Diagnostic tools for a multivariate negative binomial model for fitting correlated data with overdispersion

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Abstract

We focus on the development of diagnostic tools and an R package called MNB for a multivariate negative binomial (MNB) regression model for detecting atypical and influential subjects. The MNB model is deduced from a Poisson mixed model in which the random intercept follows the generalized log-gamma (GLG) distribution. The MNB model for correlated count data leads to an MNB regression model that inherits the features of a hierarchical model to accommodate the intraclass correlation and the occurrence of overdispersion simultaneously. The asymptotic consistency of the dispersion parameter estimator depends on the asymmetry of the GLG distribution. Inferential procedures for the MNB regression model are simple, although it can provide inconsistent estimates of the asymptotic variance when the correlation structure is misspecified. We propose the randomized quantile residual for checking the adequacy of the multivariate model, and derive global and local influence measures from the multivariate model to assess influential subjects. Finally, two applications are presented in the data analysis section. The code for installing the MNB package and the code used in the two examples is exhibited in the Appendix.

keywords: Count data; Overdispersion; Multivariate negative binomial distribution; MNB package.

1 Introduction

Hierarchical models have been suggested for analyzing correlated count data due to their feature of allowing one to model the intraclass correlation and accommodate the occurrence of overdispersion simultaneously. This is handled through the inclusion of random effects in the systematic component of generalized linear models. Using this approach, it is possible to relax the assumption about the distribution of the random effects, taking into account the empirical distributions of the data or individual profiles (Lee et al. 2006, Molenberghs et al. 2007 and Fabio et al. 2012). Several methods have been proposed for inferential procedures in hierarchical models due to the intractable integrals involved in inference functions. The latter fact has been an obstacle in the development of diagnostic tools, leading to completely numerical
procedures being used. In such cases, a multivariate model deduced from the random effects approach (Molenberghs and Verbeke 2010) can be an alternative to a hierarchical model for fitting correlated count data with extra variability. Fabio et al. (2012) proposed the random intercept Poisson mixed regression model by assuming that the random effects follow a generalized log-gamma (GLG) distribution (Lawless 1987). This distribution can be skewed to the right or skewed to the left, with the normal distribution as a particular case. Thus, the random intercept Poisson-GLG model reduces to a multivariate negative binomial (MNB) model when it is assumed that the scale and shape parameters of the GLG distribution are equal. The random intercept of a Poisson-GLG model is able to accommodate intraclass correlation and handle overdispersion, due to the several degrees of asymmetry that the GLG distribution can assume. The MNB inherits these features, with the overdispersion parameter $\phi^{-1} = \lambda^2$ and simpler correlation structures. In the literature, the MNB regression (MNBR) model has been used for modeling correlated count data from several areas, for instance, health (Solis-Trapala and Farewell 2005), spatial (Moller and Rubak 2010) and economics (Sung and Lee 2018) data.

We focus on developing diagnostic tools and an R (R Core Team 2017) package for the MNBR model under overdispersion, which are essential for detecting outliers and for checking the adequacy of the model (Cook and Weisberg 1983). Simulation studies are also conducted to evaluate the asymptotic properties of the maximum likelihood (ML) estimator and to analyze how these properties are impacted on the random effect distribution misspecification. As noted in Solis-Trapala and Farewell (2005), the MNBR model can provide inconsistent estimates of the asymptotic variance of the regression coefficient when the covariance matrix of the random effect is misspecified. We use randomized quantile residuals (Dunn and Smyth 1996) for checking the adequacy of the MNBR model. Following Cook (1977, 1986) approach, global and local influence measures are developed from the MNBR model to detect influential subjects. These methodologies are useful to assess the impact on the estimation procedure by removing the subject from the data set and by proposing perturbation models, respectively. The total local influence measure suggested by Lesaffre and Verbeke (1998) is also extended for the MNBR model. These measures are helpful for identifying outlying subjects that matter in the MNBR model and interpret them according to the application. The inferences and diagnostic analysis from MNBR are performed by using the MNB package developed by the authors.

The paper is organized as follows: In Section 2 we provide some background about the MNBR model approach by Fabio et al. (2012). In Section 3 we discuss diagnostic analysis methodologies for the MNBR model. In Section 4 we perform a simulation study to evaluate the asymptotic behavior of the ML estimator. In Section 5 the diagnostic analysis is applied to two real data sets, using the MNB package. The code for installing the MNB package is presented in the Appendix. Finally, in Section 6 we provide some discussions.

## 2 MNBR model

Let $y_{ij}$ denote the $j$th measurement taken on the $i$th subject or cluster, for $j = 1, \ldots, m_i$ and $i = 1, \ldots, n$. Further, let $b_i$ be random effects that follow the GLG distribution (Lawless 2002). Assuming that $y_{ij} | b_i$ are independent outcomes with probability mass function represented by a Poisson distribution, Fabio et al. (2012) proposed a random intercept Poisson-GLG model with the following hierarchical structure: (i) $y_{ij} | b_i \iid \text{Poisson}(u_{ij})$, (ii) $u_{ij} = \mu_{ij} \exp(b_i)$, and (iii) $b_i \iid \text{GLG}(0, \sigma, \lambda)$, where $\mu_{ij} = \exp(\mathbf{x}_{ij}^\top \beta)$, with $\mathbf{x}_{ij} = (x_{ij1}, \ldots, x_{ijp})^\top$ containing the values of explanatory variables, $\beta = (\beta_1, \ldots, \beta_p)^\top$ the vector of regression coefficients, and $\sigma > 0$ and $\lambda \in \mathbb{R}$ the scale and shape parameters of the GLG distribution. In general, in the random effects approach, the marginal distribution of the $i$th subject does not have an explicit form
The ML estimates are obtained by integrating out the random effect and maximizing the log-likelihood function. Fabio et al. (2012) showed that the integral can be solved analytically when the scale and shape parameters of the GLG distribution are equal \((\sigma = \lambda, \text{ with } \lambda \in \mathbb{R}^+)\). When \(\phi = \lambda^{-2}\), the MNB distribution is deduced from the random intercept Poisson-GLG model of the following form:

\[
f(y_i; \beta, \phi) = \frac{\Gamma(\phi + y_{i+}) \phi^{\phi} \exp \left(\sum_{j=1}^{m_i} y_{ij} \log(\mu_{ij})\right)}{\left(\prod_{j=1}^{m_i} y_{ij}!\right) \Gamma(\phi) (\phi + \mu_{i+})^{\phi + y_{i+}}},
\]

where \(y_i = (y_{i1}, \ldots, y_{im_i})^T\) is the vector of measurements available for the \(i\)th subject, \(\phi\) is the dispersion parameter, \(\Gamma(\cdot)\) is the gamma function, \(y_{i+} = \sum_{j=1}^{m_i} y_{ij}\), and \(\mu_{i+} = \sum_{j=1}^{m_i} \mu_{ij}\). According to Johnson et al. (1997), the MNB distribution belongs to the discrete multivariate exponential family of distributions, and its marginals \(f(y_{ij})\) are negative binomial distributions with \(E(y_{ij}) = \mu_{ij}\) and \(\text{Var}(y_{ij}) = \mu_{ij} + \mu_{ij}^2/\phi\), for \(i = 1, \ldots, n\) and \(j = 1, \ldots, m_i\). The covariances \(\text{Cov}(y_{ij}, y_{i'j'}) = \mu_{ij}\mu_{i'j'}/\phi\) and intraclass correlations \(\text{Corr}(y_{ij}, y_{i'j'}) = \sqrt{\mu_{ij}\mu_{i'j'}/(\phi + \mu_{ij} \sqrt{\phi + \mu_{i'j'}})}\) for \(j \neq j'\) are always positive. When \(\phi^{-1}\) indicates the amount of excess correlation in the data (Hilbe 2011), the parameter \(\phi\) is also called an overdispersion parameter. For large values of \(\phi\), the marginals of the MNB distribution behave approximately as independent Poisson distributions with mean \(\mu_{ij}\). By \(y_i \sim \text{MNB}(\mu_i, \phi)\), we denote independent vectors of random outcomes that follow the probability function given in \(\ref{Molenberghs}\), with \(\mu_i = (\mu_{i1}, \ldots, \mu_{im_i})^T\) and \(\phi > 0\).

The MNBR model is defined by assuming (i) \(y_i \overset{\text{iid}}{\sim} \text{MNB}(\mu_i, \phi)\) and (ii) \(\log(\mu_{ij}) = x_{ij}^T \beta\). Letting \(y = (y_1^T, \ldots, y_n^T)^T\) be the vector containing all the measured outcomes for the \(i\)th subject, the log-likelihood function is given by

\[
\ell(\theta) = \sum_{i=1}^{n} \log \left\{ \frac{\Gamma(\phi + y_{i+})}{\Gamma(\phi)} \right\} - \sum_{i=1}^{n} \sum_{j=1}^{m_i} \log(y_{ij}!) \times n\phi \log(\phi) - \phi \sum_{i=1}^{n} \log(\phi + \mu_{i+}) + \sum_{i=1}^{n} \sum_{j=1}^{m_i} y_{ij} \log \left( \frac{\mu_{ij}}{\phi + \mu_{i+}} \right),
\]

where \(\theta = (\beta^T, \phi)^T\). The ML estimates \(\hat{\theta}\) of \(\theta\) are computed by using the quasi-Newton (BFGS) method. Alternatively, we can solve the nonlinear equation obtained by setting the components of the score vector equal to zero, that is, \(U_\theta = (U_{\beta}^T, U_{\phi})^T = 0\) (details about the calculations are in the Appendix). For interval estimation and hypothesis tests on the model parameters, the expected or observed Fisher information is required. Under standard regularity conditions, \(\hat{\theta} - \theta\) is asymptotically distributed as a multivariate normal distribution with mean \(0\) and covariance matrix equal to the inverse of the Fisher information matrix of the MNBR model (see Fabio et al. 2012).

3 Diagnostic analysis

This section is devoted to diagnostic tools for the MNBR model. In what follows, we will discuss the residual analysis, and the global and local influence methodologies.

3.1 Residual analysis

Let \(y_i = (y_{i1}, y_{i2}, \ldots, y_{im_i})^T\) be a random vector that follows a MNB distribution. According to Tsui (1986), the distribution of \(y_{i+} = \sum_{j=1}^{m_i} y_{ij}\) is negative binomial with probability
distribution function given by
\[ f(y_{i+}) = \frac{\Gamma(y_{i+} + \phi)}{(y_{i+})! \Gamma(\phi)} q^\phi (1 - q)^{y_{i+}}, \quad y_{i+} = 0, 1, 2, \ldots, \]

where \( q = \phi / (\phi + \mu_{i+}) \). Then, the randomized quantile residuals \( \{\text{Dunn and Smyth} 1996\} \), which follow a standard normal distribution, can be used to assess departures from the MNBR model. If \( F(y_{i+}; \mu, \phi) \) is the cumulative distribution of \( f(y_{i+}) \), \( a_i = \lim_{y \to y_{i+}} F(y; \hat{\mu}_i, \hat{\phi}) \), and \( b_i = F(y_{i+}; \hat{\mu}_i, \hat{\phi}) \), then the randomized quantile residuals for \( y_i \) are given by \( r_{q,i} = \Phi^{-1}(u_i) \), where \( \Phi(\cdot) \) is the cumulative distribution function of the standard normal and \( u_i \) is a uniform random variable on the interval \((a_i, b_i)\).

### 3.2 Global influence

Based on the case-deletion approach \( \{\text{Cook} 1977\} \), we propose the generalized Cook’s distance as a global influence measure to assess the impact on the ML estimates of the MNBR model when the \( i \)th subject (or cluster) is removed from the data set. Let \( y_{(i)} \) be a vector of random outcomes after deleting the \( i \)th subject. Let \( \hat{\theta}(i) \) be the ML estimate of \( \theta \) computed from \( \ell(i)(\theta) \), where \( \ell(i)(\theta) \) is obtained from (2) after removing the \( i \)th subject. The generalized Cook’s distance is defined as the standardized norm of the distance between \( \hat{\theta}(i) \) and \( \hat{\theta} \), given by the expression
\[ GD_i(\theta) = (\hat{\theta}(i) - \hat{\theta})^\top [\ell_{\theta\theta}]^{-1} (\hat{\theta}(i) - \hat{\theta}), \]

where \( \ell_{\theta\theta} \) (see the Appendix) is the Fisher information matrix of the MNBR model. Large values of \( GD_i \) indicate that the ML estimates are strongly influenced by deleting the \( i \)th subject.

Another popular measure of the difference between \( \hat{\theta}(i) \) and \( \hat{\theta} \) is the likelihood displacement given by \( LD(i)(\theta) = 2\{\ell(\hat{\theta}) - \ell(\hat{\theta}_i)\} \).

### 3.3 Local influence

The local influence methodology was proposed by \( \{\text{Cook} 1986\} \) for assessing the sensitivity of the parameters estimated when small perturbations are introduced in the model. Consider the perturbation vector \( \omega = (\omega_1, \ldots, \omega_v)^\top \), varying in some open subset \( \Omega \subset \mathbb{R}^v \). Let \( \ell(\theta|\omega) \) denote the log-likelihood function of the perturbed model. It is assumed there exists \( \omega_0 \in \Omega \) such that \( \ell(\theta|\omega_0) = \ell(\theta) \) for all \( \theta \). The influence of the minor perturbation on the ML estimate \( \hat{\theta} \) may be assessed by the likelihood displacement \( LD(\omega) = 2\{\ell(\hat{\theta}) - \ell(\hat{\theta}_0)\} \), where \( \hat{\theta}_0 \) denotes the ML estimate from the perturbed model. A plot of \( LD(\omega) \) versus \( \omega \) contains essential information about the influence of the perturbation scheme. Cook’s idea consists of selecting a unit direction \( d \) and evaluating the plot \( LD(\omega_0 + ad) \), where \( a \in \mathbb{R} \). This plot is called a lifted line, and each fitted line can be obtained by considering the normal curvature defined by \( C_d(\theta) = 2[d^\top \Delta^\top \ell_{\theta\theta}^{-1} \Delta d] \) around \( a = 0 \), where \( \ell_{\theta\theta} = \partial^2 \ell(\theta)/\partial \theta \partial \theta^\top \) is evaluated at \( \hat{\theta} \) and \( \Delta = \partial^2 \ell(\theta|\omega)/\partial \theta \partial \omega^\top \) is evaluated at \( \hat{\theta} \) and \( \omega_0 \). Large values of \( C_d(\theta) \) indicate the sensitivity induced by perturbation schemes in direction \( d \). Cook \( \{1986\} \) suggests the local influence measure \( C_{d_{\text{max}}}(\theta) \), evaluated in the direction \( d_{\text{max}} \) corresponding to the eigenvector with maximal normal curvature. If the \( i \)th component of \( d_{\text{max}} \) is relatively large, this indicates that perturbations may lead to substantial changes in the ML estimates. Based on this approach, Lesaffre and Verbeke \( \{1998\} \) suggested the total local curvature corresponding to the \( i \)th element. This local influence measure is obtained by taking the direction \( d_i \), an \( n \times 1 \) vector of zeros with a 1 in the \( i \)th position. The total local curvature in direction \( d_i \) assumes the form \( C_i(\theta) = 2[\Delta_i^\top \ell_{\theta\theta}^{-1} \Delta_i] \), where \( \Delta_i = \partial^2 \ell_i(\theta|\omega)/\partial \theta \partial \omega^\top \) denotes the \( i \)th row of \( \Delta \), such that \( \ell_i(\theta|\omega) \) is the contribution
of the \( i \)th individual to the log-likelihood function. \( \Delta \) is evaluated at \( \hat{\theta} \) and \( \omega_0 \), and it is recommended to look at the index plot of \( C_i(\theta) \) to assess influential subjects. Usually, in the literature, three types of perturbation schemes are considered for count data: case weights, explanatory variable, and dispersion parameter perturbation schemes.

**Case weights perturbation for the \( i \)th subject**

The log-likelihood function of the perturbed model takes the form

\[
\ell(\theta|\omega) = \sum_{i=1}^{n} \omega_i \left\{ \log \left( \Gamma(\phi + y_{i+}) \right) - \log \left( \Gamma(\phi) \right) - \frac{1}{m_i} \log(y_{ij}!) + \phi \log(\phi) \right. \\
- \phi \log(\phi + \mu_{i+}) + \sum_{j=1}^{m_i} y_{ij} \log(\mu_{ij}) - \left. \sum_{j=1}^{m_i} y_{ij} \log(\phi + \mu_{i+}) \right\}.
\]

The \( \Delta \) matrix in \( C_q(\theta) \) is given by \( \Delta^T = (\Delta_\beta^T, \Delta_\phi^T)^T \), with \( \Delta_\beta^T = (\Delta_{\beta_1}, \Delta_{\beta_2}, \ldots, \Delta_{\beta_p}) \) and \( \Delta_{\beta_k} = (\Delta_{k1}, \Delta_{k2}, \ldots, \Delta_{ki}, \ldots, \Delta_{kn}) \), where

\[
\Delta_{ki} = \sum_{j=1}^{m_i} \left\{ y_{ij} \left[ \frac{\hat{\phi} + y_{i+}}{\hat{\phi} + \mu_{i+}} \right] \exp(x_{ij}^\top \hat{\beta}) \right\} x_{ijk} = \sum_{j=1}^{m_i} (y_{ij} - \hat{\alpha}_i \hat{\mu}_{ij}) x_{ijk},
\]

and \( \Delta_\phi = (\Delta_{\phi1}, \Delta_{\phi2}, \ldots, \Delta_{\phi1}, \ldots, \Delta_{\phi n}) \), with

\[
\Delta_{\phi i} = \psi(\hat{\phi} + y_{i+}) - \psi(\hat{\phi}) + \log \left( \frac{\hat{\phi}}{\hat{\phi} + \mu_{i+}} \right) + \left( \frac{\mu_{i+} - y_{i+}}{\hat{\phi} + \mu_{i+}} \right),
\]

where \( \psi(\cdot) \) is the digamma function, \( \hat{\mu}_{i+} = \sum_{j=1}^{m_i} \hat{\mu}_{ij} \), and \( \hat{\mu}_{ij} = \exp(x_{ij}^\top \hat{\beta}) \), for \( j = 1, \ldots, m_i \) and \( i = 1, \ldots, n \).

**Case weights perturbation for the \( j \)th measurement of the \( i \)th subject**

For this perturbation scheme, the log-likelihood function can be expressed as

\[
\ell(\theta|\omega) = \sum_{i=1}^{n} \sum_{j=1}^{m_i} \omega_{ij} \left\{ \frac{1}{m_i} \log \Gamma(\phi + y_{i+}) - \frac{1}{m_i} \log \Gamma(\phi) - \log(y_{ij}!) \right. \\
+ \frac{1}{m_i} \phi \log(\phi) - \frac{1}{m_i} \phi \log(\phi + \mu_{i+}) + y_{ij} \log(\mu_{ij}) - y_{ij} \log(\phi + \mu_{i+}) \left\}.
\]

The matrix \( \Delta = (\Delta_\beta^T, \Delta_\phi^T)^T \), in which element \( ij \) of \( \Delta_\beta^T \) and \( \Delta_\phi^T \), respectively, is given by

\[
\Delta_{kij} = y_{ij} x_{ijk} - \frac{\hat{\phi}/m_i + y_{ij}}{\hat{\phi} + \hat{\mu}_{i+}} \sum_{j=1}^{m_i} \hat{\mu}_{ij} x_{ijk}, \quad k = 1, \ldots, p \quad \text{and}
\]

\[
\Delta_{\phi ij} = \frac{1}{m_i} (\psi(\hat{\phi} + y_{i+}) - \psi(\hat{\phi})) + \frac{1}{m_i} (1 + \log(\hat{\phi}) - \log(\hat{\phi} + \hat{\mu}_{i+})) \\
- \frac{\hat{\phi}/m_i + y_{ij}}{\hat{\phi} + \hat{\mu}_{i+}}.
\]
Explanatory variable perturbation

We now consider an additive perturbation on a particular continuous explanatory variable, \( x_{ijk}, j = 1, \ldots, m_i, i = 1, \ldots, n, k = 1, \ldots, p \), by setting \( x_{ijk}^* = x_{ijk} + \omega_i S_x \), where \( S_x \) is a scale factor and \( \omega_i \in \mathbb{R} \). This perturbation scheme leads to the following expression for the log-likelihood function:

\[
\ell(\theta|\omega) = \sum_{i=1}^{n} \left\{ \log \left( \Gamma(\phi + y_{i+}) \right) - \log \left( \Gamma(\phi) \right) - \sum_{j=1}^{m_i} \log(y_{ij}) + \phi \log(\phi) \right. \\
- \phi \log(\phi + \mu_{i+}) + \sum_{j=1}^{m_i} y_{ij} \log(\mu_{ij}^*) - \sum_{j=1}^{m_i} y_{ij} \log(\phi + \mu_{i+}^*) \right\},
\]

where \( \mu_{i+}^* = \sum_{j=1}^{m_i} \mu_{ij}^*, \mu_{ij}^* = \exp(x_{ij}^T \beta), \ x_{ij}^T \beta = \beta_1 + \beta_2 x_{ij2} + \cdots + \beta_k (x_{ijk} + \omega_i S_x) + \cdots + \beta_p x_{ijp} \), and \( \omega_0 = (0, \ldots, 0)^T \). For \( k = 1, \ldots, p \), if \( t = k \), \( \Delta_t \) is given by

\[
\Delta_t = \frac{\hat{\beta}_t S_x \phi \exp(x_{ij}^T \hat{\beta})}{\phi + \hat{\mu}_{i+}} \left( 1 - \frac{\hat{\mu}_{i+}}{\phi + \hat{\mu}_{i+}} \right) x_{ijt} + \frac{S_x \exp(x_{ij}^T \hat{\beta})}{\phi + \hat{\mu}_{i+}} \sum_{j=1}^{m_i} y_{ij} \left[ S_x + \left( \beta_t S_x - \frac{1}{\hat{\mu}_{ij}} \right) x_{ijt} \right] + \sum_{j=1}^{m_i} y_{ij} \exp(x_{ij}^T \hat{\beta}) \phi + \hat{\mu}_{i+} \\
\times \left[ S_x + (\beta_t S_x - 1) x_{ijt} \right].
\]

If \( t \neq k \),

\[
\Delta_t = \frac{\hat{\beta}_t S_x \phi \exp(x_{ij}^T \hat{\beta})}{\phi + \hat{\mu}_{i+}} \left( 1 - \frac{\hat{\mu}_{i+}}{\phi + \hat{\mu}_{i+}} \right) x_{ijt} + \sum_{j=1}^{m_i} y_{ij} x_{ijt} \left[ \beta_t S_x - \frac{1}{\hat{\mu}_{ij}} \right] + \sum_{j=1}^{m_i} \frac{\exp(x_{ij}^T \hat{\beta})}{\phi + \hat{\mu}_{i+}} y_{ij} x_{ijt},
\]

and the \( i \)th element of \( \Delta^T_{\phi} \) is

\[
\Delta_{\phi_i} = \frac{\hat{\beta}_t S_x \phi \hat{\mu}_{i+}}{\phi + \hat{\mu}_{i+}} \left( \frac{\phi}{\phi + \hat{\mu}_{i+}} - 1 \right) + \hat{\beta}_t S_x \sum_{j=1}^{m_i} \frac{y_{ij} \mu_{i+}}{(\phi + \hat{\mu}_{i+})^2}.
\]

Dispersion parameter perturbation

Let \( \phi^*_i = \omega_i \times \phi \) be the dispersion parameter perturbation, where \( \omega_i \in \mathbb{R}^+ \). The log-likelihood function of the perturbed model takes the form

\[
\ell(\theta|\omega) = \sum_{i=1}^{n} \left\{ \log \left( \Gamma(\phi^*_i + y_{i+}) \right) - \log \left( \Gamma(\phi_i^*) \right) - \sum_{j=1}^{m_i} \log(y_{ij}) + \phi_i^* \log(\phi_i^*) \right. \\
- \phi_i^* \log(\phi_i^* + \mu_{i+}) + \sum_{j=1}^{m_i} y_{ij} \log(\mu_{ij}) - \sum_{j=1}^{m_i} y_{ij} \log(\phi_i^* + \mu_{i+}) \right\}.
\]
\[ \Delta = (\Delta_\beta, \Delta_\phi)^T \], where the \( i \)-th elements of \( \Delta_\beta \) and \( \Delta_\phi \), respectively, are given by

\[
\Delta_{\beta_i} = \frac{\hat{\phi}_i^s \mu_{i+}(y_{ij} - \hat{\mu}_{i+})}{(\hat{\phi}_i^s + \hat{\mu}_{i+})^2} x_{ijk} \quad \text{and} \\
\Delta_{\phi_i} = \psi(\hat{\phi}_i^s + y_{i1}) - \psi(\hat{\phi}_i^s) + \frac{\hat{\mu}_{i+} \psi'(\hat{\phi}_i^s + y_{i1})}{(\hat{\phi}_i^s + \hat{\mu}_{i+})^2} + 1 \\
+ \log \left( \frac{\hat{\phi}_i^s}{\hat{\phi}_i^s + \hat{\mu}_{i+}} \right) + \frac{\hat{\mu}_{i+}}{\hat{\phi}_i^s + \hat{\mu}_{i+}} + \frac{y_{i1} + \hat{\mu}_{i+}}{(\hat{\phi}_i^s + \hat{\mu}_{i+})^2} + \frac{\hat{\phi}_i^s (2 \hat{\mu}_{i+} + \hat{\phi}_i^s)}{(\hat{\phi}_i^s + \hat{\mu}_{i+})^2}.
\]

For all the perturbation schemes, the \( \bar{\ell}(\theta) \) matrix in \( C_d(\theta) \) is described in the Appendix.

### 4 Numerical results

First, a simulation study is conducted to evaluate the asymptotic behavior of the ML estimator, \( \hat{\theta} \). The vector \( y = (y_1^T, \ldots, y_n^T)^T \), where \( y_i \sim \text{MNBR}(\mu, \phi) \), is generated from a random intercept Poisson-GLG model with \( (i) \) \( y_{ij} | b_i \sim \text{Poisson}(u_{ij}) \), \( (ii) \) \( \log(u_{ij}) = \beta_0 + \beta_1 x_{i1j} + \beta_2 x_{i2j} + b_i \), and \( (iii) b_i \sim \text{GLG}(0, \lambda, \lambda) \), where \( x_{i1j} \sim N(0,1) \) and \( x_{i2j} \) is a dummy variable with two levels, for \( i = 1, \ldots, n \) and \( j = 1, 2, 3 \). Further, it is assumed that \( \beta = (1.5, 1.0, 0.0)^T \) and \( \lambda = \phi^{-1/2} \) in the GLG distribution. The Bias, root mean square error (RMSE) and coverage probabilities for the 95% confidence level are obtained from \( R = 10,000 \) Monte Carlo replications performed for a sample size of \( n = 50, 100, 150, \) and \( 200 \) and for three different values of the dispersion parameter, namely, \( \phi = 3, 5 \) and \( 7 \). The estimates of the Bias and RMSE for \( \theta \) are obtained from:

\[
\text{Bias}(\theta_s) = \bar{\theta}_s - \theta_s \quad \text{and} \quad \text{RMSE}(\theta_s) = \sqrt{\frac{\sum_{r=1}^{R} (\bar{\theta}_s^{(r)} - \theta_s)^2}{R}},
\]

where \( \bar{\theta}_s = \frac{1}{R} \sum_{r=1}^{R} \bar{\theta}_s^{(r)} \) and \( \bar{\theta}_s^{(r)} \) is the estimate from \( r \)-th parameter obtained in \( r \)-th Monte Carlo replication. These simulation results are presented in Table 1. As expected, the Bias and RMSE values of the regression coefficients estimates decrease as the sample size and values of the \( \phi \) parameter increase. The coverage probabilities are close to 0.95. Moreover, the results show that the dispersion parameter exhibits a desirable asymptotic behavior when \( \phi \) assumes small values. Since \( \phi = \lambda^{-2} \), it is possible to affirm that the asymptotic properties of the dispersion parameter estimator are associated with the asymmetry of the GLG distribution. A second simulation study is performed to evaluate the impact of misspecifying the random effect distribution on the ML estimates of the MNBR model. It is assumed that the random intercept is normally distributed and negatively correlated. For sample size \( n = 50, 100, \) and \( 150 \), the vector \( y = (y_1^T, \ldots, y_n^T)^T \) is generated from a random intercept Poisson-Normal distribution with the following hierarchical structure:

\[
(i) \ y_{ij} | b_i \sim \text{Poisson}(u_{ij}), \quad (ii) \ \log(u_{ij}) = \beta_0 + \beta_1 x_{i1j} + b_i \quad \text{and} \quad (iii) b_i \sim \text{N}(0, \sigma^2), \quad \sigma^2 = \phi^{-1}
\]

and \( \phi^{-1} = 4.0 \). In Table 2, we present the Bias and root mean square error (RMSE), calculated by fitting the MNBR model on 1,000 Monte Carlo replications for different sample sizes. Based on the assumption that \( b_i \sim \text{N}(0, \sigma^2) \), we observe that the parameter estimates of \( \phi \) and \( \beta_0 \) are biased. To summarize, we conclude that the MNBR model provides inconsistent estimates of the asymptotic variance of the ML estimators when the covariance matrix of the random effect is misspecified.
A third simulation study is conducted to evaluate the variance-to-mean ratio, VMR = Var(\(y\))/E(\(y\)). Considering three different values for the dispersion parameter, \(\phi = 0.1\), 1.0 and 50, random samples are generated and the VMR statistic are computed. The ranges to VMR, for each value of \(\phi\), are (122.39, 220.24), (19.38, 29.35) and (5.85, 16.87), respectively. In the Table 3, we reported the bias, RMSE and coverage of the confidence intervals. As expected, Table 3 shows that the ML estimates present a desirable asymptotic behavior when the sample size increases. In addition, we observe that when \(\phi\) increases the VMR statistic decreases and assumes values more than one. Thus, it is possible to conclude that the MNBR model is an overdispersion model. When the dispersion parameter is more than 50 similar results are obtained.

| \(\phi(\lambda)\) | Measure | \(n\) | \(\phi\) | \(\beta_0\) | \(\beta_1\) | \(\beta_2\) |
|------------------|---------|--------|----------|-----------|-----------|-----------|
| 3.0(0.58)        | RMSE    | 50     | 0.3931   | -0.0078   | -0.0014   | -0.0029   |
|                  |         | 100    | 0.1778   | -0.0041   | 0.0003    | 0.0000    |
|                  |         | 150    | 0.0995   | -0.0034   | 0.0001    | 0.0000    |
|                  |         | 200    | 0.0735   | -0.0031   | -0.0002   | 0.0000    |
|                  | Coverage| 50     | 96.72    | 93.92     | 94.61     | 93.73     |
|                  |         | 100    | 96.00    | 94.33     | 95.17     | 94.23     |
|                  |         | 150    | 95.75    | 94.80     | 95.15     | 94.73     |
|                  |         | 200    | 95.28    | 94.93     | 95.22     | 94.93     |
| 5.0(0.44)        | RMSE    | 50     | 2.1448   | 0.1078    | 0.0492    | 0.1505    |
|                  |         | 100    | 1.1021   | 0.0741    | 0.0299    | 0.1038    |
|                  |         | 150    | 0.8531   | 0.0613    | 0.0264    | 0.0829    |
|                  |         | 200    | 0.7190   | 0.0534    | 0.0228    | 0.0724    |
|                  | Coverage| 50     | 97.22    | 93.93     | 94.94     | 93.51     |
|                  |         | 100    | 95.94    | 94.59     | 95.02     | 94.26     |
|                  |         | 150    | 95.32    | 94.59     | 94.87     | 95.21     |
|                  |         | 200    | 95.18    | 94.64     | 95.24     | 94.87     |
| 7.0(0.38)        | RMSE    | 50     | 3.6728   | 0.0976    | 0.0470    | 0.1343    |
|                  |         | 100    | 1.7556   | 0.0668    | 0.0304    | 0.0901    |
|                  |         | 150    | 1.3277   | 0.0540    | 0.0256    | 0.0731    |
|                  |         | 200    | 1.1060   | 0.0473    | 0.0219    | 0.0632    |
|                  | Coverage| 50     | 97.13    | 93.97     | 95.01     | 93.36     |
|                  |         | 100    | 96.92    | 94.54     | 94.94     | 94.83     |
|                  |         | 150    | 95.83    | 94.80     | 94.85     | 95.05     |
|                  |         | 200    | 95.81    | 94.76     | 94.76     | 95.07     |
Table 2: Bias and root mean square error (RMSE) when the covariance matrix of the random response variable is misspecified.

| Variance | n  | Measure | $\phi$    | $\beta_0$ | $\beta_1$ |
|----------|----|---------|-----------|-----------|-----------|
| $\sigma^2$ |    | Bias    | -0.4285  | -1.8818   | 0.0561    |
|          | 50 | RMSE    | 0.4584   | 1.9805    | 1.0931    |
|          |    | Bias    | -0.3799  | -1.9408   | 0.0497    |
|          | 100| RMSE    | 0.3968   | 2.0068    | 0.9257    |
|          |    | Bias    | -0.3633  | -1.9282   | -0.0129   |
|          | 150| RMSE    | 0.3750   | 1.9754    | 0.6798    |
| $\Sigma$ |    | Bias    | -0.4965  | -1.8623   | 0.0068    |
|          | 50 | RMSE    | 0.5301   | 1.9669    | 1.0656    |
|          |    | Bias    | -0.4375  | -1.9014   | 0.0315    |
|          | 100| RMSE    | 0.4560   | 1.9601    | 0.8784    |
|          |    | Bias    | -0.4196  | -1.9228   | -0.0372   |
|          | 150| RMSE    | 0.4353   | 1.9953    | 0.8282    |

5 Data analysis

In this section, we present two examples illustrating the diagnostic tools for the MNBR model. The data sets and programs can be found in the MNB package available on the R platform.

Seizures data

The data set described in [Diggle et al. (2013)] refers to an experiment in which 59 epileptic patients were randomly assigned to one of two treatment groups: treatment (progabide drug) and placebo groups. The number of seizures experienced by each patient during the baseline period (week eight) and the four consecutive periods (every two weeks) was recorded. The main goal of this application is to analyze the drug effect with respect to the placebo. Two dummy covariates are considered in this study; Group which assumes values equal to 1 if the patient belongs to treatment group and 0 otherwise, and Period which assumes values equal to 1 if the number of seizures are recorded during the treatment and 0 if are measured in the baseline period. Taking into account the irregular measurement of rate seizures during the time, the variable Time is considered as an offset for fitting the data, where Time assumes values equal 8 if the number of seizures is observed in the baseline period and 2 otherwise. The individual profiles of the patients belonging to the placebo and progabide groups are shown in Figure 1(a) and (b), respectively. The atypical individual profiles correspond to patient $\#25(18, 24, 76, 25)$ of the placebo group, who presented a high number of seizures in the third visit compared to other clinic visits, and patient $\#49(102, 65, 72, 63)$ of the progabide group, who suffered a high number of seizures in every clinic visit, indicating the ineffectiveness of the drug in patients with complex seizures. In both groups, it is possible to see the right skewness of the empirical distributions of individual profiles. Figure 1(c) shows a normal probability plot with simulated envelope for the Pearson residual [Faraway (2016), p.135] computed by fitting the Poisson regression model to seizures data. We confirm the occurrence of the overdispersion phenomenon. Thus, based on Figure 1(a) - (c), which shows the asymmetric behavior of the empirical distribution of individual profiles, the MNBR model is proposed for modeling this behavior according to the following structure: (i) $y_i \sim \text{MNB}(\mu_i, \phi)$ and (ii) $\log(\mu_{ij}) = \beta_0 + \beta_1 \text{Group}_{i} + \beta_2 \text{Period}_{ij} + \beta_3 (\text{Group}_{i} \times \text{Period}_{ij}) + \log(\text{Time}_{ij})$, where $y_i = (y_{i1}, y_{i2}, y_{i3}, y_{i4})^T$, $\mu_i = (\mu_{i1}, \mu_{i2}, \mu_{i3}, \mu_{i4})^T$, for $i = 1, \ldots, 59$, $\beta_1$ is the logarithm of the ratio of the average rate of the treatment group to the placebo group at baseline, $\beta_2$ is the logarithm of the ratio of the seizure mean after treatment period to before treatment period for the placebo group, and $\exp(\beta_3)$ is the treatment
Table 3: Bias, root mean square error (RMSE), coverage (%) of 95% confidence intervals.

| φ  | Measure | n  | \(\bar{\phi}\) | \(\beta_0\) | \(\beta_1\) | \(\beta_2\) | VMR  |
|----|---------|----|----------------|-------------|-------------|-------------|-------|
|    | Bias    | 50 | 0.0093        | -0.1769     | -0.0006     | 0.0575      |       |
|    |         | 100| 0.0051        | -0.1201     | -0.0004     | 0.0347      |       |
|    |         | 150| 0.0027        | -0.0838     | -0.0003     | 0.0310      |       |
|    |         | 200| 0.0020        | -0.0331     | -0.0001     | 0.0226      |       |
| 0.1| RMSE    | 50 | 0.0299        | 0.7048      | 0.0707      | 0.9794      | (122.39,220.24) |
|    |         | 100| 0.0198        | 0.5105      | 0.0411      | 0.6742      |       |
|    |         | 150| 0.0151        | 0.3891      | 0.0298      | 0.5531      |       |
|    |         | 200| 0.0130        | 0.3203      | 0.0253      | 0.4468      |       |
|    | Coverage| 50 | 95.4          | 91.3        | 95.0        | 91.1        |       |
|    |         | 100| 95.0          | 92.8        | 94.2        | 92.8        |       |
|    |         | 150| 95.3          | 93.7        | 94.9        | 92.9        |       |
|    |         | 200| 95.5          | 94.5        | 95.1        | 94.7        |       |
| 1.0| RMSE    | 50 | 0.2706        | 0.2188      | 0.0552      | 0.3046      | (19.38,29.35) |
|    |         | 100| 0.1627        | 0.1550      | 0.0380      | 0.2132      |       |
|    |         | 150| 0.1351        | 0.1249      | 0.0291      | 0.1712      |       |
|    |         | 200| 0.1065        | 0.1069      | 0.0244      | 0.1477      |       |
|    | Coverage| 50 | 95.7          | 93.9        | 94.7        | 92.2        |       |
|    |         | 100| 95.4          | 94.3        | 95.6        | 93.5        |       |
|    |         | 150| 95.3          | 94.9        | 95.2        | 94.1        |       |
|    |         | 200| 95.1          | 95.2        | 94.9        | 94.7        |       |
| 50 | RMSE    | 50 | 36.1329       | -0.0034     | 0.0000      | 0.0022      | (5.85,16.87) |
|    |         | 100| 17.2463       | -0.0030     | 0.0000      | 0.0015      |       |
|    |         | 150| 11.0381       | -0.0009     | 0.0000      | 0.0011      |       |
|    |         | 200| 9.1020        | -0.0008     | 0.0000      | 0.0021      |       |
|    | Coverage| 50 | 95.0          | 95.0        | 93.2        | 95.3        |       |
|    |         | 100| 94.2          | 95.5        | 94.1        | 95.4        |       |
|    |         | 150| 94.0          | 93.9        | 94.0        | 94.1        |       |
|    |         | 200| 95.7          | 93.4        | 94.1        | 94.5        |       |

effect, and it is the ratio of post- to pre-treatment mean seizure ratios between treatment and placebo groups. The parameter estimates obtained by using the \texttt{fit.MNB} function from the \texttt{MNB} package are shown in Table 4. It is not observed evidence of the treatment effect. The shape parameter estimate indicates that the variability of individual profiles with respect their average is asymmetric to the left with dispersion equal to 1.607 (\(\lambda = 1/\sqrt{\phi} = 0.789\)). The randomized quantile residual presented in Section 3.1 is used to investigate the presence of outliers or any indication of lack of fit. Figure 2(a) and (b) shows the absence of extra variability and evidence that patient \(\#49\) is atypical. The \texttt{qMNB} and \texttt{envelope.MNB} functions from the \texttt{MNB} package is used to display the graphics of the randomized quantile residual.

The global influential graphics presented in Figure 3(a) and (b) reveal that patients \#49, and \#25 can impact the ML estimates of the MNBR model when they are removed from the model. The local and total local influential graphics exhibited in Figure 4(a) and (b) indicate the sensitivity of the estimate associated with patient \#49 when the minor perturbation is induced.
Figure 1: Individual profiles of the patients in (a) the placebo group, (b) the progabide group, and (c) the simulated envelope plot of the Pearson residuals.

Table 4: Parameter estimates with their respective approximate standard errors (Std. error), z-values, and p-values for the MNBR model fitted to the epileptic data.

| Parameter | Estimate | Std. error | z-value | p-value |
|-----------|----------|------------|---------|---------|
| \( \phi \) | 1.607 | 0.278 | - | - |
| \( \beta_0 \) | 1.348 | 0.153 | 8.813 | < 0.001 |
| \( \beta_1 \) | 0.028 | 0.211 | 0.131 | 0.896 |
| \( \beta_2 \) | 0.112 | 0.047 | 2.386 | 0.017 |
| \( \beta_3 \) | -0.105 | 0.065 | -1.610 | 0.107 |
| \( \lambda \) | 0.789 | |

Figure 2: Index plot of the randomized quantile residuals (a) and (b) the simulated envelope plot of the randomized quantile residuals.
Figure 3: Index plot of (a) the generalized Cook distance and (b) the likelihood displacement.

Figure 4: Index plot of $|d_{max}|$ for the case weight perturbation scheme: (a) local influence and (b) total local influence on the $i$th patient.

in the directions of $d_{max}$ and $d_i$, respectively. According to Figure 5(a) and (b), the number of epileptic seizures of patient 49 recorded on the first and last clinic visits of the trial are more influential. The dispersion perturbation scheme did not show evidence of any possible influential observations.

Finally, the percentage relative deviations $PRD=\frac{|\hat{\theta}-\hat{\theta}^*|}{\hat{\theta}} \times 100\%$, where $\hat{\theta}^*$ is the estimator of $\theta$ obtained after deleting one or more atypical subjects, are calculated and the results are
Figure 5: Index plot of $|d_{\text{max}}|$ for case weight perturbation scheme: (a) local influence and (b) total influence of the $j$th measurement of each patient.

presented in Table 5. We can observe significantly changes are associated with the estimates of $\beta_1$ and $\beta_3$. Noting that the signal of the estimate $\beta_1$ is indicating that the treatment decreases the number of seizures, its descriptive-level keeps nonsignificant though. For the parameter $\beta_3$ we observe that the interaction effect increased 50% and that its descriptive-level becomes significant.

Table 5: Parameter estimates, standard errors (Std. error), $p$-values, and percentage relative deviations (PRD).

| Dropping | Parameter | Estimate | Std. error | $p$-value | PRD(%) |
|----------|-----------|----------|------------|-----------|--------|
| $\phi$   | 2.060     | 0.371    | –          | -28.21    |
| $\beta_0$| 1.348     | 0.136    | < 0.000    | 0.00      |
| $\beta_1$| -0.107    | 0.189    | 0.573      | 487.95    |
| $\beta_2$| 0.112     | 0.047    | 0.017      | 0.00      |
| $\beta_3$| -0.302    | 0.070    | < 0.000    | -188.73   |

**Accident data**

Karlis (2003) provides a data set which refers to the number of car accidents in 24 central roads in Athens, for a time period of 1987 to 1991. In this paper, we are interested in modeling the number of car accidents per road length during the period of 5 years. Thus, the dummy covariate years is considered for fitting the data including the road length as an offset. Figure 6(a) presents the individual profiles of the central roads for the number of car accidents recorded on each road over time. In general, the highest number of car accidents occurred in 1989 and the smallest in 1991. The empirical distribution of individual profiles is skewed to the right. Figure 6(b) reveals that Patision and Peiraios roads are considered as outliers and evidence of variability between the individual profiles and across the years is suggested in Figure 6(c).
In the fitting the Poisson regression model to the accidents data, Figure 6(c), we observe the occurrence of the overdispersion phenomenon. Based on Figure 6(a) - (b) showing the asymmetric behavior of the empirical distribution of individual profiles, we propose the MNBR model with the following structure for modeling the data: 

(i) \( y_i \overset{\text{ind}}{\sim} \text{MNB}(\mu_i, \phi) \) and 
(ii) \( \log(\mu_{ij}) = \beta_0 + \beta_t \text{year}_j + \log(\text{length}_i) \), where \( y_i = (y_{i1}, y_{i2}, y_{i3}, y_{i4}, y_{i5})^\top \), \( \mu_i = (\mu_{i1}, \mu_{i2}, \mu_{i3}, \mu_{i4}, \mu_{i5})^\top \), \( t = 1, 2, 3, 4 \), \( \beta_t \) is the logarithm of the ratio of the average car accidents per road length for year \( t \) to year 1987. The ML estimates for the MNBR model are presented in Table 6. We observe the estimates are significant and that the small difference in the logarithm of the rate average of the number of car accidents per length of the roads occurred between the years 1987 and 1991.

Table 6: Parameter estimates, standard errors (Std. error), z-values, and p-values for the MNBR model fitted to the accidents data.

| Parameter | Estimate | Std. error | z-value | p-value |
|-----------|----------|------------|---------|---------|
| \( \phi \) | 3.364 | 0.954 | 3.526 | - |
| \( \beta_0 \) | 2.250 | 0.119 | 18.899 | < 0.001 |
| \( \beta_1 \) | 0.366 | 0.053 | 6.890 | < 0.001 |
| \( \beta_2 \) | 0.586 | 0.051 | 11.490 | < 0.001 |
| \( \beta_3 \) | 0.474 | 0.052 | 9.102 | < 0.001 |
| \( \beta_4 \) | -0.322 | 0.063 | -5.112 | < 0.001 |

The randomized quantile residuals in Figure 7(a) shows the absence of extra variability and atypical road, and Figure 7(b) shows a normal probability plot with simulated envelope for the randomized quantile residual.

The global influential graphic in Figure 8(a) indicates that Leof. Kavalas, Leof. Athinon and Panepistimiou can impact the ML estimates when they are removed. Leof. Kavalas (4,6,12,9,3) and Panepistimiou (24, 58, 40, 36, 05) are small roads, 2.0 and 1.1 kilometers long, respectively. Leof. Athinon (15,11,16,21,28) is a large road, 6.1 kilometers long. Furthermore, two roads that can impact the ML estimates are showed in Figure 8(b), Patision (80,108,114,113,86) and Katehaki(2,3,27,24,7), which are 4.1 and 1.4 kilometers long, respectively. In Figure 9(a) and (b) are showed influential roads, Peraiois (86 89 109 90 49) and Aharnon (44, 79, 91, 88, 33), which are 8.0 and 5.5 kilometers long, respectively.
Figure 7: Index plot of the randomized quantile residuals (a) and (b) the simulated envelope plot of the randomized quantile residuals.

Figure 8: Index plot of (a) the generalized Cook distance and (b) the likelihood displacement for the number of car accidents on central Athenian roads in 1989-1991.

Finally, the percentage relative deviations (PRD) are calculated and we verify that the most significant changes in the ML estimates are associated with the removal of the influential roads *Patision* and *Peiraios*. The results in Table 7 show that the estimates are affected when *Patision* and *Peiraios* are removed simultaneously.
Figure 9: Index plot of $|d_{max}|$ for the case weight perturbation scheme: (a) local influence and (b) total local influence for the number of car accidents on central Athenian roads in 1989-1991.

Figure 10: Index plot of $|d_{max}|$ for the case weight perturbation scheme: (a) local influence and (b) total local influence on $j$th measurement of the number of car accidents for each atypical central Athenian road.

6 Discussion

In this study, we developed diagnostic tools for the MNBR model derived from the Poisson mixed model where the GLG distribution is assumed for the random effect. Simulation results exhibited the features of the MNBR model and its association with the hierarchical model, which
Figure 11: Index plot of $|d_{\max}|$ for the dispersion perturbation scheme, (a) local influence and (b) total local influence for the number of car accident on central Athenian roads of 1989-1991.

Table 7: Parameter estimates, standard errors (Std. Error), z-values, p-values, and PRD(%) when Patision road is deleted from the accidents data.

| Dropping               | Parameter | Estimate | Std. Error | z-value | p-value | PRD(%) |
|------------------------|-----------|----------|------------|---------|---------|--------|
| Patision               | $\phi$    | 3.507    | 1.021      | –       | –       | –      |
|                        | $\beta_0$ | 2.199    | 0.120      | 18.291  | < 0.001 | 2.27   |
|                        | $\beta_1$ | 0.376    | 0.057      | 6.596   | < 0.001 | -2.65  |
|                        | $\beta_2$ | 0.617    | 0.054      | 11.331  | < 0.001 | -5.36  |
|                        | $\beta_3$ | 0.492    | 0.055      | 8.831   | < 0.001 | -3.86  |
|                        | $\beta_4$ | -0.399   | 0.069      | -5.765  | < 0.001 | -23.97 |
| Peiraios               | $\phi$    | 3.235    | 0.934      | –       | –       | –      |
|                        | $\beta_0$ | 2.215    | 0.124      | 17.795  | < 0.001 | 1.54   |
|                        | $\beta_1$ | 0.413    | 0.057      | 7.249   | < 0.001 | -12.63 |
|                        | $\beta_2$ | 0.634    | 0.056      | 11.605  | < 0.001 | -8.23  |
|                        | $\beta_3$ | 0.531    | 0.055      | 9.534   | < 0.001 | -11.98 |
|                        | $\beta_4$ | -0.287   | 0.067      | -4.257  | < 0.001 | 10.91  |
| Peiraios and Patision  | $\phi$    | 3.366    | 0.934      | –       | –       | –      |
|                        | $\beta_0$ | 2.154    | 0.126      | 17.070  | < 0.001 | 4.24   |
|                        | $\beta_1$ | 0.432    | 0.062      | 7.001   | < 0.001 | -17.95 |
|                        | $\beta_2$ | 0.678    | 0.059      | 11.491  | < 0.001 | -15.76 |
|                        | $\beta_3$ | 0.561    | 0.060      | 9.319   | < 0.001 | -18.47 |
|                        | $\beta_4$ | -0.370   | 0.075      | -4.924  | < 0.001 | -14.91 |

was essential for explaining that the asymptotic consistency of the estimators of the regression coefficients and the dispersion parameter depends on the asymmetry of the GLG distribution. As expected, the MNBR model provides inconsistent estimates of the asymptotic variance of the ML estimators when the covariance matrix of the response variable is misspecified. The randomized
quantile residuals can be used to assess possible departures of the data from the MNBR model assumptions. Following the approaches of Cook (1977, 1986) and Lesaffre and Verbeke (1998), global and local measures for the MNBR model were derived and implemented in the authors’ MNB package. The application of the MNB package to two data sets was presented and it was shown that the asymmetric behavior of the empirical distributions of the individual profiles can indicate the need to use the multivariate model to better fit these profiles. The proposed methodology was helpful for identifying outlying subjects that matter in the MNBR model over time and handle the overdispersion phenomenon. The code for installing the MNB package is presented in the Appendix.

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References

Cook, R. D. (1977). Detection of influential observations in linear regression. *Technometrics*, **19**, 15–18.
Cook, R. D. (1986). Assessment of local influence (with discussion). *Journal of the Royal Statistical Society Series B*, **48**, 133–169.
Cook, R. D. and Weisberg, S. (1983). *Residuals and Influence in Regression*. Chapman and Hall, New York.
Diggles, P. J., Liang, K. Y., and Zeger, S. L. (2013). *Analysis of Longitudinal Data*. Oxford University Press, N.Y., 2 edition.
Dunn, P. K. and Smyth, G. K. (1996). Randomized quantile residuals. *Journal of Computational and Graphical Statistics*, **5**, 236–244.
Fabio, L., Paula, G. A., and de Castro, M. (2012). A Poisson mixed model with nonormal random effect distribution. *Computational Statistics and Data Analysis*, **56**, 1499–1510.
Faraway, F. (2016). *Extending the Linear Model with R: Generalized Linear, Mixed Effects and nonparametric regression models*. Chapman & Hall/CRC, New York.
Hilbe, J. M. (2011). *Negative Binomial Regression*. Cambridge, United Kingdom.
Johnson, N., Kotz, S., and Balakrishnan, N. (1997). *Discrete Multivariate Distributions*. Wiley, New York.
Karlis, D. (2003). An EM algorithm for multivariate Poisson distribution and related models. *Journal of Applied Statistics*, **30**, 63–77.
Lawless, J. (1987). Negative binomial and mixed Poisson regression. *The Canadian Journal of Statistics*, **15**, 209–225.
Lawless, J. F. (2002). *Statistical Models and Methods for Lifetime Data*. Wiley-Interscience, New York.
Lee, Y., Nelder, J. A., and Pawitan, Y. (2006). *Generalized linear models with random effects. Unified analysis via H-likelihood*. Chapman and Hall/CRC, Boca Raton.
Lesaffre, E. and Verbeke, G. (1998). Local influence in linear mixed models. *Biometrics*, **54**, 570–582.
Molenberghs, G. and Verbeke, G. (2010). *Models for Discrete Longitudinal Data*. Springer, New York.
Molenberghs, G., Verbeke, G., and Demétrio, C. G. B. (2007). An extended random-effects
Moller, J. and Rubak, E. (2010). A model for positively correlated count variables. *International Statistical Review, 78*, 65–80.  
R Core Team (2017). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria.  
Solis-Trapala, I. and Farewell, V. (2005). Regression analysis of overdispersed correlated count data with subject specific covariates. *Statistics in Medicine, 24*, 2557–2575.  
Sung, Y. and Lee, K. (2018). Negative binomial loglinear mixed models with general random effects covariance matrix. *Communications for Statistical Applications and Methods, 25*, 61–70.  
Tsui, K.-W. (1986). Multiparameter estimation for some multivariate discrete distributions with possibly dependent components. *Annals of the Institute of Statistical Mathematics, 38*, 45–56.

**Appendix**

1. The score vector and the observed Fisher information matrix

The score vector $U_\beta = (U_\beta^\top, U_\phi^\top)^\top$ is obtained by deriving the log-likelihood function (2) with respect to the parameters $\beta$ and $\phi$, respectively. Thus,

$$U_\beta = \sum_{i=1}^{n} X_i^\top (y_i - a_i \mu_i) \quad \text{and}$$

$$U_\phi = \sum_{i=1}^{n} \left\{ \psi(\phi + y_i +) - \psi(\phi) + \log \left( \frac{\phi}{\phi + \mu_i +} \right) + \left( \frac{\mu_i + - y_i +}{\phi + \mu_i +} \right) \right\}; \quad (3)$$

where $a_i = (\phi + y_i +)/(\phi + \mu_i +)$, $\psi(\cdot)$ is the digamma function, and $X_i$ is an $m_i \times p$ matrix with row $x_{ij}^\top$ for $i = 1, \ldots, n$ and $j = 1, \ldots, m_i$. However, using the fact that $\Gamma(\phi + y_i +)/\Gamma(\phi) = \phi(\phi + 1)(\phi + 2) \cdots (\phi + y_i + - 1)$ in (3), $U_\phi$ takes the following form

$$U_\phi = \sum_{i=1}^{n} \left\{ \sum_{j=0}^{y_i + 1} (j + \phi)^{-1} - \frac{y_i +}{\phi + \mu_i +} - \log(1 + \phi^{-1} \mu_i +) + \frac{\mu_i +}{\phi + \mu_i +} \right\}. $$

The observed information matrix is obtained by deriving the score vector with respect to $\beta$ and $\phi$. Thus,

$$-\tilde{\ell}(\theta) = \begin{bmatrix} -\tilde{\ell}_{\beta \beta} & -\tilde{\ell}_{\beta \phi} \\ -\tilde{\ell}_{\phi \beta} & -\tilde{\ell}_{\phi \phi} \end{bmatrix}$$

where

$$\tilde{\ell}_{\beta \beta} = -\sum_{i=1}^{n} \frac{(\phi + y_i +)}{(\phi + \mu_i +)} \sum_{j=1}^{m_i} x_{ij} x_{ij}^\top \mu_{ij} + \sum_{i=1}^{n} \frac{(\phi + y_i +)}{(\phi + \mu_i +)^2} \sum_{j=1}^{m_i} x_{ij} \mu_{ij} \sum_{j=1}^{m_i} x_{ij}^\top \mu_{ij},$$

$$\tilde{\ell}_{\beta \phi} = \tilde{\ell}_{\phi \beta} = -\sum_{j=1}^{m_i} x_{ijk} \mu_{ij} \left( \frac{\mu_i + - y_i +}{(\phi + \mu_i +)^2} \right) \text{ and}$$

$$\tilde{\ell}_{\phi \phi} = -\sum_{i=1}^{n} \left\{ \sum_{s=0}^{y_i +} \frac{1}{(s + \phi)^2} + \phi^{-1} \mu_i + \frac{\mu_i +}{(\phi + \mu_i +)^2} - \frac{y_i +}{(\phi + \mu_i +)^2} \right\}.$$
2. How to install and use the MNB package

We present the R platform code used to install the MNB package.

```r
require(devtools)
devtools::install_github("carrascojalmar/MNB")
```

2.1. Codes for Seizures data

```r
require(MNB)
data(seizures)
star <- list(phi=1, beta0=1, beta1=1, beta2=1, beta3=1)
mod <- fit.MNB(formula=Y ~ trt + period + trt:period + offset(log(weeks)), star=star, dataSet=seizures, tab=FALSE)
mod

par <- mod$par
cases(par)<-c()
res.q <- qMNB(par=par,formula=Y ~ trt + period + trt:period + offset(log(weeks)), dataSet=seizures)
plot(res.q,ylim=c(-3,4.5),ylab="Randomized quantile residual",xlab="Index",pch=15,cex.lab=1.5,cex=0.6,bg=5)
abline(h=c(-2,0,2),lty=3)

envelope.MNB(formula=Y ~ trt + period + trt:period + offset(weeks),star=star,nsim=21,n.r=6, dataSet=seizures,plot=TRUE)

global.MNB(formula=Y ~ trt + period + offset(log(weeks)),star=star, dataSet=seizures,plot=TRUE)

local.MNB(formula=Y ~ trt + period + offset(log(weeks)),star=star, dataSet=seizures, schemes="weight",plot=TRUE)
```

2.2. Codes for Accident data

```r
require(MNB)
accident <- read.table("...\accident.txt",h=TRUE)
temp <- apply(accident[,2:6],1,t)
Y <- matrix(temp,ncol=1)
length.x <- rep(accident$length,each=5)
ind <- rep(1:24,each=5)
year <- as.factor(rep(1:5,24))
accident2 <- data.frame(Y,year,length.x,ind)

star <- list(phi=10, beta1=2, beta2=0.4, beta3= 0.6, beta4=0.5, beta5=-0.3)
mod <- fit.MNB(Y ~ year + offset(log(length.x)),star=star, dataSet=accident2,tab=FALSE)
mod

par <- mod$par
cases(par)<-c()
qMNB(par=par,formula=Y ~ year + offset(log(length.x)), dataSet=accident2)
envelope.MNB(formula=Y ~ year + offset(log(length.x)),star=star,nsim=21,n.r=6, dataSet=accident2,plot=TRUE)
global.MNB(Y ~ year + offset(log(length.x)),star=star, dataSet=accident2,plot=TRUE)

local.MNB(Y ~ year + offset(log(length.x)),star=star, dataSet=accident2, schemes="weight",plot=TRUE)
```