
MONTE CARLO TEST FOR POLYNOMIAL COVARIATES

Authors: ABDELJELIL FARHAT
– Research Unit: Applied Economics and Simulation, Mahdia, Tunisia
Abdeljelil.Farhat@fsegma.rnu.tn

SAMI MESTIRI
– Research Unit: Applied Economics and Simulation, Mahdia, Tunisia
mestirisami2007@gmail.com

Received: December 2009 Revised: November 2011 Accepted: November 2011

Abstract:

- In this paper, we review the score test procedure used for testing polynomial covariate effects in a semi parametric additive mixed model. This test is based on the mixed model representation of the smoothing spline estimator of the nonparametric function and treating the inverse of the smoothing parameter as an extra variance component. Zhang and Lin (2003) found that the score test of polynomial test for non Gaussian responses follows a scaled chi-squared distribution. Simulation studies showed that their approximation is less satisfactory for binary data. To overcome this deficiency, we apply the technique of Monte Carlo in order to obtain provably exact procedures. Derivation and performance of each testing procedure are discussed throughout the simulations that we conducted.

Key-Words:

- *semi parametric additive mixed models; polynomial test; score test; Monte Carlo test.*

AMS Subject Classification:

- 62G08, 62J12, 62H15.

1. INTRODUCTION

Linear mixed models [Laird and Ware (1982)] and their extension, generalized linear mixed models (GLMMs) [Breslow and Clayton (1993); Zeger and Karim (1991)] are popular statistical models for analyzing correlated data. An important feature of these models is that the conditional mean of the response given covariates and random effects, after transformed by a link function, is linearly related to the fixed covariate effects and random effects. Since this parametric assumption in GLMMs is strong and may not be appropriate for data with complex covariate effects, Lin and Zhang (1999) proposed generalized additive mixed models (GAMMs) that allow for flexible modeling of the covariate effects by replacing the linear predictor in GLMMs with an additive combination of nonparametric functions of covariates and random effects. Therefore, it is of practical importance to check the adequacy of the assumption for the parametric linear covariate effects.

In order to evaluate the adequacy of a parametric covariate effect in a regression model, one common approach is to cast the problem in the hypothesis testing framework. In practice, the resulting estimates of a nonparametric function is used as the alternatives for testing the adequacy of the parametric covariate effects. Brumback *et al.* (1999) showed that a nonparametric function estimated via penalized splines or smoothing splines has a mixed effects representation. An appealing feature of using the mixed effects representation is that one can cast the hypothesis test of parametric against nonparametric covariate effects as a variance component test. Zhang and Lin (2003) developed the variance component score test to construct a goodness-of-fit test of polynomial regression in semi parametric additive mixed models (SAMMs), a special case of GAMMs. Due to the special structure of the smoothing matrix, the distribution of statistic score is approximated by a scaled chi-squared distribution. Simulation studies showed that the score test is conservative and not very powerful for binary response.

For checking the adequacy of parametric covariate effects, Huang and Zhang (2008) have presented an overview on score test applied in the context of SAMMs. Their simulations indicate that the score test shows less performance for binary data. In this paper, we propose to use the technique of Monte Carlo (MC) tests in order to improve the test score, for small size sample. Indeed, we adapte MC test to solve the problem of control the power of score test. The MC approach allows us to introduce a new test that differs in two respects from the tests existing in the literature. First, the test is exact in the sense that the probability of rejecting the null hypothesis when it is true is always less than or equal to the nominal level of the test. Secondly, this approach allows to obtain exact randomized test using very small numbers of MC replications of the original test statistic under the null hypothesis. Finally, MC test is a reliable and easy instrument for testing

polynomial degree of non parametric function. So, the aim of this paper is to solve the problem of distortion of power of score test. By conducting simulations studies, we show that the MC technique can improve the power of test.

The paper is organized as follows. Section 1 introduces the SAMMs model. In Section 2, we describe the polynomial tests in SAMMs and we describe how exact MC tests can be implemented. In Section 3, we present the results from a small simulation study to compare the performance of the asymptotic score test and the MC test. The paper is concluded in Section 4 with some discussion.

2. THE MODEL SPECIFICATION

In this section, we briefly present SAMMs for clustered data, and this estimation procedure. These models are special cases of GAMMs considered by Lin and Zhang (1999). Let the data consist of a response variable y_{ij} for the j^{th} observation ($j = 1, \dots, n$) of the i^{th} cluster ($i = 1, \dots, N$), a scalar covariate x_{ij} , and a scalar covariate s_{ij} associated with fixed effects, and a scalar covariate z_{ij} associated with random effects. Conditional on a $(q, 1)$ vector of random effects b_i , the y_{ij} are assumed to be independent with conditional means $E(y_{ij}|b_i) = \mu_{ij}^b$ and conditional variances $\text{var}(y_{ij}|b_i) = \phi \varpi_{ij}^{-1} v(\mu_{ij}^b)$, where ϕ is a dispersion parameter, ϖ_{ij} is a known prior weight, and v is a variance function. The SAMM assumes that the conditional mean μ_{ij}^b takes this form:

$$(2.1) \quad g(\mu_{ij}^b) = s_{ij} \gamma + f(x_{ij}) + z_{ij} b_i ,$$

where γ is a fixed effect, $f(x)$ is an arbitrary smooth function and g is a known link function. b_i is a random effect associated with covariates z_{ij} . It is further assumed that the random effects b_i are independent and have a normal distribution $N(0, \sigma_b^2)$.

We propose to transforme the model (2.1) to fully parametric model where the unknown smoothing function $f(x_{ij})$ may be expressed as a linear combination of proper basis functions. We consider the truncated power basis usually used in this context, as by Ruppert *et al.* (2003) or Ngo and Wand (2004). A penalized linear spline model for (2.1) is

$$(2.2) \quad g(\mu_{ij}^b) = s_{ij} \gamma + \sum_{h=1}^H \delta_h x_{ij}^h + \sum_{k=1}^K a_k (x_{ij} - \kappa_k)_+ + z_{ij} b_i ,$$

where $\kappa_1, \dots, \kappa_K$ is a set of distinct knots in the range of x_{ij} and $x_+ = \max(0; x)$. The number of knots K is fixed and large enough (in this case $K = 40$) to ensure the exibility of the curve. The knots are chosen as quantiles of x with probabilities $1/(K+1), \dots, K/(K+1)$. We use truncated lines as the basis for regression since

their simple mathematical form is very useful in formulating complicated models. More complex basis such as B-splines and radial basis functions (with better numerical properties) could also be used.

Let Y, X, B and b denote the matrix obtained from stacking up the N subject-specific vectors of the same symbol. Also, let $Z = \text{diag}(Z_1, \dots, Z_N)$ and $a = (a_1, \dots, a_K)'$. Zhang and Lin (2003) suggested that a can be treated as random effects following $N(0, \tau I)$, so the model (2.2) is considered as a linear combination of the fixed effects β and the random effects a and b . Under this mixed-model representation of the smoothing spline estimator of f , the SAMM (2.1) can be written as the following GLMM:

$$(2.3) \quad g(\mu^b) = X\beta + Ba + Zb ,$$

where β is the fixed effect associated with covariates matrix X . The vector a is Normal $(0, \tau I)$, the independent random effect b is Normal $(0, \sigma_b^2)$. This GLMM representation takes the same form as that Lin and Zhang (1999) used for natural cubic spline estimators. For detailed justification of the estimation procedure, see Lin and Zhang (1999).

3. THE POLYNOMIAL TEST

3.1. Asymptotic score test

Zhang and Lin (2003) considered the problem of testing the nonparametric function $f(x)$ in model (2.1) being a h -order polynomial. They first estimated $f(x)$ by a h -order smoothing spline and expressed f with a mixed effects representation. Then, they tested if $f(x)$ is h order. Testing $f(x)$ in SAMM (2.1) being a h -order polynomial is equivalent to testing $H_0: \tau = 0$ in the induced GLMM in (2.3). Under the induced GLMM in (2.3), Zhang and Lin (2003) showed that the score U_τ for testing $H_0: \tau = 0$ takes the following form:

$$(3.1) \quad \begin{aligned} U_\tau(\hat{\psi}) &= \left. \frac{\partial l_M(\tau, \psi; y)}{\partial \tau} \right|_{\tau=0} \\ &= \frac{1}{2} \left\{ (y - X\beta)' V^{-1} B B' V^{-1} (y - X\beta) - \text{tr}(P B B') \right\} \Big|_{\beta=\hat{\beta}, \psi=\hat{\psi}} , \end{aligned}$$

where $\psi = (\sigma_b^2, \phi)$ is the nuisance parameter vector, and $l_M(\tau, \psi)$ is the marginal log likelihood function of τ and ψ (by integrating out random effects b and fixed effects β). $\hat{\beta}$ is the maximum likelihood estimator (MLE) of β and $\hat{\psi}$ is the restricted

maximum likelihood estimator (REML) of ψ , and $Y = X\beta + Zb + \Delta(y - \mu^b)$ is the working vector from the following null GLMM

$$(3.2) \quad g(\mu^b) = X\beta + Zb ,$$

where $\Delta = \text{diag}\{g'(\mu_{ij}^b)\}$, $W = \text{diag}\{\omega_{ij}\}$ is the working weight and $\omega_{ij} = \{\phi \varpi_{ij}^{-1} v(\mu_{ij}) [g'(\mu_{ij})]^2\}^{-1}$, $b \sim N(0, \sigma_b^2)$, $P = V^{-1} - V^{-1}X(X'V^{-1}X)^{-1}X'$ and $V = W^{-1} + ZDZ'$. W is working weight matrix evaluated at the conditional expectation μ^b and taken under the null hypothesis $\tau = 0$. One can use the existing software such as the R packages (glmmPQL) to obtain the estimates $\hat{\beta}$ and $\hat{\psi}$ by fitting the model (3.2).

Zhang and Lin (2003) showed that the null distribution of U_τ can be approximated by a scaled chi-squared distribution. A major problem in the score test context comes from the fact that applicable procedure rely heavily on asymptotic approximations whose accuracy can be quiet poor. This is evident from the study simulation reported in Zhang and Lin (2003). In any case, it is widely acknowledged that score asymptotic test is unreliable in finite sample, in the sense that the test was a little conservative and not very powerful. We reemphasize this fact and propose to use the technique of Monte Carlo test [Dwass (1957), Barnard (1963), Dufour and Khalaf (2002)] in order to obtain provably exact procedures.

3.2. Monte Carlo test

In this paper, we describe the MC test methodology for testing the polynomial degree of $f(x)$. In effect, it is possible to apply the test of MC because the statistic of score U_τ under the null distribution is a continuous pivotal function (its distribution does not depend on unknown parameter). Let U_0 denote the observed test statistic of score calculated on the basis of data observed. Then the critical region of a test with level α can be expressed as $G(U_0) \leq \alpha$ such as $G(U_0) = P(U \geq U_0/H_0)$ is the critical function for a right tailed test. $G(U_0)$ is unknown and it will be estimated by generating under null assumption M independent replications or exchangeable statistics U_1, \dots, U_M [see Dwass (1957) and Dufour *et al.* (1998)]. For the application of the technique of the tests of MC, we define

$$(3.3) \quad \hat{G}_M(U_0) = \frac{1}{M} \sum_{i=1}^M I_{[0, \infty)}(U_i - U_0) , \quad I_A(z) = \begin{cases} 1, & \text{if } z \in A, \\ 0, & \text{if } z \notin A. \end{cases}$$

In other words, $M\hat{G}_M(U_0)$ is the number of simulated statistics which are greater or equal to U_0 , $\hat{R}_M(U_0) = M - M\hat{G}_M(U_0) + 1$ gives the rank of U_0 among

the variables U_0, U_1, \dots, U_M . The estimated critical function is then given by this formula:

$$(3.4) \quad \hat{p}_M(U_0) = \frac{M\hat{G}_M(U_0) + 1}{M + 1} .$$

Thus the critical region of level α associated with a test MC is expressed by $\hat{p}_M(U_0) \leq \alpha$ such as $\hat{p}_M(U_0)$ represents the empirical probability that the value more superior than U_0 is realized if the null hypothesis is true. Hence $\hat{p}_M(U_0)$ may be viewed as a MC-value. Note that the MC decision rule may also be expressed in terms of $\hat{R}_M(U_0)$. Indeed the critical region $\frac{M\hat{G}_M(kU_0)+1}{M+1} < \alpha$ is equivalent to $\hat{R}_M(U_0) \geq (M + 1)(1 - \alpha) + 1$.

In other words, the MC test is significant at a 5% level if the rank of U_0 in the series U_0, U_1, \dots, U_M is at least equal to 96. If the null distribution of U_0 is nuisance-parameter-free and $\alpha(M + 1)$ is an integer, then the critical region is probably exact, in the sense

$$(3.5) \quad P\left[\hat{p}_M(U_0) \leq \alpha\right] = \alpha$$

or alternatively

$$(3.6) \quad P\left[\hat{R}_M(U_0) \geq (M + 1)(1 - \alpha) + 1\right] = \alpha .$$

The proof of the equation (3.5) and (3.6) is based on the theorem concerning the distribution of the ranks associated with a finite dimensional array of exchangeable statistics; see Dufour (2006) for more informations.

The determination of the Monte Carlo p-Value for the polynomial degree test to the model (2.1), is described as follows:

- Fit the model on original data set $Y^{(0)}$ and calculate the ML estimates $\hat{\beta}, \hat{\psi} = (\hat{\sigma}_b^2, \hat{\sigma}_\varepsilon^2)$ and $\hat{\tau}$.
- Obtain the score statistic based on $\hat{\psi}$ and denote it $U_\tau^{(0)}$.
- Treat $\hat{\psi}$ as fixed and fitted from the null model $g(\mu) = X\beta + Zb$ (under the null hypothesis $H_0: \tau = 0$ and $\psi = \hat{\psi}$), repeat the following steps for $m = 1, \dots, M$.
 - Draw the vector $\tilde{b}^{(m)}$ as i.i.d. $N(0, \hat{\sigma}_b^2)$ and the vector $\tilde{\varepsilon}^{(m)}$ as i.i.d. $N(0, \hat{\sigma}_\varepsilon^2)$.
 - Obtain the simulated independent variable $\tilde{Y}^{(m)} = X\beta + Z\tilde{b}^{(m)} + \tilde{\varepsilon}^{(m)}$ where $\tilde{Y} = X\beta + Ba + Zb + \Delta(y - \mu^b)$ is working vector, such as $\Delta = \text{diag}\{g'(\mu_{ij}^b)\}$.
 - Regress $\tilde{Y}^{(m)}$ on X and B (fit the model $g(\mu) = X\beta + Ba + Zb$ on simulated data set).

- Derive the score statistic test U_1, \dots, U_M associated with the regression of $\tilde{Y}^{(m)}$ on X and B .
- Obtain the rank $\hat{R}_M(U_0)$ in the series U_0, U_1, \dots, U_M .
- Reject the null $H_0: \tau = 0$ if $\hat{R}_M(U_0) \geq (M + 1)(1 - \alpha) + 1$.

Furthermore, a MC p-value may be obtained as $\hat{p}_M(U_0) = \frac{M+1-\hat{R}_M(U_0)}{M+1}$. We choose M so that $\alpha(M + 1)$ is an integer (for example, for $\alpha = 0.05$; we can take $M = 19; 39; 99\dots$).

MC test can be interpreted as a parametric bootstrap method applied to statistics whose null distribution does not depend on nuisance parameters. However the central additional observation is that the randomization allows one to exactly control the size of the test for a given (possibly small) number of MC simulations. For further discussion of Monte Carlo tests (including its relation with the bootstrap), Kiviet and Duffour (1997) and Dufour *et al.* (1998).

4. SIMULATION EXPERIMENTS

In order to assess the performance of two test procedures discussed above, we conduct a small simulation study. The performance of the polynomial test are evaluated and compared for clustered data with different types of responses and different magnitudes of correlation. For illustration purpose, we consider testing the linearity of covariate effects under the partially linear model framework, i.e. whether $f(x)$ is a linear function of x in model (2.1). Following the penalized spline, we formulate the asymptotic score test as variance component test based on the GLMM representation (2.3) as discussed above. In addition, for testing the same null hypothesis, we also formulate the Monte Carlo test which is exact in the sense that the probability of rejection the null hypothesis when is true is always less than or equal to the nominal size of the test. In our case, we are testing whether $f(x)$ is a 1-degree polynomial of x . Conditional on the cluster-specific random intercept $b_i \sim N(0, \sigma_b)$ with $\sigma_b = 0.5$ and $\sigma_b = 1$, independent Gaussian and Binary responses y_{ij} (for $i = 1, \dots, N$ and $j = 1, \dots, n$) were generated respectively under the model

$$(4.1) \quad g(\mu_{ij}) = \gamma_0 + s_{ij} \gamma_1 + f(x_{ij}) + b_i ,$$

where $g(\mu) = \mu$ for Gaussian response, and $g(\mu) = \text{logit}(\mu)$ for Binary responses. The scale parameter ϕ was estimated for Gaussian responses and was set to be one for Binary responses. Where s_{ij} is generated from Normal law $N(0, 0.1)$, x_{ij} is generated from Uniform law ($U[0, 1]$), the true values of γ_0 and γ_1 are taken to be $\gamma_0 = 1$ and $\gamma_1 = 2$; two sample sizes are used ($N = 2, n = 5$) and ($N = 4, n = 5$);

five different functions of $f(x)$ are considered:

$$f_c(x) = (0.25 c) x \cdot \exp(2 - 2x) - x + 0.5, \quad \text{for } c = (0, 1, 2, 3, 4) .$$

Note that when $c = 0$, $f_c(x)$ is a linear function of x and $f_c(x)$ deviates further from linearity with increasing c . The functions $f_c(x)$ are plotted in Figure 1.

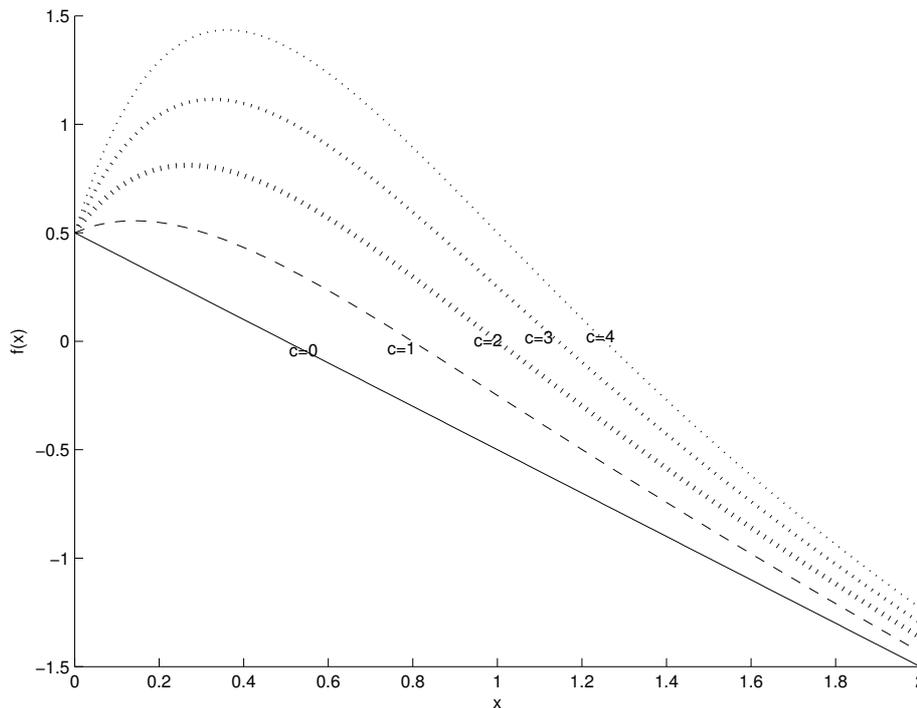


Figure 1: Functions $f_c(x)$ for $c = (0, 1, 2, 3, 4)$ used in the simulation studies for the polynomial test.

We apply the Asymptotic score (*Asy.Sco*) and the Monte Carlo (*MC.Sco*) testing procedures to each simulated data set. The simulation results are based on 1000 Monte Carlo simulation runs. For testing the null hypothesis that $f(x)$ is a linear function of x , the size and the power of each testing procedures are calculated by setting $c = 0$ and $c \neq 0$ respectively. We used a penalized spline to estimate $f(x)$, the number of knots for the penalized spline is set to be 40. The number of trials for the MC test was set to 19. The number of overall replications was 1000. All experiments were performed with language R (version 7.2.1). The simulation results are presented in the table 1 and 2, which report rejection percentages from 1000 replications at the nominal level 5% under the null hypothesis.

Table 1: Empirical sizes and powers of linearity test for two types of data where $N = 2$ and $n = 5$.

Variance random effect	Data Type	Test	Size		Powers		
			$c = 0$	$c = 1$	$c = 2$	$c = 3$	$c = 4$
$\sigma_b = 0.05$	Gaussian	<i>Asy</i>	0.055	0.178	0.624	0.934	0.995
		<i>MC</i>	0.051	0.211	0.645	1.000	1.000
	Binary	<i>Asy</i>	0.033	0.073	0.167	0.260	0.511
		<i>MC</i>	0.054	0.291	0.711	0.887	1.000
$\sigma_b = 1$	Gaussian	<i>Asy</i>	0.048	0.202	0.591	0.942	0.995
		<i>MC</i>	0.054	0.251	0.671	1.000	1.000
	Binary	<i>Asy</i>	0.040	0.068	0.120	0.271	0.442
		<i>MC</i>	0.061	0.125	0.741	0.910	1.000

Table 2: Empirical sizes and powers of linearity test for two types of data where $N = 4$ and $n = 5$.

Variance random effect	Data Type	Test	Size		Powers		
			$c = 0$	$c = 1$	$c = 2$	$c = 3$	$c = 4$
$\sigma_b = 0.05$	Gaussian	<i>Asy</i>	0.055	0.199	0.627	0.914	0.990
		<i>MC</i>	0.050	0.223	0.775	1.000	1.000
	Binary	<i>Asy</i>	0.047	0.095	0.211	0.310	0.621
		<i>MC</i>	0.052	0.325	0.812	0.970	1.000
$\sigma_b = 1$	Gaussian	<i>Asy</i>	0.045	0.207	0.603	0.922	0.995
		<i>MC</i>	0.050	0.304	0.789	1.000	1.000
	Binary	<i>Asy</i>	0.042	0.077	0.211	0.314	0.511
		<i>MC</i>	0.050	0.301	0.805	0.960	1.000

The results showed that the asymptotic score test for Binary responses was a conservative and not very powerful. The increased sample size brings the empirical sizes of the two tests closer to the nominal levels, whereas the variance component seems to have not much influence on them. These tests show decreased power where the variance component increases. Regarding the empirical size, our simulation results show that the linearity test with Monte Carlo is very performant for Gaussian responses for different magnitudes of the variance component. The empirical sizes were very close to the nominal size and the powers of the test were high, and were not significantly affected by the magnitude of the variance component. Indeed, the table 1 and 2 show that MC test achieves a perfect size control for Binary responses for different magnitudes of the variance component. As expected, the increased sample size improves the overall power.

In fact the simulation results show clearly that the technique of MC test correct size distortion due to poor large sample approximations. In general, our simulation indicates that the MC test is more powerful than the asymptotic score test. For simplicity, only the linearity test is considered in the current simulation; however in practice, one might be interested in testing higher-order polynomial covariate effects (i.e. $h > 1$), which can be easily carried out by using a different values of h .

5. DISCUSSION

We have reviewed in this paper a test procedure for testing whether the nonparametric function is some fixed-degree polynomial. The key idea is based on the mixed-effect representation of the natural spline estimator of the nonparametric function. Zhang and Lin (2003) developed score test and approximated its distribution by a scaled Chi-square distribution. For Binary data, the simulation studies show that the performance of the test is less satisfactory. This is mainly due to the less satisfactory performance of the Laplace approximation for the score statistic and the implicit Gaussian fourth-moment assumption when estimating the variance of the score statistic. We have hence proposed the simulation based procedures to derived exact p-value for polynomial test for SAMM. We have exploited the fact the score test is pivotal under the null hypothesis which allows one to apply the technique of MC tests.

The feasibility of our approach was illustrated trough a simulation experiment. The results show that asymptotic score test is unreliable for binary response in contrast MC test achieve perfect size control and have a good power. It is important to emphasis that MC procedure require less calculation with modern computer facilities. Zhang and Davidian (2004) have proposed a conditional estimation procedure built on likelihood inference for generalized additive mixed models. It is interesting for future research to extend our Monte Carlo test considering the conditional estimation procedure.

However, The score test is sensitive to outliers. Recently, Qin and Zhu (2008) focus on robust estimation of mean parameters of partial linear mixed model. They proposed to approximate the nonparametric function f by a regression spline and to estimate both the linear parameter and the spline coefficients by a M-estimator. It is interesting for future research to extend our Monte Carlo test considering the robust score test.

ACKNOWLEDGMENTS

The authors acknowledge helpful suggestions by the editor and the referees of this paper.

REFERENCES

- [1] BRESLOW, N.E. and CLAYTON, D.G. (1993). Approximate inference in generalized linear mixed models, *Journal of the American Statistical Association*, **88**, 9–25.
- [2] BARNARD, G.A. (1963). Comment on ‘The Spectral Analysis of Point Processes’ by M.S. Bartlett, *Journal of the Royal Statistical Society, Series*, **25**, 294.
- [3] BRUMBACK, BABETTE A.; RUPPERT, DAVID and WAND, M.P. (1999). Variable selection and function estimation in additive nonparametric regression using a data-based prior: Comment, *Journal of the American Statistical Association*, **94**, 794–7.
- [4] DUFOUR, J.-M. (2006). Monte Carlo tests with nuisance parameters: A general approach to finite-sample inference and nonstandard asymptotics, *Journal of Econometrics*, **133**(2), 443–477.
- [5] DUFOUR, J.-M. and KHALAF, L. (2002). Simulation based finite and large sample tests in multivariate regressions, *Journal of Econometrics*, **111**, 303–322.
- [6] DUFOUR, J.-M.; FARHAT, A.; GARDOL, L. and KHALAF, L. (1998). Simulation-based finite sample normality tests in linear regressions, *The Econometrics Journal*, **1**, 154–173.
- [7] DWASS, M. (1957). Modified randomization tests for nonparametric hypotheses, *Annals of Mathematical Statistics*, **28**, 181–187.
- [8] HUANG, M. and ZHANG, D. (2008). Testing polynomial covariate effects in linear and generalized linear mixed models, *Statistics Surveys*, **2**, 154–169.
- [9] QIN, G.Y. and ZHU, Z.Y. (2008). Robust estimation in partial linear mixed model for longitudinal data, *Acta Mathematica Scientia*, **28**, 334–348.
- [10] KIVIET, J.F. and DUFOUR, J.-M. (1997). Exact tests in single equation autoregressive distributed lag models, *Journal of Econometrics*, **80**, 325–353.
- [11] LAIRD, N.M. and WARE, J.H. (1982). Random effects models for longitudinal data, *Biometrics*, **38**, 963–974.
- [12] LIN, X. and ZHANG, D. (1999). Inference in generalized additive mixed models using smoothing splines, *Journal of the Royal Statistical Society*, **61**, 381–400.
- [13] NGO, L. and WAND, M.P. (2004). Smoothing with mixed model software, *Journal of Statistical Software*, **9**, 1–54.
- [14] RUPPERT, D.; WAND, M.P. and CARROLL, R.J. (2003). *Semiparametric Regression*, Cambridge University Press.

- [15] ZHANG, D. and DAVIDIAN, M. (2004). Likelihood and conditional likelihood inference for generalized additive mixed models for clustered data, *Journal of Multivariate Analysis*, **91**, 90–106.
- [16] ZHANG, D. and LIN, X. (2003). Hypothesis testing in semiparametric additive mixed models, *Biostatistics*, **4**, 57–74.
- [17] ZEGER, S.L. and KARIM, M.R. (1991). Generalized linear models with random effects; A Gibbs sampling approach, *Journal of the American Statistical Association* **86**, 413, 79-86.