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SIMEX Variance Component Tests in Generalized Linear Mixed Measurement Error Models

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SUMMARY. In the analysis of clustered data with covariates measured with error, a problem of common interest is to test for correlation within clusters and heterogeneity across clusters. We examined this problem in the framework of generalized linear mixed measurement error models. We propose using the simulation extrapolation (SIMEX) method to construct a score test for the null hypothesis that all variance components are zero. A key feature of this SIMEX score test is that no assumptions need to be made regarding the distributions of the random effects and the unobserved covariates. We illustrate this test by analyzing Framingham heart disease data and evaluate its performance by simulation. We also propose individual SIMEX score tests for testing the variance components separately. Both tests can be easily implemented using existing statistical software.

KEY WORDS: Measurement error; Random effects; Score tests; Variance components.

1. Introduction

It is of substantial interest in the analysis of clustered and longitudinal data to test for correlation within clusters and heterogeneity across clusters. These tests are useful in many fields of research, such as genetic epidemiology, ecologic studies, and clinical trials. For example, in genetic epidemiology, one is often interested in studying familial aggregation of a disease, which may indicate a genetic factor; in longitudinal studies, one is often interested in examining whether observations measured within the same subject are correlated. (See Commenges et al. (1994) and Lin (1997) for other examples.) Lin (1997) examined this problem in the framework of generalized linear mixed models (Breslow and Clayton, 1993) and proposed global and individual score tests for variance components equal to zero. Special cases of these tests were considered by Liang (1987) and Commenges et al. (1994), among others.

A common problem in the analysis of clustered data is the presence of covariate measurement error. For example, in a subset of the Framingham heart disease data, 75 coronary heart disease patients were examined every 2 years in an 8-year period for the presence of left ventricular hypertrophy (LVH). The study objectives were (1) to study the association of the risk of LVH and systolic blood pressure (SBP), baseline age, smoking status, body mass index, and exam number (1–4) and (2) to test for correlation of observations within the same subject. A main difficulty in analyzing this dataset is that systolic blood pressure was measured with substantial measurement error (Carroll, Ruppert, and Stefanski, 1995). To address the first question, Wang et al. (1998) introduced generalized linear mixed measurement error models (GLMMeMs), which extend generalized linear mixed models (GLMMs) by allowing covariates to be measured with error. They used the simulation extrapolation (SIMEX) method (Cook and Stefanski, 1994) to estimate regression coefficients and variance components. We focus in this paper on addressing the second question.

Specifically, we propose using the SIMEX method to construct a score test for the null hypothesis that all variance components are zero in GLMMeMs. This SIMEX score test extends the results of Lin (1997) by allowing covariates to be measured with error. A key feature of this SIMEX score test is that no assumptions need to be made regarding the distributions of the random effects and the unobserved covariates. We illustrate this test by analyzing the Framingham heart disease data and evaluate its performance by simulation. We also propose individual SIMEX score tests for testing the variance components separately. Both tests can be easily implemented using existing statistical software.

2. The Generalized Linear Mixed Measurement Error Model

Let the data be arranged in M clusters with the jth observation ($j = 1, \ldots, n_i$) of the ith cluster consisting of an outcome variable Y_{ij}, unobserved covariates $\mathbf{X}_{ij}$, observed $\mathbf{X}_{ij}$-related covariates $\mathbf{W}_{ij}$, and other observed, accurately measured covariates $\mathbf{Z}_{ij}$ and $\mathbf{S}_{ij}$. The covariates $(\mathbf{X}_{ij}, \mathbf{Z}_{ij})$ and $\mathbf{S}_{ij}$ are associated with fixed and random effects, respectively. Conditional on the random effects $\mathbf{b}_i$, the Y_{ij} are independent with means $\mathrm{E}(Y_{ij} \mid \mathbf{b}_i) = \mu_{ij}^{\mathbf{b}_i}$ and variances $V(\mu_{ij}^{\mathbf{b}_i}) = \phi m_{ij}^{-1} v(\mu_{ij}^{\mathbf{b}_i})$. Here ϕ is a scale parameter and m_{ij} is a prior weight (e.g., binomial denominator). Conditional on the covariates $(\mathbf{X}_{ij}, \mathbf{Z}_{ij}, \mathbf{S}_{ij})$, the observations Y_{ij} follow a generalized linear mixed model (GLMM)

$$g(\mu_{ij}^{\mathbf{b}_i}) = \beta_0 + \mathbf{X}_{ij}^{\mathrm{T}}\beta_x + \mathbf{Z}_{ij}^{\mathrm{T}}\beta_z + \mathbf{S}_{ij}^{\mathrm{T}}\mathbf{b}_i, \qquad (1)$$

where $g(\cdot)$ is a monotonic differential link function, $\boldsymbol{\beta} = (\beta_0, \beta_x, \beta_z)$ are regression coefficients, the random effects $\mathbf{b}_i$ follow $\mathrm{N}(0, \mathbf{D}(\boldsymbol{\theta}))$, and $\boldsymbol{\theta}$ is a $c \times 1$ vector of variance components.

We further assume that the measurement error is additive, i.e.,

$$\mathbf{W}_{ij} = \mathbf{X}_{ij} + \mathbf{U}_{ij}, \qquad (2)$$

where the $\mathbf{U}_{ij}$ are independent and distributed as $\mathrm{N}(0, \boldsymbol{\Sigma}_u)$. Note that we do not assume a distribution for $\mathbf{X}_{ij}$. Our main interest in this paper is to use the observed data $(Y_{ij}, \mathbf{W}_{ij}, \mathbf{Z}_{ij}, \mathbf{S}_{ij})$ to construct score tests for the variance components. We first briefly review in Section 3 the score tests for variance components in GLMMs when there is no measurement error. We then propose in Section 4 the SIMEX score tests for variance components in GLMMs when covariates are measured with error.

3. The Score Tests for Variance Components in GLMMs Without Measurement Error

Lin (1997) proposed a global score test for the null hypothesis that all variance components equal zero (H_0: $\boldsymbol{\theta} = 0$) in the GLMM (1), where the $\mathbf{X}_{ij}$ are observed and there is no measurement error. The null hypothesis H_0: $\boldsymbol{\theta} = 0$ corresponds to no correlation and no overdispersion. Lin (1997) showed that this test is a locally most stringent test and is robust in the sense that one does not need to specify a distribution of the random effects except for the first two moments. A key feature of this test is that it can be easily implemented by fitting a generalized linear model (GLM) to the data.

Let $\delta_{ij} = 1/g'(\mu_{ij}), \omega_{ij} = V^{-1}(\mu_i)\delta_{ij}^2, \omega_{oij} = \omega_{ij} + e_{ij}(Y_{ij} - \mu_{ij})$, where $\mu_{ij} = \mathrm{E}(Y_{ij})$ under H_0 and satisfies the GLM

$$g(\mu_{ij}) = \beta_0 + \mathbf{X}_{ij}^{\mathrm{T}}\beta_x + \mathbf{Z}_{ij}^{\mathrm{T}}\beta_z \qquad (3)$$

and $e_i = \{V'(\mu_i)g'(\mu_i) + V(\mu_i)g''(\mu_i)\}/[V^2(\mu_i)\{g'(\mu_i)\}^3]$ and is zero for canonical links. Note that the ω_{ij} are the working weights under the GLM (3) and $\omega_{ij} = \mathrm{E}(\omega_{oij})$ under H_0.

Denote $\boldsymbol{\mu}_i = (\mu_{i1}, \ldots, \mu_{in_i})^{\mathrm{T}}$, $\mathbf{S}_i = (\mathbf{S}_{i1}^{\mathrm{T}}, \ldots, \mathbf{S}_{in_i}^{\mathrm{T}})^{\mathrm{T}}$, $\dot{\mathbf{D}}_k = \partial\mathbf{D}/\partial\theta_k|_{\theta=0}$ ($k = 1, \ldots, c$), and by the matrices $\boldsymbol{\Delta}_i$, $\boldsymbol{\Omega}_i$, and $\boldsymbol{\Omega}_{oi}$ the diagonal matrices with elements δ_{ij}, ω_{ij}, and ω_{oij} ($j = 1, \ldots, n_i$). The global score statistic for testing H_0: $\boldsymbol{\theta} = 0$ can be written as

$$\chi_G^2 = \mathcal{U}(\hat{\boldsymbol{\beta}})^{\mathrm{T}}\mathcal{I}(\hat{\boldsymbol{\beta}})^{-1}\mathcal{U}(\hat{\boldsymbol{\beta}}), \qquad (4)$$

where $\hat{\boldsymbol{\beta}}$ is the maximum likelihood estimator of $\boldsymbol{\beta}$ under the GLM (3) and $\mathcal{U}(\hat{\boldsymbol{\beta}})$ is the efficient score for $\boldsymbol{\theta}$ at $\boldsymbol{\theta} = \mathbf{0}$ with the kth component

$$\begin{aligned}\mathcal{U}_k(\hat{\boldsymbol{\beta}}) &= \frac{1}{2}\sum_{i=1}^{M}\Big\{(\mathbf{Y}_i - \boldsymbol{\mu}_i)^{\mathrm{T}}\boldsymbol{\Delta}_i^{-1}\boldsymbol{\Omega}_i\mathbf{S}_i\dot{\mathbf{D}}_k\mathbf{S}_i^{\mathrm{T}}\boldsymbol{\Omega}_i\boldsymbol{\Delta}_i^{-1}(\mathbf{Y}_i - \boldsymbol{\mu}_i) \\ &\quad - \mathrm{tr}\left(\boldsymbol{\Omega}_{oi}\mathbf{S}_i\dot{\mathbf{D}}_k\mathbf{S}_i^{\mathrm{T}}\right)\Big\}, \end{aligned} \qquad (5)$$

and $\mathcal{I}$ is the efficient information matrix of $\boldsymbol{\theta}$ evaluated under H_0,

$$\mathcal{I} = \mathbf{I}_{\theta\theta} - \mathbf{I}_{\beta\theta}^{\mathrm{T}}\mathbf{I}_{\beta\beta}^{-1}\mathbf{I}_{\beta\theta}. \qquad (6)$$

The expressions of $(\mathbf{I}_{\theta\theta}, \mathbf{I}_{\beta\theta}, \mathbf{I}_{\beta\beta})$ are given in Appendix 1. Lin (1997) also proposed individual score tests for testing variance components equal to zero separately, i.e., H_0: $\theta_k = 0$, in GLMMs with independent random effects. See Section 4 of Lin (1997) for details.

4. The SIMEX Score Tests for Variance Components in GLMMeMs

The global and individual score tests for variance components of Lin (1997) are applicable to GLMMs with no covariate measurement error. We propose in this section using the SIMEX method (Cook and Stefanski, 1994) to construct such score tests for variance components in the presence of measurement error under the GLMMeM equations (1) and (2), where the $\mathbf{X}_{ij}$ are not observed and their error-prone covariates $\mathbf{W}_{ij}$ are observed. Specifically, we focus on applying SIMEX to the global score test for variance components. A virtually identical procedure can be used to construct the SIMEX individual score tests for variance components in GLMMeMs. See the Discussion for more details.

SIMEX is a simulation-based functional method for inference on the model parameters, where no distributional assumptions are made on the unobserved covariates $\mathbf{X}_{ij}$. Details of the SIMEX method are given in Cook and Stefanski (1994) and Carroll et al. (1995). The SIMEX procedure consists of two steps, the simulation step and the extrapolation step. In the simulation step, given $\lambda > 0$, one adds to the $\mathbf{W}_{ij}$ independent errors with mean 0 and covariance $\lambda\boldsymbol{\Sigma}_v$ and computes the estimates of the model parameters using the resulting simulated data, which have measurement error covariance equal to $(1 + \lambda)\boldsymbol{\Sigma}_u$. This procedure is repeated a large number of times and the average (or median) of these naive estimates is calculated. One does this for a series of values of λ and plots these averages (or medians) against the λ values. In the extrapolation step, a regression model is fit to these averaged naive estimates as a function of λ. Extrapolation back to $\lambda = -1$ (no measurement error) yields the SIMEX estimates of the model parameters.

We apply this SIMEX idea to construct a global score test for variance components in the GLMMeM (1)–(2). Examination of the global score test statistic $\chi_G^2 = \mathcal{U}(\hat{\boldsymbol{\beta}})^{\mathrm{T}}\mathcal{I}(\hat{\boldsymbol{\beta}})^{-1}\mathcal{U}(\hat{\boldsymbol{\beta}})$ in (4) suggests that it has the same setup as that studied by Stefanski and Cook (1995, Section 5.2) when the error variance is known and by Carroll et al. (1996) when the error variance is estimated. We hence propose using SIMEX to extrapolate the "numerator" $\mathcal{U}(\cdot)$ of the score test, which is given in equation (5), as if it were a parameter estimator. We use SIMEX variance methods (see Carroll et al., 1995, Section 4.3.5) to calculate the variance of this estimator. Denoting the results by $\mathcal{U}_{\text{simex}}(\cdot)$ and $\mathcal{I}_{\text{simex}}(\cdot)$, respectively, the SIMEX score statistic is simply $\mathcal{U}_{\text{simex}}(\cdot)^{\mathrm{T}}\{\mathcal{I}_{\text{simex}}(\cdot)\}^{-1}\mathcal{U}_{\text{simex}}(\cdot)$. If the measurement error variance is unknown, then the estimating equation methods described in Section 4.7.2 of Carroll et al. (1995) can be used to obtain $\mathcal{I}_{\text{simex}}(\cdot)$. A sketch of the technical justification for this method is given in Appendices 2–4.

We demonstrate this procedure using Figure 1, which shows application of the SIMEX score test for variance component to the Framingham data example in Section 5 under the logistic model (7). This model consists of a scalar covariate $X = \log(\text{SBP} - 50)$ that is measured with error and a random intercept with a scalar variance component θ. We denote by $\hat{\sigma}_u^2$ an estimate of the scalar measurement error variance σ_u^2. In the simulation step, one calculates the naive score $\mathcal{U}$ in (5) using simulated data obtained by adding to the W_{ij} independent random variables following $\mathrm{N}(0, \lambda\hat{\sigma}_u^2)$. This procedure is repeated for a large number B times and the median of the resulting B scores are calculated. One does this for $\lambda = (0, 0.5, 1.0, 1.5, 2.0)$ and plots the resulting naive scores against λ. These are shown in small solid squares in Figure 1. In the extrapolation step, a model is fit to these small solid squares as a function of λ, which is the solid line in Figure 1. The literature suggests that a quadratic model often provides a good approximation of the true bias curve and often works well (Carroll et al., 1995). One then extrapolates the model to the values less than $\hat{\sigma}_u^2$, which is the dashed curve in Figure 1. The extrapolated value at $\lambda = -1$, which corresponds to zero measurement error variance, is the SIMEX score estimator $\mathcal{U}_{\text{simex}}$.

5. Application to the Framingham Heart Disease Data

We applied our SIMEX score test to the analysis of the Framingham heart disease data introduced in Section 1. Two SBP measures were taken during each exam and were transformed to $\log(\text{SBP} - 50)$ as suggested in Carroll et al. (1995) to make the normality assumption for the measurement errors more plausible. The covariates included X, average log-transformed SBP, and $\mathbf{Z}$, age, smoking status, body mass index, and the exam number (values 1–4). Our objective is to test the correlation among observations within the same subject. We considered a measurement error logistic mixed model with random intercepts

$$\operatorname{logit}\{\mathrm{E}(Y_{ij} \mid b_i)\} = \beta_0 + X_{ij}\beta_x + \mathbf{Z}_{ij}^{\mathrm{T}}\boldsymbol{\beta}_z + b_i, \qquad (7)$$

where Y_{ij} is a binary indicator for the presence of LVH and b_i follows $\mathrm{N}(0, \theta)$. We assumed the observed log transformed SBP W_{ij} was related to X_{ij} through $W_{ij} = X_{ij} + U_{ij}$, where U_{ij} is the measurement error and follows $\mathrm{N}(0, \sigma_u^2)$. A null hypothesis $\theta = 0$ corresponds to no correlation within each subject.

Since blood pressure might change over time, estimation of the measurement error variance σ_u^2 requires that SBP be obtained over a number of days within a relatively short period of time. However, SBP was obtained only every 2 years in the

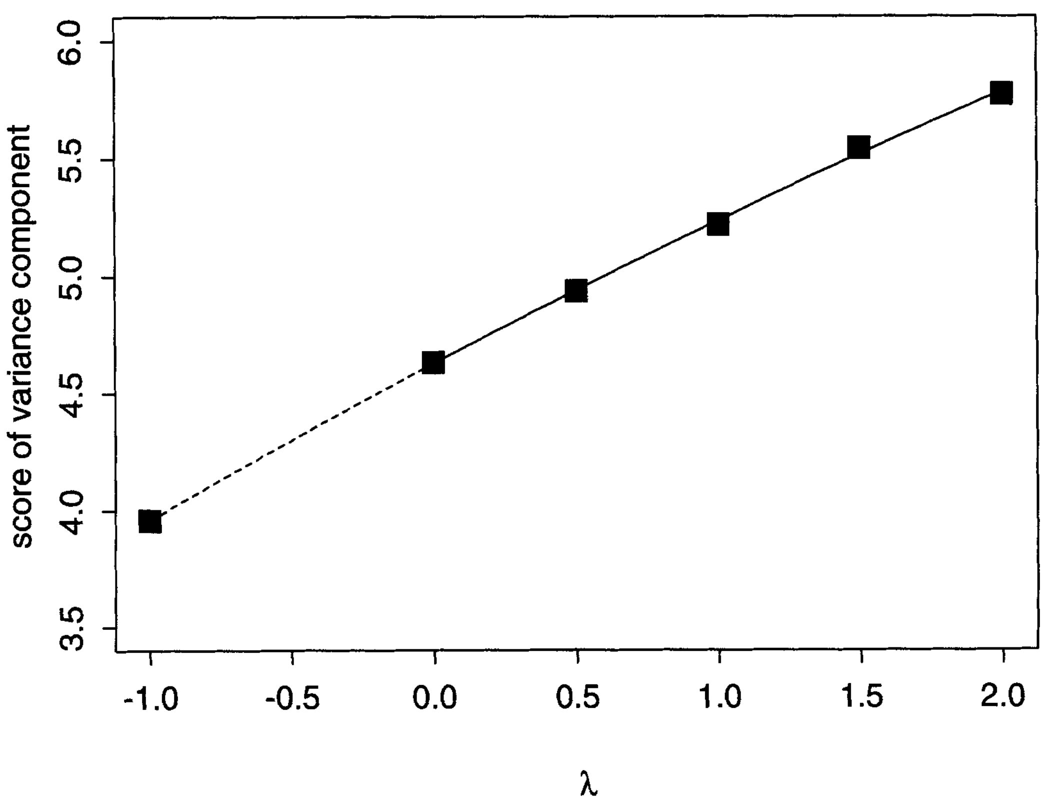

Figure 1. SIMEX extrapolation of the score $\mathcal{U}$ as a function of λ in the Framingham data when $\sigma_u^2 = 0.016$. The value of $\mathcal{U}$ at $\lambda = -1$ is the SIMEX score $\mathcal{U}_{\text{simex}}$.

Table 1
Empirical sizes and powers of naive and SIMEX score tests for variance components observed in 2000 simulations

		θ				
σ_u^2	Method	0.00	0.25	0.50	0.75	1.00
1/3	Naive	0.081				
	SIMEX	0.054	0.200	0.384	0.618	0.806
2/3	Naive	0.101				
	SIMEX	0.054	0.264	0.504	0.723	0.890

Framingham data. We hence could not directly estimate σ_u^2 from the data. Following Wang et al. (1998), we estimated σ_u^2 by assuming, for the ith cluster, X_{ij} given $\mathbf{Z}_{ij}$ followed a linear mixed model,

$$X_{ij} = \alpha_0 + \mathbf{Z}_{ij}^{\mathrm{T}}\boldsymbol{\alpha} + a_i + \epsilon_{ij},$$

where a_i and ϵ_{ij} are independent, a_i has mean zero and variance $\sigma_{x\mu}^2$, and ϵ_{ij} has mean zero and variance σ_x^2. This model allows the X_{ij} to be correlated within each subject. It follows that $\mathbf{W}_i = (W_{i1}, \ldots, W_{in_i})^{\mathrm{T}}$ given $\mathbf{Z}_i = (\mathbf{Z}_{i1}^{\mathrm{T}}, \ldots, \mathbf{Z}_{in_i}^{\mathrm{T}})^{\mathrm{T}}$ has mean $\alpha_0\mathbf{1} + \mathbf{Z}_i\boldsymbol{\alpha}$ and covariance $(\sigma_x^2 + \sigma_u^2)\mathbf{I} + \sigma_{x\mu}^2\mathbf{J}$, where $\mathbf{J}$ is a matrix of ones. This suggests that we could only estimate the sum of σ_x^2 and σ_u^2 but not each of them separately. Note that here we did not assume a full distribution for the X_{ij} except for the first two moments.

We used the method of moments to estimate $\sigma_x^2 + \sigma_u^2$ as 0.016 and the between-subject variance $\sigma_{x\mu}^2$ as 0.032. For illustrative purposes, we fixed the between-subject variance $\sigma_{x\mu}^2$ as 0.032, which allows the underlying unobserved SBP to be correlated with the same subject. We then varied the measurement error variance between two extreme cases, $\sigma_u^2 = 0$ and $\sigma_x^2 = 0$, where the first case ($\sigma_u^2 = 0$) assumes no measurement error, the second case ($\sigma_x^2 = 0$) assumes that the true SBP does not vary over time for each subject, and the within-subject variation in the observed SBP is fully due to measurement error. We further treated σ_u^2 as fixed and known and hence used the standard error estimation methods of Stefanski and Cook (1995) to calculate $\mathcal{I}(\cdot)$. The SIMEX method was applied with $B = 100$, which took only 40 seconds on a SPARC Ultra.

The naive score statistic for H_0: $\theta = 0$ calculated by ignoring the measurement error, i.e., assuming $\sigma_u^2 = 0$, was $\mathcal{U}/\mathcal{I}^{1/2} = 4.63/1.41 = 3.28$ (p value < 0.001). The SIMEX score statistic accounted for the measurement error by assuming $\sigma_u^2 = 0.016$ was $\mathcal{U}_{\text{simex}}/\mathcal{I}_{\text{simex}}^{1/2} = 3.98/1.58 = 2.52$ (p value $= 0.006$). Note here a one-sided test was used since the alternative hypothesis is H_a: $\theta > 0$. This suggests that there is a significant correlation among observations within the same subject. In fact, Wang et al. (1998) estimated the variance component θ as 2.05 (SE = 1.57) when $\sigma_u^2 = 0$ (no measurement error) using an approximate maximum likelihood method and estimated θ as 1.85 (SE = 1.52) when $\sigma_u^2 = 0.016$ using the SIMEX method to account for the measurement error. Note that the standard error of the estimate of θ cannot be used directly for testing $\theta = 0$ since the null hypothesis is on the boundary of the parameter space and the Wald statistic is not asymptotically distributed as a chi square (Lin, 1997).

6. Simulation Study

We conducted a simulation study to assess the size and power of the proposed SIMEX score tests for variance components. The design considered in the simulation study was similar to that in the Framingham data example in Section 5, where there were $m = 75$ clusters with $n = 4$ observations per cluster. The variable Z was the exam number (1–4) within each cluster, while $\mathbf{X}_i$ was generated as normal with mean zero and covariance matrix $\sigma_x^2\mathbf{I} + \sigma_{x\mu}^2\mathbf{J}$, where $\sigma_x^2 = 0$ and $\sigma_{x\mu}^2 = 2/3$. The observed X_{ij}-related covariates W_{ij} were generated by assuming the measurement error variance $\sigma_u^2 = 1/3$ and $\sigma_u^2 = 2/3$, where the first scenario ($\sigma_u^2 = 1/3$) mimics the Framingham data example in Section 5. A logistic mixed model with random intercepts in the form of equation (7) was considered. The regression parameters were set as $(\beta_0, \beta_x, \beta_z) = (-2, 1, 0)$. The SIMEX method was applied with $B = 100$, and there were 2000 simulated data sets for each parameter configuration.

We varied θ as 0.00, 0.25, 0.50, 0.75, and 1.00 to study the size and power of the SIMEX score test for variance components. For the purpose of comparison, we also studied the size of the naive score test for variance components obtained by ignoring the measurement error and by replacing X_{ij} with W_{ij} when calculating $\mathcal{U}$ and $\mathcal{I}$. Note that both size and power were calculated using a one-sided test. The nominal size was set to be 0.05. Table 1 gives the empirical size and power of the tests.

The results in Table 1 support the theoretical development suggesting that the level of the naive score test calculated by ignoring the measurement error will be too high. The performance of the naive score test becomes significantly worse as the measurement error becomes larger. However, the SIMEX score test performs well and still has a level very close to the nominal value. As the variance component θ increases, the power of the SIMEX score test increases and approaches one quickly.

7. Discussion

We have proposed in this paper a simple SIMEX global score test for variance components in generalized linear mixed models with covariates measured with error. Key features of the SIMEX global score test are that it is robust and easy to implement. Specifically, no distributions need to be assumed regarding the unobserved covariates and the random effects, and one only needs to fit generalized linear models to the data. Our simulation study shows that ignoring measurement error could result in a level of the score test for variance components that is higher than the nominal value. However, the SIMEX score test performs well, yielding an appropriate level and good statistical power.

The SIMEX method can be easily used to construct individual score tests to test for variance components separately in GLMMeMs. Such SIMEX individual score tests are constructed in an almost identical way to the SIMEX global score test. To avoid redundancy, we have not discussed them in detail in this paper. Specially, to test the null hypothesis H_0: $\theta_k = 0$ in GLMMeMs with independent random effects (see equation [6] of Lin, 1997), for each simulated data set generated in the SIMEX simulation step, instead of calculating the global score vector $\mathcal{U}$ in (5) and the global efficient information $\mathcal{I}$ in (6), one simply needs to calculate the score and the efficient information of θ_k or their approximations under the new hypothesis H_0: $\theta_k = 0$, which are given in equations (19) and (22) and equations (25) and (26) of Lin (1997). The rest of the SIMEX procedure described in Section 4 can then be applied directly without modifications to construct the SIMEX individual score tests for variance components.

We consider in this paper score tests for variance components using the SIMEX method, which assumes no distribution for the unobserved covariates $\mathbf{X}$. The SIMEX score test hence is robust to misspecification of the distribution of $\mathbf{X}$. However, SIMEX score tests could be less powerful compared to fully parametric score tests constructed by assuming a parametric distribution for $\mathbf{X}$. Unlike the SIMEX score tests, which often have closed-form expressions and can be easily implemented using existing statistical software, difficulties in constructing such fully parametric score tests are that closed-form expressions are often not available and often involve multidimensional integration and that new statistical software usually needs to be developed. Another disadvantage of the fully parametric score tests is that they are not robust to misspecification of the distribution of $\mathbf{X}$. Further research is needed to compare the performance of the SIMEX score tests and the fully parametric score tests for variance components.

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RÉSUMÉ

Un problème rencontré couramment dans l'analyse de données groupées avec des erreurs sur les covariables est celui du test des corrélations intra-groupes et de l'hétérogénéité intergroupes. Nous traitons ce problème dans le cadre des modèles linéaires généralisés mixtes avec erreurs. Nous proposons de construire un test du score de l'hypothèse H_0 que toutes les composantes de variance sont nulles, à l'aide de la méthode SIMEX. Une caractéristique essentielle de ce test du score SIMEX est qu'il ne requiert aucune hypothèse sur les distributions des effets aléatoires ou des covariables manquantes. Nous appliquons la méthode à des données de l'enquête de Framingham et nous évaluons ses performances à l'aide de simulations. Nous proposons également des tests du score SIMEX individuels pour tester séparément la nullité des différentes composantes de variance. L'implantation de ces tests à partir de logiciels courants est facile.

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APPENDIX 1

Calculations of the Efficient Information Matrix $\mathcal{I}$ in Section 3

Suppose κ_{3ij} and κ_{4ij} are the third and fourth cumulants of Y_{ij} under H_0: $\boldsymbol{\theta} = 0$ and are related to the second cumulant via $\kappa_{(r+1)ij} = \kappa_{2ij}\partial\kappa_{rij}/\partial\mu_{ij}$ $(r = 2, 3)$, where $\kappa_{2ij} = \phi m_{ij}^{-1} v(\mu_{ij})$. They take the form

$$\kappa_{3ij} = (\phi m_{ij}^{-1})^2 v'(\mu_{ij}) v(\mu_{ij}),$$
$$\kappa_{4i} = (\phi m_{ij}^{-1})^3 \left[v''(\mu_{ij}) v(\mu_{ij}) + \left\{v'(\mu_{ij})\right\}^2\right] v(\mu_{ij}).$$

Let $\mathbf{A}_i^k = \mathbf{S}_i \dot{\mathbf{D}}_k \mathbf{S}_i^{\mathrm{T}}$ and $\mathbf{a}_i^k$ be an $n_i \times 1$ vector containing the diagonal elements of $\mathbf{A}_i^k$ $(k = 1, \ldots, c)$. Let $\mathbf{R}_i$ be an $n_i \times n_i$ matrix with diagonal elements $\omega_{ij}^4 \delta_{ij}^{-4} \kappa_{4ij} + 2\omega_{ij}^2 + e_{ij}^2 \kappa_{2ij} - 2\omega_{ij}^2 \delta_{ij}^{-2} e_{ij} \kappa_{3ij}$ and off-diagonal elements $2\omega_{ij}\omega_{ij'}$ $(j \neq j')$. Finally, let $\mathbf{C}_i$ be a diagonal matrix with diagonal elements

$\omega_{ij}^3\delta_{ij}^{-3}\kappa_{3ij} - \omega_{ij}\delta_{ij}^{-1}e_{ij}\kappa_{2ij}$. The efficient information matrix is $\mathcal{I} = \mathbf{I}_{\boldsymbol{\theta}\boldsymbol{\theta}} - \mathbf{I}_{\boldsymbol{\beta}\boldsymbol{\theta}}^{\mathrm{T}}\mathbf{I}_{\boldsymbol{\beta}\boldsymbol{\beta}}^{-1}\mathbf{I}_{\boldsymbol{\beta}\boldsymbol{\theta}}$, where

$$\mathbf{I}_{\theta_k\theta_l} = \sum_{i=1}^{M} \frac{1}{4}\mathbf{1}^{\mathrm{T}}(\mathbf{A}_i^k \cdot \mathbf{R}_i \cdot \mathbf{A}_i^l)\mathbf{1},$$
$$\mathbf{I}_{\boldsymbol{\beta}\theta_k} = \sum_{i=1}^{M} \frac{1}{2}\mathbf{X}_i^{\mathrm{T}}\mathbf{C}_i\mathbf{a}_i^k,$$
$$\mathbf{I}_{\boldsymbol{\beta}\boldsymbol{\beta}} = \sum_{i=1}^{M} \mathbf{X}_i^{\mathrm{T}}\boldsymbol{\Omega}_i^{-1}\mathbf{X}_i, \tag{A.1}$$

where $\mathbf{1}$ is a vector of ones, $\mathbf{G}\cdot\mathbf{H}$ denotes component-wise multiplication of comformable matrices $\mathbf{G}$ and $\mathbf{H}$. For detailed derivations of (A.1), see Lin (1997).

Appendix 2

Justification of the SIMEX Score Test

The SIMEX score test is most easily justified in the explicit special case of a canonical GLMM with random intercept having variance component θ, scalar X, constant number n of observations per cluster, and number of SIMEX simulations $B < \infty$. The restriction to canonical GLMMs with a random intercept and constant cluster size is only for convenience; the general case is easily handled but with far more notational complexity. For example, to extend the proof in Appendix 3 to the case with varying cluster sizes, multiple random effects, and noncanonical links, one needs to replace the scalar score function in equation (A.2) by the score vector given in equation (5) and evaluated at σ_u^2. To allow $\mathbf{X}$ to be a vector, one needs to replace the scalar measurement error variance σ_u^2 by a measurement error covariance matrix $\boldsymbol{\Sigma}_u$ in (A.2). Virtually identical arguments to those given in Appendix 3 can then be applied to prove the asymptotic behavior of the SIMEX score test in such general cases. The restriction that $B < \infty$ is no real restriction since this would be the case in practice and, in addition, Carroll et al. (1996) note that the case $B = \infty$ involves difficult asymptotic theory for which rigorous results are available only in limited special cases.

Our argument is in two steps. We first show that, with changes in notation, the results of Stefanski and Cook (1995, σ_u^2 known) and Carroll et al. (1996, σ_u^2 estimated) apply to obtain consistent standard error estimates for the score test statistic in Section 4. We then indicate that, with the exact extrapolant, the SIMEX score test has the correct level asymptotically.

Appendix 3

Asymptotics

Let $\{\hat\beta_0(\sigma_u^2), \hat\beta_x(\sigma_u^2), \hat{\boldsymbol{\beta}}_z(\sigma_u^2)\}$ be the ordinary estimates of the coefficients under the null model ($\theta = 0$) with data having measurement error variance σ_u^2. Note that the null model corresponds to the generalized linear models with measurement error. Define $\hat\mu_{ij}(\sigma_u^2) = g^{-1}\{\hat\beta_0(\sigma_u^2) + W_{ij}\hat\beta_x(\sigma_u^2) + \mathbf{Z}_{ij}^{\mathrm{T}}\hat{\boldsymbol{\beta}}_z(\sigma_u^2)\}$, $\hat\delta_{ij}(\sigma_u^2) = 1/g'\{\hat\mu_{ij}(\sigma_u^2)\}$, and $\hat\omega_{ij}(\sigma_u^2) = [V\{\hat\mu_{ij}(\sigma_u^2)\}/\hat\delta_{ij}^2(\sigma_u^2)]^{-1}$, where $V(\cdot) = \phi m_{ij}^{-1}v(\cdot)$ and $g' = 1/v(\cdot)$. Denote the ensemble of responses by $\mathbf{Y}$ and let $\mathbf{X}$, $\mathbf{Z}$, and $\mathbf{W}$ be defined similarly. The score statistic is

$$\hat{\mathcal{U}}_M(\mathbf{Y},\mathbf{Z},\mathbf{W},\sigma_u^2) = M^{-1}\sum_{i=1}^{M}\frac{1}{2}\left(\left[\sum_{j=1}^{n}\left\{\hat\omega_{ij}\left(\sigma_u^2\right)/\hat\delta_{ij}\left(\sigma_u^2\right)\right\} \times \left\{Y_{ij} - \hat\mu_{ij}\left(\sigma_u^2\right)\right\}\right]^2 - \sum_{j=1}^{n}\hat\omega_{ij}\left(\sigma_u^2\right)\right). \tag{A.2}$$

Now let $\{\beta_0(\sigma_u^2), \boldsymbol{\beta}_x(\sigma_u^2), \boldsymbol{\beta}_z(\sigma_u^2)\}$ be the probability limits (assumed to exist) of the parameters as $M \to \infty$, still as $\theta = 0$. Further define $\mu_{ij}(\sigma_u^2) = g^{-1}\{\beta_0(\sigma_u^2) + W_{ij}\boldsymbol{\beta}_x(\sigma_u^2) + \mathbf{Z}_{ij}^{\mathrm{T}}\boldsymbol{\beta}_z(\sigma_u^2)\}$ and define $\omega_{ij}(\sigma_u^2)$, $\delta_{ij}(\sigma_u^2)$, and $\mathcal{U}_M(\mathbf{Y},\mathbf{Z},\mathbf{W}, \sigma_u^2)$ similarly. Finally, define

$$\Gamma\left(\sigma_u^2\right) = \mathrm{E}\left\{\frac{1}{2}\left(\left[\sum_{j=1}^{n}\left\{\omega_{ij}\left(\sigma_u^2\right)/\delta_{ij}\left(\sigma_u^2\right)\right\}\left\{Y_{ij} - \mu_{ij}\left(\sigma_u^2\right)\right\}\right]^2 - \sum_{j=1}^{n}\omega_{ij}\left(\sigma_u^2\right)\right)\right\}.$$

By ordinary delta method calculations, for some function $\chi(\cdot)$, we have the expansion

$$M^{1/2}\begin{bmatrix}\hat\beta_0\left(\sigma_u^2\right) - \beta_0\left(\sigma_u^2\right)\\ \hat{\boldsymbol{\beta}}_x\left(\sigma_u^2\right) - \boldsymbol{\beta}_x\left(\sigma_u^2\right)\\ \hat{\boldsymbol{\beta}}_z\left(\sigma_u^2\right) - \boldsymbol{\beta}_z\left(\sigma_u^2\right)\end{bmatrix} = M^{-1/2}\sum_{i=1}^{M}\chi\left(\mathbf{Y}_i,\mathbf{Z}_i,\mathbf{W}_i,\sigma_u^2\right) + o_p\left(M^{-1/2}\right), \tag{A.3}$$

where $\mathrm{E}\{\chi(\mathbf{Y}_i,\mathbf{Z}_i,\mathbf{W}_i,\sigma_u^2)\} = 0$ (cf., Stefanski and Cook, 1995, Section 5.3). Applying a delta method expansion to (A.2) and using (A.3), it is easily seen that, for some function $\Psi(\cdot)$,

$$M^{1/2}\left\{\hat{\mathcal{U}}_M\left(\mathbf{Y},\mathbf{Z},\mathbf{W},\sigma_u^2\right) - \Gamma\left(\sigma_u^2\right)\right\} = M^{-1/2}\sum_{j=1}^{M}\Psi\left(\mathbf{Y}_i,\mathbf{Z}_i,\mathbf{W}_i,\sigma_u^2\right) + o_p\left(M^{-1/2}\right), \tag{A.4}$$

where $\mathrm{E}\{\Psi(\mathbf{Y}_i,\mathbf{Z}_i,\mathbf{W}_i,\sigma_u^2)\} = 0$. Except for differences in notation, (A.4) is identical to the definition of $\hat{\boldsymbol{\theta}}_b(\lambda)$ in Section 5.2 of Stefanski and Cook (1995) and to equation (7) of Carroll et al. (1996). This verifies that their methods yield consistent variance estimates for the score statistic.

Appendix 4

Level of the Test

The SIMEX method extrapolates the estimates (in this case the score statistic) $\hat{\mathcal{U}}_M(\mathbf{Y},\mathbf{Z},\mathbf{W},\sigma_u^2)$ back to the case that there is no measurement error. If the correct or "exact" extrapolant function is used, then the SIMEX method yields a consistent estimate of the limit, which in our notation is $\Gamma(\sigma_u^2 = 0)$. Under the null model that the variance component is zero ($\theta = 0$), $\Gamma(\sigma_u^2 = 0) = 0$ so that, if the exact extrapolant is used, the level of the SIMEX score test is asymptotically correct.

In practice, the exact extrapolant function is typically unknown, and an approximation to it is the best that can be obtained. As long as the approximation is reasonable, the actual level of the SIMEX score test should be near the nominal.