics. Corrections to the robust variance estimator have focused on bias reduction. We proposed variance-based corrections to the sandwich variance estimator. Corrections to the degrees of freedom of test statistics have not been successful in the literature (Lu et al., 2007; Braun, 2007). However, hybrid approaches combining corrections to the variance estimator and the degrees of freedom of the test statistic might offer improvements over current methodology. This topic of research has been suggested by Pan and Wall (2003) and Braun (2007).

Outcome dependent sampling

Our work on WCR and WCPR resembles work in the literature on outcome dependent sampling. Schildcrout and Heagerty (2005) studied the effect of design features on bias and efficiency of GEE in the analysis of longitudinal binary data. They state that if the model includes time dependent covariates, cross-sectional models may be biased unless the mean response is the same for multiple lagged values of the covariates or if an independence correlation structure for GEE is used. This resembles statements on the validity of WCR under informative cluster sizes. Schildcrout and Heagerty (2005) study different working covariance models and their effect on bias and efficiency of parameter estimates in this setting. Their work has parallels to our work on the validity of unweighted GEE with informative cluster sizes. A review of the literature on outcome dependent sampling may reveal connections to our work on resampling methods and highlight future areas of research.

Appendix

A.2.1 Proof of results in the missing data model in §2.3.4.

Proof. Since

$$\begin{aligned}
E[T_i|N_i > 0] &= \sum_{k=1}^{n_i^*} \Pr(N_i = k|N_i > 0) E[T_i|N_i = k] \\
&= \sum_{k=1}^{n_i^*} \Pr(N_i = k|N_i > 0) k \frac{p_i\gamma_1}{p_i\gamma_1 + (1-p_i)\gamma_0} \\
&= \frac{p_i\gamma_1}{p_i\gamma_1 + (1-p_i)\gamma_0} E[N_i|N_i > 0],
\end{aligned}$$

it follows that

$$\frac{E[T_i|N_i > 0]}{E[N_i|N_i > 0]} = \frac{p_i\gamma_1}{p_i\gamma_1 + (1-p_i)\gamma_0}.$$

Similarly

$$\begin{aligned}
E[\frac{T_i}{N_i}|N_i > 0] &= \sum_{k=1}^{n_i^*} \Pr(N_i = k|N_i > 0) E[\frac{T_i}{N_i}|N_i = k] \\
&= \sum_{k=1}^{n_i^*} \Pr(N_i = k|N_i > 0) \frac{1}{k} k \frac{p_i\gamma_1}{p_i\gamma_1 + (1-p_i)\gamma_0} \\
&= \frac{p_i\gamma_1}{p_i\gamma_1 + (1-p_i)\gamma_0} \sum_{k=1}^{n_i^*} \Pr(N_i = k|N_i > 0) \\
&= \frac{p_i\gamma_1}{p_i\gamma_1 + (1-p_i)\gamma_0}.
\end{aligned}$$

Therefore

$$\frac{E[T_i|N_i > 0]}{E[N_i|N_i > 0]} = E[\frac{T_i}{N_i}|N_i > 0].$$

This completes the proof. □

A.3.1 Proof that $\lim_{k\to\infty}\hat{\boldsymbol{\gamma}}_1^{(k)} = \frac{1}{n-p}\mathbf{JS}$, the OLS estimator.

Proof. For simplicity, let us write $(\mathbf{DP})^{\infty} := \lim_{k\to\infty}(\mathbf{DP})^k$. We want to prove that $(\mathbf{DP})^{\infty}\mathbf{D} = \frac{1}{n-p}\mathbf{J}$.

The matrix $\mathbf{DP}$ has diagonal elements $(1-h_{ii})$ and off-diagonal elements $h_{ij}^2/(1-h_{ii})$. Hence the sum of the elements on its i-th row is equal to 1:

$$\sum_{j=1}^{n}(\mathbf{DP})_{ij} = (1-h_{ii}) + \sum_{j\neq i}\frac{h_{ij}^2}{1-h_{ii}} = 1.$$

It follows that $\mathbf{DP1} = \mathbf{1}$, where $\mathbf{1}$ is a vector with all elements equal to 1, and therefore $\mathbf{DP}$ is a transition matrix.

Proving that $(\mathbf{DP})^{\infty}\mathbf{D} = \frac{1}{n-p}\mathbf{J}$ is equivalent to proving that the transition matrix $\mathbf{DP}$ has limiting distribution $\frac{1}{n-p}\mathbf{JD}^{-1}$, also equivalent to showing that $\frac{1}{n-p}\mathbf{JD}^{-1}(\mathbf{DP}) = \frac{1}{n-p}\mathbf{JD}^{-1}$.

By properties of the hat matrix $\mathbf{H}$, $\sum_j \mathbf{P}_{ij} = 1-h_{ii}$, and $\mathbf{JD}^{-1} = \mathbf{JP}$. It follows that $\frac{1}{n-p}\mathbf{JD}^{-1}(\mathbf{DP}) = \frac{1}{n-p}\mathbf{JP} = \frac{1}{n-p}\mathbf{JD}^{-1}$ which completes the proof. □

A.3.2 Proof of Property 1 in §3.2.3.

Proof. In order to prove that $E(\hat{\boldsymbol{\gamma}}_1^{(k)}) = \boldsymbol{\gamma}$ under homoscedasticity, write

$$E(\hat{\boldsymbol{\gamma}}_1^{(k)}) = (\mathbf{DP})^k\mathbf{D}E(\mathbf{S}) = (\mathbf{DP})^k\mathbf{DP}\boldsymbol{\gamma} = (\mathbf{DP})^{k+1}\mathbf{1}\sigma^2.$$

We proved in **A.3.1** that $\mathbf{DP}$ is a transition matrix, it follows that $(\mathbf{DP})^{k+1}$ is also a transition matrix and therefore $(\mathbf{DP})^{k+1}\mathbf{1}\sigma^2 = \mathbf{1}\sigma^2$. □

A.3.3 Proof of Theorem 3.1.

Proof. Let the k-th *Schur power* (Marcus and Minc, 1964, p.120) of a vector or matrix $\mathbf{B} = (b_{ij})$ be defined as $\mathbf{B}^{*k} = (b_{ij}^k)$.

The estimator $\mathbf{z^T}\hat{\mathbf{\Gamma}}_\delta^{(k)}\mathbf{z}$ can be written as

$$\mathbf{z^T}\hat{\mathbf{\Gamma}}_\delta^{(k)}\mathbf{z} = (\mathbf{z}^T)^{*2}\hat{\boldsymbol{\gamma}}_\delta^{(k)} = \mathbf{u}_\delta^T(\mathbf{DP})^k\mathbf{DS}$$

where $\mathbf{u}_\delta^T = (\mathbf{z}^T)^{*2}\mathbf{D}^{\delta-1}$. Therefore we can write:

$$\mathrm{Var}(\mathbf{z^T}\hat{\mathbf{\Gamma}}_\delta^{(k+1)}\mathbf{z}) = \mathbf{u}_\delta^T(\mathbf{DP})^{k+1}\mathbf{D}\mathrm{Var}(\mathbf{S})\mathbf{D}(\mathbf{PD})^{k+1}\mathbf{u}_\delta$$

and

$$\mathrm{Var}(\mathbf{z^T}\hat{\mathbf{\Gamma}}_\delta^{(k)}\mathbf{z}) = \mathbf{u}_\delta^T(\mathbf{DP})^{k}\mathbf{D}\mathrm{Var}(\mathbf{S})\mathbf{D}(\mathbf{PD})^{k}\mathbf{u}_\delta.$$

Proving that $\mathrm{Var}(\mathbf{z^T}\hat{\mathbf{\Gamma}}_\delta^{(k+1)}\mathbf{z}) \leq \mathrm{Var}(\mathbf{z^T}\hat{\mathbf{\Gamma}}_\delta^{(k)}\mathbf{z})$ is equivalent to proving that

$$\frac{\mathrm{Var}(\mathbf{z^T}\hat{\mathbf{\Gamma}}_\delta^{(k+1)}\mathbf{z})}{\mathrm{Var}(\mathbf{z^T}\hat{\mathbf{\Gamma}}_\delta^{(k)}\mathbf{z})} \leq 1 \text{ for all } \mathbf{z}.$$

From the expressions of $\mathrm{Var}(\mathbf{z^T}\hat{\mathbf{\Gamma}}_\delta^{(k)}\mathbf{z})$ and $\mathrm{Var}(\mathbf{z^T}\hat{\mathbf{\Gamma}}_\delta^{(k+1)}\mathbf{z})$ above, it suffices to show that

$$\mathbf{C} := ((\mathbf{DP})^k\mathbf{D}\mathrm{Var}(\mathbf{S})\mathbf{D}(\mathbf{PD})^k)^{-1}(\mathbf{DP})^{k+1}\mathbf{D}\mathrm{Var}(\mathbf{S})\mathbf{D}(\mathbf{PD})^{k+1}$$

has all eigenvalues less than or equal to 1.

Under normality and homoscedasticity, $\text{Var}(\mathbf{S}) = 2\sigma^4(\mathbf{I}-\mathbf{H})^{*2} = 2\sigma^4\mathbf{P}$. In general, if $\text{Var}(\mathbf{S}) \propto \mathbf{P}$ we can write

$$\begin{aligned}\mathbf{C} &= ((\mathbf{DP})^k\mathbf{DPD}(\mathbf{PD})^k)^{-1}(\mathbf{DP})^{k+1}\mathbf{DPD}(\mathbf{PD})^{k+1}\\ &= ((\mathbf{PD})^k)^{-1}(\mathbf{PD})^k\mathbf{PDPD} = \mathbf{PDPD}.\end{aligned}$$

Finally, we have shown before that $\mathbf{DP}$ is a strictly positive transition matrix: $\mathbf{DP1} = \mathbf{1}$ and $(\mathbf{DP})_{ij} > 0$. Therefore $\mathbf{C}^T = \mathbf{DPDP}$ is also a strictly positive transition matrix. Hence $\mathbf{C}$ has one eigenvalue equal to 1 and the remaining eigenvalues less than or equal to 1. This completes the proof. □

A.3.4 Proof of Property 3 in §3.2.3.

Proof. Dorfman (1991) proved this property for the case $k = 0$. The case $k = 0$ requires regularity conditions of the leverages h_{ii}, in particular, that $\max_{1\le i\le n}(h_{ii}) \to 0$ as $n \to \infty$. To extend the proof to other values of k we need conditions under which $||(\mathbf{DP})^k - \mathbf{I}_n|| \to 0$ as $n \to \infty$ for fixed k. Again the sufficient condition is that $\max_{1\le i\le n}(h_{ii}) \to 0$ as $n \to \infty$. Since $(\mathbf{DP})^k$ is a transition matrix it follows that $||(\mathbf{DP})^k - \mathbf{I}_n||_2 = ||(\mathbf{DP})^k - \mathbf{I}_n||_\infty = 0$. Regularity of the leverages guarantees that the max norm $||\mathbf{DP} - \mathbf{I}_n||_{max} = \max_{1\le i\le n}(h_{ii}) \to 0$. □

A.3.5 Proof of Theorem 3.2.

Proof. Let $\mathbf{R}$ be the vector of residuals r_i, then $\mathbf{R} \sim N(\mathbf{0}, (\mathbf{I}-\mathbf{H})\mathbf{\Gamma}(\mathbf{I}-\mathbf{H}))$.

Evaluating $(\mathbf{I}-\mathbf{H})\mathbf{\Gamma}(\mathbf{I}-\mathbf{H})$ under homoscedasticity, and by properties of $\mathbf{H}$, we obtain that $\text{Var}(r_i) = \sigma^2(1-h_{ii})$ and $\text{Cov}(r_i, r_j) = -h_{ij}\sigma^2$.

Using fourth order moments of the multivariate normal distribution we obtain $\text{Cov}(r_i^2, r_j^2) = 2\text{Cov}(r_i, r_j)^2$ and $\text{Var}(r_i^2) = 2\text{Var}(r_i)^2$. So that $\text{Corr}(r_i^2, r_j^2) = h_{ij}^2/(1-h_{ii})(1-h_{jj}) = (\mathbf{DPD})_{ij}$ if $i \neq j$ and $(\mathbf{DPD})_{ii} = 1$. □

A.4.1

Liang and Zeger (1986) showed that under regularity conditions, BC0 $\xrightarrow{p}$ $\text{cov}(\hat{\boldsymbol{\beta}})$ as $M \to \infty$, where $\text{cov}(\hat{\boldsymbol{\beta}})$ is given in (4.4). The necessary conditions are sufficient moments of $\mathbf{X}$, $\mathbf{Y}$ and smoothness of $g(\mu_i)$. If these conditions hold then $\max_{(ij)}||\mathbf{H}_{ij}|| = O(M^{-1})$. This follows from $\mathbf{H}_{ij} = \mathbf{D}_i \left(\sum_{l=1}^{M} \mathbf{D}_l^T \mathbf{V}_l^{-1} \mathbf{D}_l\right)^{-1} \mathbf{D}_j^T \mathbf{V}_j^{-1}$; the norm $|| \left(\sum_{l=1}^{M} \mathbf{D}_l^T \mathbf{V}_l^{-1} \mathbf{D}_l\right)^{-1} || = O(M^{-1})$ while the rest of the terms in $\mathbf{H}_{ij}$ are $O(1)$.

Theorem 4.1 If regularity conditions are met such that $\max_{(ij)}||\mathbf{H}_{ij}|| = O(M^{-1})$ then BC1, BC1$^{(1)}$, BC2 and BC2$^{(1)}$ are consistent for $\text{cov}(\hat{\boldsymbol{\beta}})$ as $M \to \infty$.

Proof. Liang and Zeger (1986) showed that substituting $\mathbf{\Gamma}_i$ in (4.4) by $(\hat{\mathbf{\Gamma}}_0^{(0)})_i = \mathbf{r}_i \mathbf{r}_i^T$ guarantees convergence of BC0 as long as $E(\mathbf{r}_i \mathbf{r}_i^T) = \mathbf{\Gamma}_i\{1 + O(M^{-1})\}$. This follows from

$$E(\mathbf{r}_i \mathbf{r}_i^T) = (\mathbf{I}_i - \mathbf{H}_{ii})\mathbf{\Gamma}_i(\mathbf{I}_i - \mathbf{H}_{ii})^T + \sum_{j \neq i} \mathbf{H}_{ij} \mathbf{\Gamma}_j \mathbf{H}_{ij}^T + O(M^{-2})$$

as long as $||\mathbf{H}_{ij}|| = O(M^{-1})$ for all $\{i, j\}$.

We want to prove that $(\hat{\mathbf{\Gamma}}_1^{(0)})_i$, $(\hat{\mathbf{\Gamma}}_2^{(0)})_i$, $(\hat{\mathbf{\Gamma}}_1^{(1)})_i$ and $(\hat{\mathbf{\Gamma}}_2^{(1)})_i$ share the same asymptotic expectation as $(\hat{\boldsymbol{\Gamma}}_0^{(0)})_i$. This result follows directly from the structure of these estimators:

$$\begin{aligned}
(\hat{\boldsymbol{\Gamma}}_1^{(0)})_i &= (\mathbf{I}_{n_i} - \mathbf{H}_{ii})^{-1/2}\mathbf{r}_i\mathbf{r}_i^T(\mathbf{I}_{n_i} - \mathbf{H}_{ii})^{-1/2T}
\end{aligned}$$

$$\begin{aligned}
(\hat{\boldsymbol{\Gamma}}_1^{(1)})_i &= \mathbf{r}_i\mathbf{r}_i^T \\
&+ (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{1}{2}}\left(\sum_{j\neq i}\mathbf{H}_{ij}(\mathbf{I}_j - \mathbf{H}_{jj})^{-\frac{1}{2}}\mathbf{r}_j\mathbf{r}_j^T(\mathbf{I}_j - \mathbf{H}_{jj})^{-\frac{1}{2}T}\mathbf{H}_{ij}^T\right)(\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{1}{2}T}
\end{aligned}$$

$$\begin{aligned}
(\hat{\boldsymbol{\Gamma}}_2^{(0)})_i &= (\mathbf{I}_{n_i} - \mathbf{H}_{ii})^{-1}\mathbf{r}_i\mathbf{r}_i^T(\mathbf{I}_{n_i} - \mathbf{H}_{ii})^{-1T}
\end{aligned}$$

$$\begin{aligned}
(\hat{\boldsymbol{\Gamma}}_2^{(1)})_i &= (\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{1}{2}}\mathbf{r}_i\mathbf{r}_i^T(\mathbf{I}_i - \mathbf{H}_{ii})^{-\frac{1}{2}T} \\
&+ ((\mathbf{I}_i - \mathbf{H}_{ii})^{-1}\left(\sum_{j\neq i}\mathbf{H}_{ij}(\mathbf{I}_j - \mathbf{H}_{jj})^{-\frac{1}{2}}\mathbf{r}_j\mathbf{r}_j^T(\mathbf{I}_j - \mathbf{H}_{jj})^{-\frac{1}{2}T}\mathbf{H}_{ij}^T\right)(\mathbf{I}_i - \mathbf{H}_{ii})^{-1T}.
\end{aligned}$$

If $\max_{(ij)}||\mathbf{H}_{ij}|| = O(M^{-1})$ then $(\hat{\boldsymbol{\Gamma}}_\delta^{(k)})_i = \mathbf{r}_i\mathbf{r}_i^T + O(M^{-1})$ for $\delta = 1, 2$, $k = 0, 1$ and therefore

$$E(\hat{\boldsymbol{\Gamma}}_\delta^{(k)})_i = \boldsymbol{\Gamma}_i + O(M^{-1}) \qquad \delta = 1, 2 \quad k = 0, 1$$

Then, by the arguments of Liang and Zeger (1986), BC1, BC1$^{(1)}$, BC2 and BC2$^{(1)}$ are consistent for $\text{cov}(\hat{\boldsymbol{\beta}})$ as $M \to \infty$.

□

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