Actual Correlation Structure Selection in Multivariate Models Associated with Repeated Measures: Applied on the Heart’s MRIT2* and Liver of Patients with Thalassemia

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Abstract: Proper selection of practical correlation structure in parameters estimation course with generalized estimating equations method (GEE) can decrease or eliminate bias meanwhile a high effectiveness. This method depends on correlation type, sample size, time intervals of measurements etc. While generalized estimating equations are not well defined, estimation of regression coefficients would be still consistent and asymptotically normal. Nevertheless, due to some reasons such as improvement of estimations efficiency, researchers are willing to apply practical correlation structure. Selecting a proper structure needs evaluating criterions corresponding to quasi-likelihood estimation. In recent years, various criterions have been presented for selecting a proper structure. However, the number of studies regarding the number of these criterions in applicable examples seems inadequate. The purpose of this study is to compare QIC, CIC, RJ1 and RJ2 criterions in determination of a proper practical correlation structure by bootstrap simulation method on data of T2-weighted magnetic resonance imaging (MRI T2*) test of heart and liver of thalasemic patients.

Key words: Criterions, Thalassemic, Bootstrap, Generalized estimating equation, Working correlation matrix

INTRODUCTION

In medical studies, one may confront with variables that need to be repeatedly measured while it seems that there may be a correlation between measured variables [1-4]. Such data require specific methods to be analyzed. Depend on the type of variables and the nature of study, one of the three models including random effect model, transition model and marginal model can be utilized [5,6]. The term “marginal model” is usually applied to describe a model which its response mean is determined by fixed effect covariates and also within-person correlation or the correlation during time is embedded in estimation methodology. When the outcomes are continuous and treat almost normally, linear models of mixed effect can be applied [7]. While for ordinal outcomes [8], the issue of discrete multivariate distribution undoes the extension of likelihood model based methods. Therefore, with the publication of the original article of Liang and Ziger [9], Generalized Estimation Equation (GEE) method has been considered for both continuous and discrete variables. These models can be regarded as an extension of generalized linear models (GLMs) for correlated outcomes. The method is based on quasi-likelihood estimation and is no need to fully detect multivariate distribution of iterative responses and just two first moments of...
outcome vectors are need to be given [10, 11]. Also it is not necessary to know the correlation structure of response variable. Beside, practical correlation structure should be given to obtain consistent and asymptotically normal distributions [12]. Selecting this practical correlation structure not only raise the effectiveness, but also decrease or eliminate the bias. So, trying to achieve a practical correlation matrix that is close as much as possible to the actual correlation matrix is essential. To this end, the analyzer needs a tool for making right decision. Utilizing the maximum likelihood method and its evaluating criterions is not conceivable in GEE models, thereby various criterions were presented for selecting a practical correlation structure in recent years [13, 14]. Rotnitzky and Jewell [15] have introduced a criterion named RJ criterion for determination of an actual practical correlation structure. Based on their results, a true correlation structure is a structure that its RJ criterion is close to 1. This quasi-log-likelihood under the independence model Information Criterion (QIC) was firstly suggested by Pan, considering the Akaike Information Criterion (AIC) [12]. This criterion is created by replacing the likelihood with quasi-likelihood and using marginal expectation of response variables, \( \hat{E}(y_i | x_i) = \mu_i \) is related to linear predictor by means of link function, \( g(\mu_i) = \eta_i = x_i \beta \) in which \( \beta \) is the \( p \times 1 \) vector of regression parameters and \( x_i \) is the \( p \)th row of \( X \). Secondly, the variance of each \( y_i \) provided by covariates can be depended on the mean value i.e. \( \text{var}(y_i) = \phi(\mu_i) \), while \( \phi \) is the scale parameter and \( \mu_i \) is the variance function. Estimating \( \beta \) in GEE is calculated by solving the estimator equation \[
\sum_{i=1}^{n} D_i(\phi(\mu_i))^{-1/2} R_i(\hat{\alpha}_i) A_i^{1/2} (\hat{y}_i - \mu_i) = 0
\] in which \( D_i = \hat{\phi}(\hat{\mu}_i) / \hat{\sigma}_i \) is the \( m_i \times m_i \) practical correlation matrix for \( y_i \) as a \( q \times 1 \) vector of unknown parameters, \( \alpha_i \), that is the same for all people and finally \( A_i = \text{diag}(\text{var}(\mu_i)) \).

Regarding that GEE is depended on both \( \hat{\beta} \) and correlation parameters and there is no specific solution for their estimation, it is imperative to repeat the process of two-stage estimation of \( \hat{\beta} \) and nuisance parameters (\( \alpha, \Phi \)). For this purpose, fisher scoring algorithm can be used [11].

Criteria for Checking the Matrices

RJ Criterion: If covariance and mean models in GEE are properly defined, it is expected that \( \hat{\Sigma}_{M(R)} \) and \( \hat{\Sigma}_{S(R)} \) are almost the same for large sample sizes. Rotnitzky and Jewell (1990) applied this issue and represented RJ criterion for practical correlation structure [15]. If practical correlation structure be well defined, \( \hat{\Sigma}_{S(R)} \approx \hat{\Sigma}_{M(R)}^{-1} \) in which \( \hat{\Sigma}_{M(R)} \) and \( \hat{\Sigma}_{S(R)} \) are estimation of \( p \times p \) covariance matrices, should be close to identity matrix. In other words, their assumed values, RJ1 and RJ2 must approach 1.

\[
RJ2 = \text{tr}((\hat{\Sigma}_{S(R)}^{-1} - \hat{\Sigma}_{M(R)}^{-1})^2) / p
\]
Quasi-log-likelihood under the Independence Model Information (QIC) Criterion: The purpose of selecting a model is to find the most coordinated model to the real one in a set of candidate models. The best model is usually chosen according to expectation difference value. This value assess the difference between the real model and the candidate one. Nonetheless, traditional criterions of model selecting like AIC can’t be used directly for selecting the correlation structure in GEE since these types of criterions are based on likelihood and full multivariate likelihood is not utilizable in GEE. Instead, this estimation is based on quasi-likelihood estimation. Pan (2001) has introduced a model to improve AIC as follows [12, 14, 17].

\[ QIC(R) = -2Q(\hat{\beta}(R); I, \Delta) + 2tr(\hat{\Sigma}_M^{-1} \hat{\Sigma}_S(R)) \]

In which \( Q(\beta; I, \Delta) \) demonstrates quasi-likelihood under independence assumption of the data of \( \Delta \) and \( \hat{\Sigma}_M^{-1} \) is a variance estimator that is based on under independence practical correlation model of IN and \( \hat{\Sigma}_S(R) \) is a sandwich variance estimator under practical correlation structure of \( R \).

Correlation Information Criterion (CIC) Criterion Hin et al. have offered using the second part of QIC for selecting the practical correlation structure in GEE [17]. This statistic is known as correlation information criterion (CIC).

\[ CIC = tr(\hat{\Sigma}_S(R) \hat{\Sigma}_M^{-1} \hat{\Sigma}_S(R)) \]

The first term in QIC, which is based on quasi-likelihood, is independent of both practical and actual correlation structures and thereby it does not contain any information about the correlation structure. Even if the second part is considered as a penalty for selecting average variable model, QIC is hardly affected by the first part.

The Study of Simulation: In this study, the functions of QIC, CIC, RJ1 and RJ2 under practical correlation structure of IN, EX, UN and AR-1 were evaluated. To compare the correlation matrices, the results of MRI T2* test of heart and liver in thalassemic patients in Sarvar polyclinic in Mashhad were used. For this purpose, the medical records of 61 patients, who at least experienced MRI twice, was investigated. Overall, 244 repeated outputs were generated by 61 thalassemic patients for response variable. Outputs of MRI T2* for heart and liver were two variables of this study which were measured two times. Yet, covariates including ferritin level, type of chelation therapy, the patient’s age at the time of MRI test, mean number of transfusion per year and history of splenectomy were used as modulators in this model. To implement the simulation, a program was written to determine the percentage of frequency of practical
correlation structures for any of the four aforementioned criterions in R software media. To perform GEE model, initially, geeglm and geegs processes in geepack package and quasiLik of MuMln package in R software (version 3) were utilized. Then, generated models were fitted for the data in bootstrap resampling method 1000 times independently for n=50, 100 and 250. Figure 1 represents the relative frequency of selecting the practical correlation structure for QIC, CIC, RJ1 and RJ2 criterions. As it can be seen in this chart, any criterion introduces a specific structure as the proper practical correlation structure. In the first chart (n=50), QIC criterion has selected EX structure as the proper structure for 538 cases of 1000 iterations. CIC criterion, with a relatively more decisiveness (0.791), introduced UN structure as a practical correlation structure. RJ1 and RJ2 criterions represented contrary results with assigning 541 to IN structure and 0.372 to AR-1 structure, respectively. Unlike other structures, indicates a progressive trend with observable, in Figure 1, AR-1 practical correlation structure increases about 37% under RJ1 criterion. Perhaps this criterion acts like its counterpart (RJ2) by enlarging the sample size. The third chart shows the results of simulations for n= 250. This chart represents a different state for QIC criterion under this criterion. IN structure is preferred by 146% growth, assigning 855 of repeated cases to itself. Stable behavior of the CIC criterion and the growing trend in the selection of the IN structure are evident. As expected, RJ1 separated itself from the IN structure selection in n=50 and with almost 40% growth in the frequency of AR-1, it showed a similar behavior as RJ2 did. Also, RJ2 criterion represented a tolerable stability by assigning 0.827 of iterative cases to AR-1.

Figure 2 shows the trend of allocation of frequency with sample size for four structures in different criterions of practical correlation structure. IN structure, unlike other structures, indicates a progressive trend with increasing the sample size. CIC criterion represents a stable trend. Based on this criterion, UN structure follows an ascending trend, while other three structures show descending trends. However, AR-1 and IN structures under RJ1 criterion indicate an inverse trend. In this criterion, enlarging the sample size results in exchanging the proper structure from IN to AR-1 structure. Although RJ2 criterion behaves almost stable, its not as stable as CIC criterion. This criterion, like its counterpart, introduces AR-1 structure as the proper structure.
DISCUSSION

In this study, the potency of different criterions in selecting the actual practical correlation structure was perused. Accordingly, using relative frequency; the proportion of any of criterions in determining the practical correlation was drawn. Then, the trend of these frequencies was calculated for three sample sizes.

The present study showed that QIC criterion treats differently depending on sample sizes. EX structure was chosen only for n= 50 under this criterion. Because the randomization is not possible over time and as expected the correlation is decreased by increasing the time between consecutive measurements. EX correlation structure is not profitable in longitudinal studies. However, it is considered as a proper selection for small sample sizes [14]. Hin et al. indicated that RJ criterion is more sensitive and less specific in determination of EX structure, compared to other criterions [13]. It seems that QIC criterion inclines to IN structure by enlarging the sample size. Barnet et al. (2010) indicated that QIC criterion acts poorly when UN practical correlation is in the set of candidate models [19].

In the present study, it was indicated that QIC criterion unlike the other three criterions decisively designates UN practical correlation as the proper one. By enlarging the sample sizes, CIC criterion believes that there is no correlation structure between iron overload of heart and liver in two measurements as well. The other structures under this criterion follow more stable trends. Based on a simulation study carried out by Hin and Wang, CIC criterion showed a considerable growth compared to QIC criterion in selecting the proper correlation structure [17]. However, Jang [14] indicated that UN structure is just applicable when the sample size is large enough; otherwise, estimation of the structure seems unreliable. When longitudinal data are seriously imbalanced or the sample size is small, it is better to use parsimonious model [14]. RJ1 criterion is inclined to select IN structure for smaller sample sizes. By enlarging the sample size in selecting AR-1 structure with changing the number of observations from 50 to 250, RJ2 seems more willing to select AR-1 structure by 120% growth. AR-1 structure is more appropriate especially when measurements are done in almost equal periods [14]. Inequality in time intervals of response value measurements in this study is one of the main reasons for RJ1 uncertainty to select this structure in the case of smaller sample sizes. Hin et al. showed that if AR-1 be the proper correlation, RJ criterion selects EX structure as the proper one in 50-71% of cases as well [13]. Liang et al. (1992) indicated that IN variance estimators under practical correlation were similar to estimators under correlation structure, although efficiency loss was not so considerable [20]. Fitzmaurice [21] expressed that efficiency loss caused by bad identification of practical correlation structures depends on both correlation value of responses and correlation value of covariate design matrix. In this study, the correlation between efficiency of practical correlation matrix and correlation value of response was not perused and therefore it seems desirable to evaluate this item as future studies.

REFERENCES