Conditional Inference Functions for Mixed-Effects Models with Unspecified Random-Effects Distribution

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Current Challenges in Statistical Learning

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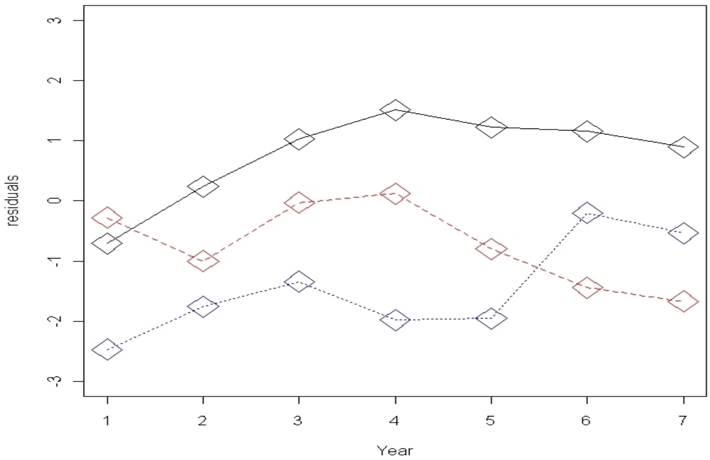
for Mathematical Innovation and Discovery

Motivating Example

- A longitudinal observational study, non-surgical periodontal treatment effect on tooth loss
- There are 722 subjects for 7-year follow up
- The main covariate: non-surgical periodontal treatment (1 or 0) for three years before the study
- Other covariates:
  - Gender
  - Age
  - Variables to measure teeth health condition
- There is subject-specific variation among subjects

A Graph of Longitudinal Data



Longitudinal Data

- Tooth loss and other covariates are recorded repeatedly over a 7-year period
- Measurements within the same subject are correlated
- Major approaches for correlated data:
  - Marginal models
  - Mixed-effects models

Marginal Models

- The inference of the population average is the main focus
- Generalized Estimating Equations (GEE) (Liang & Zeger, 1986); Quadratic Inference Functions (Qu et al., 2000):
  - Does not require likelihood function
  - Consistent even if the correlation structure is misspecified
  - Estimator is efficient with the correct working correlation
  - Provides robust sandwich variance estimator

Mixed Models

- There is heterogeneity among subjects
- Able to incorporate several sources of variation: random effects and serial correlation
- Limitations:
  - Requires parametric assumption for random effects, usually normality assumption
  - Involves high dimensional integration for non-normal random effects

Existing Methods for Generalized Linear Mixed-Effects Model

- Penalized quasilikelihood (PQL) (Breslow and Clayton, 1993)
- Hierarchical generalized linear model (HGLM) (Lee and Nelder, 1996, 2001)
- Conditional likelihood (Jiang, 1999)
- Conditional second-order generalized estimating equations (Vonesh et al., 2002)

Limitations and Assumptions

- Require normal assumption for random effects (PQL, second order GEE).
- Require estimation of variance components (PQL and conditional second order GEE).
- Do not incorporate serial correlation (PQL, HGLM and conditional likelihood).

Advantages of the Proposed Approach

- A new approach using the conditional quadratic inference function
- Does not require distribution assumption of random effects
- Does not require the likelihood function, only involves the first two moments
- Accommodates variations from both random effects and serial correlations
- Does not require estimation of unknown variance components or correlation parameters
- Challenge: the dimension of random effects parameters increases as the sample size increases

GEE

Generalized estimating equations (Liang & Zeger,1986) can be represented as

$$\sum_{i=1}^{N} \left(\frac{\partial \mu_i}{\partial \beta}\right)' A_i^{-1/2} R^{-1}(\alpha) A_i^{-1/2} (y_i - \mu_i) = 0,$$

where $y_i = (y_{i1}, ..., y_{it})$ is the response vector for the ith subject,
$\mu_i = E(y_i) = (\mu_{i1}, \ldots, \mu_{it})$ is the mean vector for the ith subject,
A_i is a diagonal matrix of variance components of y_i,
and $R(\alpha)$ is the working correlation

Representation of Correlation Matrix

- Approximate R^{-1} by $\sum_{j=1}^{m} a_j M_j$
  - $M_1, \ldots, M_m$ are known basis matrices
  - $a_1, \ldots, a_m$ are unknown constants
- The linear representation can accommodate most common working correlation structures such as AR-1, exchangeable or block diagonal

QIF Approach (Qu et al., 2000)

- GEE: $\sum_{i=1}^{N} \left(\frac{\partial \mu_i}{\partial \beta}\right)' A_i^{-1/2} R^{-1}(\alpha) A_i^{-1/2}(y_i - \mu_i) = 0$
- Substitute $R^{-1} \approx \sum_{j=1}^{m} a_j M_j$ into GEE,

$$g = \sum \dot{\mu_i}' A_i^{-1/2} (\sum_{j=1}^{m} a_j M_j) A_i^{-1/2} (y_i - \mu_i)$$

QIF Approach

- Define the extended score

$$\bar{G}_N(\beta) = \frac{1}{N}\sum g_i(\beta) = \frac{1}{N}\begin{pmatrix} \sum(\dot{\mu}_i)' A_i^{-1/2} M_1 A_i^{-1/2}(y_i - \mu_i) \\ \vdots \\ \sum(\dot{\mu}_i)' A_i^{-1/2} M_m A_i^{-1/2}(y_i - \mu_i) \end{pmatrix}$$

- The GEE is a linear combination of $\bar{G}_N(\beta)$
- The QIF estimator $\hat{\beta} = \arg\min \bar{G}_N' C_N^{-1} \bar{G}_N$, where $C_N = (1/N)\sum g_i(\beta) g_i'(\beta)$
- The QIF estimator $\hat{\beta}$ is more efficient than the GEE estimator under the misspecified correlation structure
- It provides an objective and inference function for model checking and testing

Mixed-Effects Model

A mixed effects model conditional on random effects b_i for longitudinal data is modeled as

$$E(y_{it}|x_{it}, b_i) = \mu(x_{it}'\beta + z_{it}'b_i), i = 1, ...N, t = 1, ..., n_i$$

- y_{it} is the response variable
- x_{it} are the covariates
- z_{it} are the covariates for random effects
- β are the fixed-effect parameters
- $b = (b_1, .., b_N)$ are the random-effects parameters, have the same order of dimension as the sample size

Penalized Conditional Quasilikelihood

- The conditional quasi-likelihood of y given the random effects b is $l_q^b = -\frac{1}{2\phi}\sum_{i=1}^{N} d_i(y_i, \mu_i^b)$, where $d_i(y,u) = -2\int_y^u \frac{y-u}{a_i v(u)} du$
- Require a constraint to ensure identifiability: $P_A b = 0$
- P_A is the projection matrix on the null space of $(I - P_X)Z$

Penalized conditional quasilikelihood (Jiang, 1999)

$$l_q = -\frac{1}{2\phi}\sum_{i=1}^{N} d_i(y_i, \mu_i^b) - \frac{1}{2}\lambda|P_A b|^2$$

- The penalty λ is fixed, and is chosen as 1 in Jiang (1999)
- Jiang's approach does not converge

Conditional Extended Score Corresponding for β and b

- Take the derivatives of the penalized conditional quasilikelihood l_q corresponding to β and b
- The quasi-score equation corresponding to the fixed effect β is

$$\sum_{i=1}^{N}(\frac{\partial \mu_i^b}{\partial \beta})'(\mathrm{W}_i^b)^{-1}(y_i - \mu_i^b) = 0.$$

- The quasi-score equation corresponding to the random effects b is

$$\left(\begin{array}{ccc} h_1 & = & (\frac{\partial \mu_1^{b_1}}{\partial b_1})'(\mathrm{W}_1^b)^{-1}(y_1 - \mu_1^{b_1}) - \lambda \frac{\partial P_A b}{\partial b_1} P_A b = 0 \\ & & \vdots \\ h_N & = & (\frac{\partial \mu_i^{b_N}}{\partial b_N})'(\mathrm{W}_N^b)^{-1}(y_N - \mu_N^{b_N}) - \lambda \frac{\partial P_A b}{\partial b_N} P_A b = 0 \end{array}\right)$$

Extended Score for β

- Construct extended scores associated with the fixed effect β

$$G_N^f = \frac{1}{N}\sum_{i=1}^{N} g_i^f(\beta) = \frac{1}{N}\begin{pmatrix} \sum_{\mathrm{i=1}}^{\mathrm{N}}(\frac{\partial\mu_{\mathrm{i}}^{\mathrm{b}}}{\partial\beta})'\mathrm{A}_{\mathrm{i}}^{-1/2}\mathrm{M}_1\mathrm{A}_{\mathrm{i}}^{-1/2}\left(\mathrm{y_i}-\mu_{\mathrm{i}}^{\mathrm{b}}\right) \\ \vdots \\ \sum_{\mathrm{i=1}}^{\mathrm{N}}(\frac{\partial\mu_{\mathrm{i}}^{\mathrm{b}}}{\partial\beta})'\mathrm{A}_{\mathrm{i}}^{-1/2}\mathrm{M}_{\mathrm{m}}\mathrm{A}_{\mathrm{i}}^{-1/2}\left(\mathrm{y_i}-\mu_{\mathrm{i}}^{\mathrm{b}}\right) \end{pmatrix}$$

- Conditional on b,

$$\hat{\beta} = \arg\min(\bar{G}_N^f)'(\bar{C}_N^f)^{-1}(\bar{G}_N^f)$$

where $\bar{C}_N^f = (1/N)\sum g_i^f(\beta)g_i^f(\beta)'$

Extended Score Corresponding to b

- For the ith subject, the quasi-score associated with the random effect:

$$h_i = (\frac{\partial \mu_i^{b_i}}{\partial b_i})'(\mathrm{W}_1^b)^{-1}(y_1 - \mu_1^{b_i}) - \lambda \frac{\partial P_A b}{\partial b_i} P_A b = 0$$

- Substitute $W_i = A_i^{\frac{1}{2}} R A_i^{\frac{1}{2}}$ and assume independent structure for R
- The extended score for the random effect b for subject i

$$g_i^r = \begin{pmatrix} (\frac{\partial \mu_i^{b_i}}{\partial b_i})' A_i^{-1}(y_i - \mu_i^{b_i}) \\ \lambda \frac{\partial P_A b}{\partial b_i} P_A b \end{pmatrix}$$

- In a simple random intercept model, $\frac{\partial P_A b}{\partial b_i} P_A b = \sum_{i=1}^N b_i / N$
- Jiang (1999) only considers the constraint for the random effect $P_A b = 0$
- This constraint is not sufficient to ensure algorithm convergence

Extended Score for b

- The convergence problem becomes more serious when there are high-dimensional random effects involved in the model
- We include an addditional penalty term λb_i which also controls the variance of the random effects estimators to ensure that the algorithm converges
- The new extended scores for b are

$$g^r = \left\{(g_1^r)', \lambda b_1', \ldots, (g_N^r)', \lambda b_N'\right\}'$$

- For given fixed effects β, $\hat{b} = \arg\min(g^r)'(g^r)$
- No replicate for each g_i^r, so there is no weighting matrix in the estimation

Regularity Conditions

- The parameter space S is compact
- There is a unique $\beta_0 \in S$ which satisfies $E[g(\beta_0|b_0)] = 0$
- The derivative of the score function $\dot{g}_{i,b}(\hat{\beta}|b_0) = O_p(1)$
- Expectation of the continuous score $E[g(\beta|b)]$ is continuous and differentiable in both β and b
- The weighting matrix $C_N(\beta|b) \rightarrow_{a.s.} C_0(\beta|b)$ and $A_N(\beta|b) \rightarrow_{a.s.} A_0(\beta|b)$, where $C_0^{-1}(\beta|b) = A_0(\beta|b)A_0(\beta|b)'$
- The estimating functions conditional on the estimated random effects converges to 0 in probability

$$E[E\{g_i(\beta_0|\hat{b})\}] \xrightarrow{p} 0 \quad \text{as } N \rightarrow \infty$$

- This condition is much weaker than the consistency for the random effects estimator

Asymptotic Properties

Theorem 1: Under some regularity conditions, the QIF estimator for the fixed effects $\hat{\beta}_1$ has the following properties as $N \to \infty$

I. (Consistency) $\hat{\beta}_1 \to_p \beta_0$.

II. (Asymptotic Normality) $\sqrt{N}(\hat{\beta}_1 - \beta_0) \xrightarrow{d} N(0, \Omega_1)$

Difficulties:

- No normality assumption for the random effects
- $\hat{b}$ is not required to be a consistent estimator for true b

III If $\hat{b}$ is a consistent estimator of b_0, then $\Omega_1 = \lim_{n,N\to\infty} \ddot{Q}^{-1}_{\beta\beta}(\hat{\beta}_1|\hat{b}) = \Omega_0$, where $\ddot{Q}^{-1}_{\beta\beta}(\hat{\beta}_1|\hat{b}) \approx \{\dot{G}_{N,\beta}(\hat{\beta}_1|\hat{b}) C_N^{-1}(\hat{b}) \dot{G}_{N,\beta}(\hat{\beta}_1|\hat{b})\}^{-1}$

Algorithm

- For a fixed λ, the iterative algorithms are
  1. Start with an initial estimator $\hat{\beta}$
  2. Given $\hat{\beta}$ as the fixed effects estimator, estimate the random effects by minimizing $(g^r)'(g^r)$, obtain random effects estimator $\hat{b}$
  3. Given random effect estimator $\hat{b}$ obtained in Step 2, update $\hat{\beta}$ by minimizing $(\bar{G}_N^f)'(\bar{C}_N^f)^{-1}(\bar{G}_N^f)$, iterate between Step 2 and 3 until convergence is reached
- The tuning parameter λ can be chosen by minimizing a BIC-type of criteria

$$N(\bar{G}_N^f)'(\bar{C}_N^f)^{-1}(\bar{G}_N^f) + (\log N)(P_A b)'\Sigma_b^{-1}(P_A b).$$

Handling Unbalanced Data

- For unbalanced longitudinal data, treat as missing data case
- Create the largest cluster with a size T which contains time points for all possible measurements
- Let T_i be the ith cluster size, define the $T \times T_i$ transformation matrix Λ_i
- By removing the columns of the identity matrix corresponding to the missing observations

Handling Unbalanced Data

- Define $y_i^* = \Lambda_i y_i$, $\mu_i^*(\tilde{\beta}) = \Lambda_i \mu_i(\tilde{\beta})$, and $\dot{\mu}_i^*(\tilde{\beta}) = \Lambda_i \dot{\mu}_i(\tilde{\beta})$
- Components in y_i^*, μ_i^* and $\dot{\mu}_i^*$ are the same as for the non-missing observations but are 0 for the missing components
- Let $A_i^* = \Lambda_i A_i \Lambda_i^T$ and $(A_i^*)^{-1} = \Lambda_i A_i^{-1} \Lambda_i^T$, the marginal variance A_i^* is 0 for the missing observations
- Assume that R is the common working correlation matrix for the fully observed responses
- The basis matrices $M_1, \ldots, M_m$ could still be used to model the inverse of the correlation matrix for all clusters
- The utilization for these basis matrices are different for different clusters
- After transformation, the cluster size of the unbalanced data becomes equal

Simulation Set-up for Binary Data

- Sample size: 100 ($i = 1, \ldots, 100$); cluster size: 4 or 5
- The conditional correlated binary outcomes are generated from

$$\text{logit}(\mu_i^b) = \beta_0 + b_{0i} + x_i(\beta_1 + b_{1i}),\ \texttt{corr}(y_i|x_i, b_{0i}, b_{1i}) = R$$

- The covariate x_i is generated from a uniform (0.5, 1.5), $\beta_0 = -0.3$, $\beta_1 = 0.3$
- Correlation structures: independent, exchangeable, or AR-1, correlation parameter $\rho = 0.7$
- Both random intercept b_{0i} and random slope b_{1i} are from a bimodal distribution of a rescaled Beta(0.5, 0.5)
- Apply mixed QIF with three types of working correlations, PQL, the SAS GLIMMIX and the NLMIXED

Results for Fixed-Effects β_0

Table: MSE for the estimator of the intercept $\beta_0 = -0.3$ for binary responses when $\rho = 0.7$ from 200 simulations.

Method	$N = 100$ True correlation		
	Independent	Exchangeable	AR-1
QIF (ind)	0.1464	0.1373	0.1298
QIF (exch)	0.1494	0.0762	0.1080
QIF (AR-1)	0.1499	0.0842	0.0802
PQL	0.1517	1.8556	0.6628
GLIMMIX (Ind)	0.1604[1]	1.0159	0.3912[2]
GLIMMIX (AR-1)	0.1713[3]	1.0616[4]	0.1226[5]
NLMIXED	0.1505[6]	1.1474	0.5126

Number of non-convergence outcomes from GLIMMIX and NLMIXED procedures are tabulated as follows: **1.** 173; **2.** 7; **3.** 174; **4.** 1; **5.** 174; **6.** 7.

Results for Fixed-Effects β_1

Table: MSE for the estimator of the intercept $\beta_1 = 0.3$ for binary responses when $\rho = 0.7$ from 200 simulations.

Method	$N = 100$ True correlation		
	Independent	Exchangeable	AR-1
QIF (ind)	0.1414	0.1072	0.0979
QIF (exch)	0.1425	0.0534	0.0732
QIF (AR-1)	0.1447	0.0578	0.0494
PQL	0.1451	1.1949	0.4354
GLIMMIX (Ind)	0.1445[1]	1.2468	0.3509[2]
GLIMMIX (AR-1)	0.1656[3]	1.2860[4]	0.0755[5]
NLMIXED	0.1448[6]	0.9600	0.3971

Number of non-convergence outcomes from GLIMMIX and NLMIXED procedures are tabulated as follows: **1.** 173; **2.** 7; **3.** 174; **4.** 1; **5.** 174; **6.** 7.

Results for Random-Effects of β_0

Table: Mean and the standard errors of the variance component estimator of β_0 for binary responses when $\rho = 0.7$ from 200 simulations. The true variance of the random intercept is 0.015

Method	$N = 100$ True correlation		
	Independent	Exchangeable	AR-1
QIF (ind)	$0.0051_{0.0000}$	$0.0153_{0.0000}$	$0.0133_{0.0000}$
QIF (exch)	$0.0051_{0.0000}$	$0.0154_{0.0000}$	$0.0133_{0.0000}$
QIF (AR-1)	$0.0051_{0.0000}$	$0.0154_{0.0000}$	$0.0134_{0.0000}$
PQL	$0.4602_{0.0706}$	$52.6074_{5.8626}$	$12.4455_{1.0486}$
GLIMMIX (Ind)	$0.0812^{\mathbf{1}}_{0.0043}$	$11.2695_{0.2750}$	$4.8532^{\mathbf{2}}_{0.0979}$
GLIMMIX (AR-1)	$0.1622^{\mathbf{3}}_{0.0084}$	$11.4377^{\mathbf{4}}_{0.3306}$	$0.5640^{\mathbf{5}}_{0.0313}$
NLMIXED	$0.0515^{\mathbf{6}}_{0.0067}$	$25.4358_{0.6391}$	$8.5088_{0.2236}$

Number of non-convergence outcomes from GLIMMIX procedures are tabulated as follows: **1.** 173; **2.** 7; **3.** 174; **4.** 1; **5.** 174; **6.** 7.

Results for Random-Effects of β_1

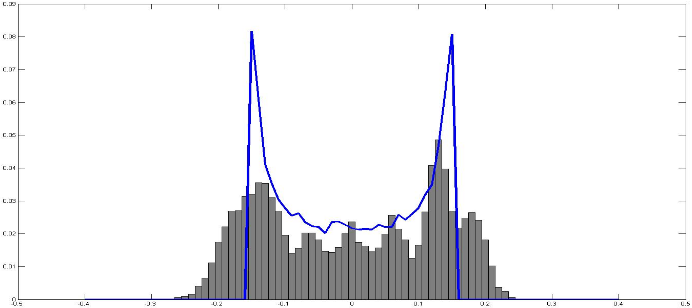
Table: Mean and the standard errors of the variance component estimator of β_1 for binary responses when $\rho = 0.7$ from 200 simulations. The true variance of the random intercept is 0.015

Method	$N = 100$ True correlation		
	Independent	Exchangeable	AR-1
QIF (ind)	$0.0073_{0.0000}$	$0.0262_{0.0000}$	$0.0212_{0.0000}$
QIF (exch)	$0.0073_{0.0000}$	$0.0263_{0.0000}$	$0.0213_{0.0000}$
QIF (AR-1)	$0.0073_{0.0000}$	$0.0263_{0.0000}$	$0.0213_{0.0000}$
PQL	$0.3573_{0.0592}$	$23.6498_{2.0657}$	$3.0542_{0.3737}$
GLIMMIX (Ind)	$0.0763^{\mathbf{1}}_{0.0049}$	$8.9704_{0.3339}$	$2.6071^{\mathbf{2}}_{0.1082}$
GLIMMIX (AR-1)	$0.0932^{\mathbf{3}}_{0.0063}$	$9.1258^{\mathbf{4}}_{0.3857}$	$0.2159^{\mathbf{5}}_{0.0136}$
NLMIXED	$0.0335^{\mathbf{6}}_{0.0060}$	$3.2856_{0.1699}$	$1.4055_{0.1175}$

Number of non-convergence outcomes from GLIMMIX procedures are tabulated as follows: **1.** 173; **2.** 7; **3.** 174; **4.** 1; **5.** 174; **6.** 7.

Distribution of the Random-Effect Estimators

Figure: Histogram of the random slope estimator from the binary data sets with $N = 100$ and $\rho = 0.7$. The true correlation structure of the data set is AR(1), and the estimators are obtained by the mixed-effect QIF method with AR(1) working correlation. The solid line provides the random-effects density function generated from the true Beta distribution.



A Binary Data Example

- An observational study, non-surgical periodontal treatment versus tooth loss
- 722 subjects, 7-year follow up
- Unbalanced data
- 550 (77%) patients have at least 5 years of follow up
- The response variable is tooth loss, a binary variable
- Apply a random-intercept model, the heterogeneity of patients is modeled as random effects
- To check whether the random-intercept model assumption is satisfied, the Chi-squared goodness-of-fit test (Qu et al., 2000) can be applied

Covariates

- Non-surgical periodontal treatment:
  - 1 if the patient continuously receives the treatment for all three years; and 0 otherwise
- Other covariates:
  - Gender
  - Age
  - Variables measuring the health condition of the teeth
    - Number of teeth (Teeth)
    - Number of diseased sites (Sites)
    - Mean pocket depth of diseased sites (Pddis)
    - Mean pocket depth of all sites (Pdall)
    - Number of non-periodontal treatments (Dent)
    - Number of non-periodontal preventive procedures (Prev)
    - Number of surgical treatments over the 3-year baseline period (Surg)
- The logistic model is

$$
\begin{aligned}
\texttt{logit}(\mu_{ij}^{b}) \quad = \quad & \beta_0 + b_i + \beta_1 \texttt{Gender}_{ij} + \beta_2 \texttt{Age}_{ij} + \beta_3 \texttt{Teeth}_{ij} + \beta_4 \texttt{Sites}_{ij} + \beta_5 \texttt{Pddis}_{ij} \\
& + \beta_6 \texttt{Pdall}_{ij} + \beta_7 \texttt{Surg}_{ij} + \beta_8 \texttt{Dent}_{ij} + \beta_9 \texttt{Prev}_{ij} + \beta_{10} \texttt{Nonsurg}_{ij}
\end{aligned}
$$

Comparison of PQL, QIF and GLIMMIX

Table: Comparison of the Mixed-Effect QIF and Other Approaches for the Periodontal Data

X	QIF_{ind}	QIF_{CS}	QIF_{AR}	PQL	GLMM_{ind}	GLMM_{AR}	NLM
Int	-7.1549	-7.4769	-8.1300	-8.0824	-9.3476	-9.5602	-6.8281
s.e.	1.3630	1.3476	1.3637	1.6265	1.7433	1.7804	1.5600
z-value	-5.2492	-5.5482	-5.9615	-4.9691	-5.3620	-5.3697	-4.3770
Gender	0.2257	0.2138	0.2409	0.2383	0.2317	0.2387	0.2526
s.e.	0.1522	0.1530	0.1589	0.1720	0.1766	0.1802	0.1588
z-value	1.4828	1.3974	1.5155	1.3865	1.3120	1.3246	1.5907
Age	0.0168	0.0175	0.0152	0.0202	0.0279	0.0291	0.0173
s.e.	0.0105	0.0104	0.0108	0.0123	0.0128	0.0131	0.0114
z-value	1.5948	1.6781	1.4072	1.6427	2.1772	2.2305	1.5109
Teeth	-0.0334	-0.0325	-0.0177	-0.0353	-0.0388	-0.0406	-0.0440
s.e.	0.0246	0.0241	0.0242	0.0271	0.2767	0.0282	0.0254
z-value	-1.3591	-1.3518	-0.7295	-1.3010	-1.4051	-1.4385	-1.7323
Sites	0.0024	0.0025	-0.0042	-0.0005	-0.0042	-0.0048	0.0032
s.e.	0.0097	0.0099	0.0090	0.0102	0.0105	0.0107	0.0098
z-value	0.2468	0.2555	-0.4684	-0.0524	-0.4029	-0.4440	0.3301

Cont'd

X	QIF_{ind}	QIF_{CS}	QIF_{AR}	PQL	GLMM_{ind}	GLMM_{AR}	NLM
Pddis	0.2689	0.3469	0.1948	0.2719	0.2944	0.2899	0.2587
s.e.	0.1864	0.1790	0.1904	0.2293	0.2370	0.2418	0.2124
z-value	1.4428	1.9377	1.0232	1.1866	1.2422	1.1989	1.2180
Pdall	0.4644	0.3960	0.7792	0.6425	0.8465	0.8885	0.4832
s.e.	0.3880	0.3946	0.3626	0.4200	0.4329	0.4423	0.4020
z-value	1.1968	1.0035	2.1489	1.5292	1.9554	2.0088	1.2020
Surg	-0.1377	0.0039	-0.1636	-0.0932	-0.1020	0.1304	-0.1087
s.e.	0.2741	0.2336	0.2863	0.2901	0.2019	0.2034	0.2790
z-value	-0.5024	0.0168	-0.5716	-0.3213	-0.5052	0.6411	-0.3896
Dent	0.1074	0.1132	0.1158	0.1205	0.1353	0.1365	0.1172
s.e.	0.0083	0.0082	0.0086	0.0080	0.0061	0.0061	0.0084
z-value	12.9164	13.8498	13.4963	15.0844	22.3636	22.4433	13.9126
Prev	0.0404	0.0271	0.0169	0.0353	0.0381	0.0395	0.0363
s.e.	0.1349	0.1353	0.1398	0.1500	0.0988	0.0990	0.1378
z-value	0.2992	0.2004	0.1207	0.2420	0.3856	0.3988	0.2636
Nonsurg	-0.2360	-0.2037	-0.2149	-0.2207	-0.1995	-0.2041	-0.2266
s.e.	0.1500	0.1504	0.1577	0.1767	0.1839	0.1876	0.1632
z-value	-1.5732	-1.3548	-1.3624	-1.2500	-1.0848	-1.0880	-1.3885

- In general, the standard errors of the conditional QIF are smaller than the PQL

Discussion

The advantages of the new approach:

- Incorporates both serial correlation from repeated measurements and heterogeneous variation from individuals
- Does not require the distribution assumption for random effects
- Does not require specifying the likelihood
- Does not need to estimate the unknown variance components or nuisance parameters associated with correlations

Discussion (Cont'd)

- Provides consistent and asymptotic normality for the fixed-effects estimator
- Outperforms the PQL, GLIMMIX, NLMIXED approaches when serial correlation is introduced, especially for binary response data
- Computationally fast even if the dimension of the random-effects parameters increases as the sample size increases
- GLIMMIX procedure tends to have a convergence problem

Thanks

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