Accurate inference in negative binomial regression

E. C. KENNE PAGUI, A. SALVAN and N. SARTORI
University of Padova, Department of Statistical Sciences
kenne@stat.unipd.it, salvan@stat.unipd.it, sartori@stat.unipd.it

Abstract

Negative binomial regression is commonly employed to analyze overdispersed count data. With small to moderate sample sizes, the maximum likelihood estimator of the dispersion parameter may be subject to a significant bias, that in turn affects inference on mean parameters. This paper proposes inference for negative binomial regression based on adjustments of the score function aimed at mean and median bias reduction. The resulting estimating equations are similar to those available for improved inference in generalized linear models and, in particular, can be solved using a suitable extension of iterative weighted least squares. Simulation studies show a remarkable performance of the new methods, which are also found to solve in many cases numerical problems of maximum likelihood estimates. The methods are illustrated and evaluated using two case studies: an Ames salmonella assay data set and data on epileptic seizures. Inference based on adjusted scores turns out to be generally preferable to explicit bias correction.

Some key words: adjusted score; iterative weighted least squares; maximum likelihood; mean and median bias reduction; parameterization invariance.

1 Introduction

Regression models for count data are very common in many contexts, especially in social sciences, economics, biology and epidemiology. It is not uncommon that empirical counts display substantial overdispersion and a popular modelling approach is negative binomial regression, see e.g. [Agresti (2015) Section 7.3] and [Hilbe (2011)] for recent accounts.

Frequentist inference about mean and dispersion parameters in negative binomial regression is typically based on the likelihood and this is the method of choice for standard software, such as the glm.nb function of the R package MASS ([Venables and Ripley, 2002]). Maximum likelihood has been studied starting from [Fisher (1941)] and [Anscombe (1950)] for independent and identically distributed data and from [Lawless (1987)] for the regression setting. In particular, existence conditions for the maximum likelihood estimate, extending the random sampling condition that the empirical variance has to exceed the sample mean, are given in [Gning and Pierre-Loti-Viaud (2013)].

With moderate sample sizes, the maximum likelihood estimator of the dispersion parameter may be subject to a substantial bias that can influence the inferential conclusions. For independent and identically distributed data, [Saha and Paul (2005)] derive...
a bias corrected maximum likelihood estimator and show that it is preferable to other methods considered in [Clark and Perry (1989)] and in [Piegorsch (1990)]. The Authors also give an example involving negative binomial regression, but do not provide the expression of the estimator.

For generalized linear models, improvement to maximum likelihood can be achieved both by explicit mean bias correction and by adjusting the likelihood equations, resulting in mean or median bias reduction [Kosmidis et al. (2020)]. Bias reduction was introduced by Firth (1993) (see also Kosmidis and Firth (2009, 2010)). Median bias reduction, developed by Kenne Pagui et al. (2017), is such that each component of the estimator is, with high accuracy, median unbiased, that is, it has the same probability of underestimating and overestimating the corresponding parameter component. Mean and median bias reduced estimators have smaller mean and median bias than the maximum likelihood estimator, respectively. Mean bias reduction is invariant under linear transformation of the parameters, while median bias reduction is invariant under monotone component-wise transformations of the parameters.

In this paper, we extend to negative binomial regression the improved maximum likelihood methods of Kosmidis et al. (2020) and of Saha and Paul (2005). As in Kosmidis et al. (2020) for generalized linear models, we derive explicit formulae for the adjusted score equations and show that they can be solved by iterative weighted least squares after an appropriate adjustment of the ordinary working variates for maximum likelihood. Moreover, the method is developed for various link functions and parameterizations of the dispersion parameter. An R implementation is given in the brnb function available in the forked brglm2 R package [Kosmidis (2020)] on GitHub (https://github.com/eulogepagui/brglm2).

All the proposed estimators are compared through an extensive simulation experiment under different scenarios and through two case studies, the Ames salmonella reverse mutagenicity assay presented in Margolin et al. (1989) and the epileptic seizures data from Thall and Vail (1990). The results indicate that mean and median bias reduction both outperform standard likelihood inference, especially with moderate sample sizes. Median bias reduction provides the best empirical coverage of Wald-type confidence intervals for all parameters. Moreover, numerical problems that lead to unavailability of the maximum likelihood estimate, and therefore of its bias correction, occur more frequently than with mean or median bias reduction. In addition, bias correction is seen to be less accurate than implicit methods when the number of covariates is large relative to the sample size.

The rest of the paper is organized as follows. In Section 2, we introduce the notation for the negative binomial regression model. In Section 3 we give the adjusted score functions for mean and median bias reduction, together with computational details. Sections 4 and 5 contain simulation results and case studies, respectively. The Supplementary Material contains additional figures and the R code to reproduce the analyses in the paper.

2 Negative binomial regression

Let $y_i, i = 1, \ldots, n$, be realizations of independent negative binomial random variables $Y_i$ with mean $\mu_i$, variance $V(Y_i) = \mu_i + \kappa \mu_i^2$, where $\kappa > 0$ is a dispersion parameter.
The probability mass function is
\[
f_{Y_i}(y_i; \mu_i, \kappa) = \frac{\Gamma(y_i + \kappa^{-1})}{y_i! \Gamma(\kappa^{-1})} \left( \frac{\kappa \mu_i}{1 + \kappa \mu_i} \right)^{y_i} \left( \frac{1}{1 + \kappa \mu_i} \right)^{1/\kappa},
\]
y_i = 0, 1, \ldots, \kappa > 0 and \mu_i > 0.

In a regression setting, we consider \( \mu_i = g^{-1}(\eta_i) \), where \( g^{-1}(\cdot) \) is the inverse of the link function, \( \eta_i = x_i \beta \) is the linear predictor, with \( \beta = (\beta_1, \ldots, \beta_p)^\top \in \mathbb{R}^p \) and \( x_i = (x_{i1}, \ldots, x_{ip}) \) a row vector of covariates. The usual choice for the link function is \( g(\cdot) = \log(\cdot) \). For sake of generality, the derivation below is for a generic smooth reparameterization of \( \kappa \), say \( \phi = \phi(\kappa) \) with inverse \( \kappa(\phi) \) and derivative with constant sign \( \kappa'(\phi) \). Common choices are \( \phi = 1/\kappa \), \( \phi = \log \kappa \) and \( \phi = \sqrt{\kappa} \).

Let \( \theta = (\beta^\top, \phi)^\top \). Noting that for any \( a > 0 \), \( \Gamma(y + a)/\Gamma(a) = a(a+1) \cdots (a+y-1) \), the log likelihood is
\[
\ell(\beta, \phi) = \sum_{i=1}^{n} m_i \left\{ \sum_{j=0}^{y_i^*} \log(1 + \kappa j) + y_i \log(\mu_i) - \frac{\mu_i}{1 + \kappa \mu_i} - \frac{1}{\kappa} \log(1 + \kappa \mu_i) \right\},
\]
where \( m_i \) is a fixed prior weight for the \( i \)th observation, \( y_i^* = y_i - 1 \), \( \sum_{j=0}^{y_i^*} \) is zero when \( y_i^* < 0 \) and \( \kappa = \kappa(\phi) \).

The score function \( U = U(\theta) = (\partial/\partial \theta) \ell(\theta) \) has components \( U_\beta = (\partial/\partial \beta) \ell(\beta, \kappa(\phi)) \) and \( U_\phi = (\partial/\partial \phi) \ell(\beta, \kappa(\phi)) \) given by
\[
U_\beta = X^\top W D^{-1}(y - \mu),
\]
\[
U_\phi = \kappa'(\phi) \sum_{i=1}^{n} m_i \left\{ S_{ii} - \frac{\mu_i y_i}{\kappa \mu_i + 1} + \frac{(\kappa \mu_i + 1) \log(\kappa \mu_i + 1) - \kappa \mu_i}{\kappa^2 \mu_i + \kappa^2} \right\},
\]
where \( D \) is a diagonal matrix with generic entry \( d_i = d \mu_i / d \eta_i \), \( W \) is a diagonal matrix with generic entry \( w_i = m_i d_i^2 / V(Y_i) \) (the \( i \)th working weight), \( y = (y_1, \ldots, y_n)^\top \), \( \mu = (\mu_1, \ldots, \mu_n)^\top \) and \( S_{ii} = \sum_{j=0}^{y_i^*} j / (\kappa j + 1) \).

The expected information, obtained in Lawless (1987), is
\[
i(\theta) = \left[ \begin{array}{cc}
i_{\beta \beta} & 0_p \\
0_p & i_{\phi \phi} \end{array} \right] = \left[ \begin{array}{cc}
X^\top W X & 0_p \\
0_p & \kappa'(\phi)^2 i_{\kappa \kappa} \end{array} \right],
\]
where \( 0_p \) is a \( p \)-vector of zeros and
\[
i_{\kappa \kappa} = \kappa^{-4} \sum_{i=1}^{n} m_i \left\{ \sum_{j=0}^{+\infty} \Pr(Y_i > j) \frac{\mu_i}{(\kappa^{-1} + j)^2} - \frac{\mu_i}{\mu_i + \kappa^{-1}} \right\}.
\]

The maximum likelihood estimate \( \hat{\theta}^\top = (\hat{\beta}^\top, \hat{\phi}) \) is obtained as solution of the equations \( U_\beta = 0 \) and \( U_\phi = 0 \) that can be solved using a Fisher scoring algorithm. Exploiting the orthogonality between \( \beta \) and \( \phi \), the current iterate \( \hat{\phi}^{(j)} \) is found by replacing \( \hat{\beta}^{(j)} \) into the \( j \)th Fisher scoring iteration for \( U_\phi = 0 \). The procedure is alternated until convergence. With simple algebra, the \( j \)th iteration of Fisher scoring algorithm for \( U_\beta = 0 \) updates the current iterate \( \hat{\beta}^{(j)} \) providing
\[
\hat{\beta}^{(j+1)} = (X^\top W^{(j)} X)^{-1} X^\top W^{(j)} z^{(j)},
\]
where the superscript \((j)\) indicates that the quantity is evaluated at \( \hat{\beta}^{(j)} \) and the generic element \( z_i = \eta_i + (y_i - \mu_i) / d_i, \ i = 1, \ldots, n, \) of \( z \) is usually called the adjusted dependent variable or working variate. This has the same form of the iterative weighted least squares (IWLS) iteration used in generalized linear models.
3 Mean and median bias reduction

Bias of maximum likelihood estimators in small samples or with sparse data can result in significant loss of accuracy of the related inferential procedures. An extensive amount of literature has focused on methods for reducing such bias either explicitly, that is subtracting from the maximum likelihood estimate an estimate of its first order bias, or implicitly, that is modifying the estimating function. We refer to Kosmidis (2014) for a unified review. See also Greenland et al. (2016) for an expository discussion of sparse data bias and available remedies.

We recall below the various analytic improvements to maximum likelihood and obtain their expression for negative binomial regression.

For a regular model with $d$-dimensional parameter $\theta$, log likelihood $\ell(\theta)$, score function $U(\theta)$, the expected information $i(\theta)$ is the assumed to be of order $n$. We let $U_{\theta_i}(\theta)$ be a generic component of $U(\theta), r = 1, \ldots, d$, and $j(\theta) = -\partial^2 \ell(\theta)/\partial \theta \partial \theta^\top$ be the observed information.

All the proposed adjustments involve the quantities

\[ P_{\theta_i}(\theta) = E_{\theta}\{U(\theta)U(\theta)^\top U_{\theta_i}(\theta)\}, \quad Q_{\theta_i}(\theta) = E_{\theta}\{-j(\theta)U_{\theta_i}(\theta)\}, \quad r = 1, \ldots, d. \]

Score adjustments have the general form $U(\theta) + A(\theta)$, with $A(\theta)$ a model-dependent modification term of order $O(1)$ under repeated sampling. The modified maximum likelihood estimator is obtained as solution of $U(\theta) + A(\theta) = 0$ and, being the correction of order $O(1)$, it has the same asymptotic distribution as the maximum likelihood estimator. In practice, standard errors are computed using diagonal elements of the inverse of the expected information, evaluated at the modified estimate.

In particular, bias of order $O(n^{-1})$ of the maximum likelihood estimator $\hat{\theta}$ is implicitly removed (Firth, 1993) with $A(\theta) = A^*(\theta)$, where $A^*(\theta)$ has generic entry

\[ A^*_{\theta_i}(\theta) = \frac{1}{2} \text{tr}\{i(\theta)^{-1}(P_{\theta_i}(\theta) + Q_{\theta_i}(\theta))\}. \quad (3) \]

We let $U^*(\theta) = U(\theta) + A^*(\theta)$ and we denote by $\theta^*$ the corresponding estimator, solution of $U^*(\theta) = 0$.

The explicitly bias corrected maximum likelihood estimate, see e.g. Cox and Hinkley (1974, Section 9.2(vii)) and Barndorff-Nielsen and Cox (1994, Section 5.3) is given by $\hat{\theta} = \theta - b(\hat{\theta})$, where $b(\theta) = -i(\theta)^{-1}A^*(\theta)$ is the $O(n^{-1})$ bias of $\hat{\theta}$.

Both $\theta^*$ and $\hat{\theta}$ have bias of order $O(n^{-2})$. When $\theta$ is the canonical parameter of a full exponential family, $\theta^*$ is the mode of the posterior distribution obtained using Jeffreys’ prior. However, both bias reduction and bias correction are tied to a specific parameterization. This means that if $\psi = \psi(\theta)$ is a nonlinear reparameterization of $\theta$, the transformed estimator $\psi(\theta^*)$ or $\psi(\hat{\theta})$ will not have reduced bias of order $O(n^{-2})$.

Equivariance under nonlinear componentwise reparameterizations is obtained with median bias reduction (Kenne Pagui et al. 2017), leading to the estimator $\theta^1$ satisfying, in the continuous case, the improved median centering property $Pr_{\theta}(\theta^1_r \leq \theta_r) = 1/2 + O(n^{-3/2}), r = 1, \ldots, d$, in contrast with the corresponding $O(n^{-1/2})$ order of error for the maximum likelihood estimator. Median bias reduction is achieved using $A(\theta) = A^1(\theta)$, given in Kenne Pagui et al. (2017, formula (10)).

For the negative binomial regression model (1), we have $d = p + 1$ and the quantity $A^*(\theta)$, whose derivation is in the Appendix, has blocks

\[ A^*_\beta = X^\top W\xi, \quad A^*_\phi = \kappa'(\phi) \sum_{i=1}^n \frac{m_i h_i d_i^2 \mu_i^2}{2 w_i V(Y_i)^2} + \frac{1}{2} i_{\phi\phi}^{-1} R_{\phi\phi}, \]
where $\xi = (\xi_1, \ldots, \xi_n)^\top$, with $\xi_i = h_id_i/(2d_iw_i)$. The quantity $h_i$ appearing in $\xi_i$ and in $A^*_\phi$ is the ‘hat’ value for the $i$th observation, obtained as the $i$th diagonal element of the matrix $H = X(X^TWX)^{-1}X^TW$ and $d_i^e = d^2\mu_i/dq_i^2$. The expression of $R_{\phi\phi}$ is given in the Appendix.

The median bias adjustment $A^j(\theta)$ for negative binomial regression has blocks

$$A^j_\beta = X^TW(\xi + Xu), \quad A^j_\phi = A^*_\phi + i_{\phi}^{-1}S_{\phi\phi},$$

(4)

where expressions for $u$ and $S_{\phi\phi}$ are given in the Appendix.

With simple algebra, the $j$th iteration of IWLS which updates the current iterate

$$\beta^{*}(j+1) = (X^TW(j)X)^{-1}X^TW(j)z^*(j),$$

(5)

where $z^*(j) = z(j) + \xi(j)$ is the adjusted version of the working variate $z$ defined in (2). The $j$th iteration of IWLS for $\tilde{\theta}$ has the same expression as (5), with adjusted version of working variate $\tilde{z} = z^* + Xu$.

All the improved methods for negative binomial regression, together with maximum likelihood fitting, are available in the `brnb` R function in the forked `brglm2` R package (Kosmidis, 2020) on GitHub (https://github.com/eulogepagui/brglm2). Maximum likelihood fitting can also be performed for instance using the `glm.nb` function of the `MASS` R library.

4 Simulation studies

In this section, the properties of the estimators are assessed through simulation under different scenarios corresponding to combination of values of $n$, $\phi$, and $\beta$. For each scenario, we run 10000 Monte Carlo replications. In all cases, we use the logarithmic link function and the identity transformation for the dispersion parameter ($\phi = \kappa$). We compute estimates using maximum likelihood (ML), mean and median bias reduction (BR) through the `brnb` R function.

Estimators are evaluated in terms of empirical probability of underestimation (PU), estimated relative (mean) bias (RBIAS), estimated coverage probability of 95% Wald-type confidence intervals (WALD) and the relative increase in mean squared error from its absolute minimum due to bias (IBMSE) given by $100B^2/SD^2$. Here, $B$ denotes the estimated mean bias and $SD$, the corresponding estimated standard deviation. The four performance measures are expressed in percentages.

We first conduct a simulation study with constant mean $\mu$, i.e. with intercept only. Mean bias reduction with a numerical example for this case was considered in Zhang et al. (2019, Example 4). In particular, we take sample sizes $n = 20$ and $n = 50$ from $NB(\mu, \kappa)$ for the combinations of $\mu = 2, 5$ ($\beta = \log 2, \log 5$) and $\kappa = 0.5, 0.75, 1, 1.5, 2$. For each setting, Table 1 gives the number of samples, out of 10000 replications, with variance less than the mean and occurrence of non convergence. The results are presented in Figure 1. For each method the results are reported only for samples with convergence. Therefore, the performance for maximum likelihood should be judged with caution. Both mean and median BR achieve the desired goals, i.e. are effective in mean and median centering, respectively, and are both preferable to ML. All three estimators improve as the sample size and $\mu$ increase. In particular, median BR provides empirical coverage of the 95% Wald-type confidence intervals closest to nominal. We finally note that ML for the dispersion parameter has smaller mean bias than median.
Table 1: Computational diagnostics in 10000 replications. \( A_1 \) indicates the number of samples with empirical variance less than mean. Of the remaining samples, \( A_2 \) is the number of non convergence samples using ML, \( A_3 \) is the number of non convergence samples using mean BR and \( A_4 \) is the number of non convergence samples using median BR.

| \( \kappa \) | \( \mu = 2 \) | \( \mu = 5 \) |
|---|---|---|
| 0.5 | 0.75 | 1 | 1.5 | 2 | 0.5 | 0.75 | 1 | 1.5 | 2 |
| \( A_1 \) | 535 | 214 | 108 | 43 | 17 | 18 | 3 | 0 | 0 | 0 |
| \( A_2 \) | 163 | 85 | 42 | 17 | 12 | 6 | 3 | 0 | 3 | 1 |
| \( A_3 \) | 2 | 1 | 0 | 0 | 1 | 0 | 0 | 2 | 1 |
| \( A_4 \) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 |

BR in this parameterization, but not when the inverse or the log parameterization is adopted. On the other hand, median BR is not targeted for reduction of the mean bias.

Figure 1: Estimated relative bias (RBIAS), probability of under estimation (PU) and coverage probability of 95% Wald-type confidence intervals (WALD) for the intercept \( \beta = \log \mu \). Results for ML (black squares), mean BR (blue circles) and median BR (red triangles).

We now consider a second simulation study involving covariates. In particular, we
let
\[ \log \mu_i = \beta_1 + \beta_2 x_{i2} + \beta_3 x_{i3} + \beta_4 x_{i4} + \beta_5 x_{i5}, \] (6)

where \( x_{i2} \) are \( n \) independent realizations of Bernoulli \( B(1, 0.8) \); \( x_{i3} \) is generated from a Bernoulli \( B(1, 0.5) \); \( x_{i4} \) is generated from a uniform \( U(1, 2) \); \( x_{i5} \) is generated from a Poisson \( P(2, 5) \), \( i = 1, \ldots, n \). The true parameter values are \( \beta_1 = 1, \beta_2 = -0.75, \beta_3 = -1.5, \beta_4 = 1 \) and \( \beta_5 = -0.5 \). Four values were considered for the dispersion parameter, \( \kappa = 0.5, 0.75, 1, 1.5 \). The sample sizes considered were \( n = 40, 80 \). For each combination of \( \beta, \kappa \) and \( n \), we run 10000 Monte Carlo replications, where the values of the explanatory variables \( x_{i2}, x_{i3}, x_{i4} \) and \( x_{i5} \) were held constant throughout the simulations.

Figure 2: Estimation of regression parameters \( \beta = (\beta_1, \beta_2, \beta_3, \beta_4, \beta_5) \) with \( \kappa = 0.75, n = 40, 80 \). Simulation results for ML (black squares), mean BR (blue circles) and median BR (red triangles).
Figure 3: Estimation of dispersion parameter \( \kappa \) with \( n = 40, 80 \). Simulation results for ML (black squares), mean BR (blue circles) and median BR (red triangles).

The summaries of the simulation results for the regression parameters when \( \kappa = 0.75 \) are presented in Figures 2. The Supplementary Material also includes results for \( \kappa = 0.5, 1, 1.5 \). Figure 3 summarizes the results for the estimators of \( \kappa \). Looking at the four performance measures, it appears that mean and median BR outperform the ML for small \( n \). On the other hand, the results improve for all three methods as \( n \) increases. As \( \kappa \) increases, for estimation of regression coefficients, median BR is comparable to mean BR in terms of estimated relative (mean) bias, while it proves to be remarkably accurate in achieving median centering. Moreover, in all scenarios, median BR provides the empirical coverages of Wald-type confidence intervals closest to the 95% nominal value. Finally, the results in Figure 3 show that the improvement given by both mean and median BR over ML are substantial in all scenarios and more pronounced than in the previous case with only the intercept parameter.
5 Case studies

We consider two case studies, namely data from an Ames salmonella assay and from an epileptic seizures study. The first data set has one explanatory variable with 6 levels and 3 observations each. The second data set has counts of epileptic seizures for 59 matched pairs.

5.1 Ames salmonella data

Data from an Ames salmonella reverse mutagenicity assay are presented in Margolin et al. (1989) and also analysed in Saha and Paul (2005, Table 2), Lawless (1987, Table 5) and Breslow (1984). The response variable $Y$ corresponds to the number of revertant colonies observed on a plate, while covariate $x$ is the dose level of quinoline on the plate. Three observations were taken at each of six dose levels.

As Breslow (1984), we focus on the analysis based on the log-linear model

$$\log \mu_i = \beta_0 + \beta_1 x_i + \beta_2 \log(x_i + 10),$$

with the identity transformation for the dispersion parameter ($\phi = \kappa$). In the above expression, the constant 10 represents the smallest non-zero dose level. The main interest is focused on testing for mutagenic effect, that is $H : \beta_2 = 0$.

Table 2: Ames salmonella assay: parameter estimates and corresponding standard errors in parenthesis.

|        | ML      | mean BC     | mean BR    | median BR   |
|--------|---------|-------------|------------|-------------|
| $\beta_0$ | 2.198 (0.325) | 2.210 (0.348) | 2.216 (0.352) | 2.211 (0.359) |
| $\beta_1$ | -0.001 (0.00039) | -0.001 (0.00042) | -0.001 (0.00042) | -0.001 (0.00043) |
| $\beta_2$ | 0.313 (0.088) | 0.311 (0.095) | 0.309 (0.096) | 0.309 (0.098) |
| $\kappa$  | 0.049 (0.028) | 0.063 (0.033) | 0.065 (0.033) | 0.069 (0.035) |

Table 2 shows the estimates obtained with ML, mean bias correction (BC), mean BR and median BR. Mean and median bias reduced estimates of the dispersion parameter are pretty much comparable, but slightly different from the maximum likelihood estimate. This is then reflected in the standard errors of the regression parameter estimates.

Table 3 displays the simulation results for the parameters considering 10000 replications, covariates fixed at the observed value and true parameters set to the ML estimates based on the observed data. We found 641, 276 and 212 samples out of 10000 where the IWLS algorithm did not reach convergence for ML (and mean BC), mean BR and median BR, respectively. The 641 non convergence samples are discarded for the results of ML and mean BC, while the results of mean and median BR discarded the 276 for which the IWLS did not converge for mean BR.

Similarly to what was seen in the previous section, both mean and median BR are superior to ML in reducing median and mean bias of the dispersion parameter. In particular, median BR presents empirical coverage of the 95% Wald-type confidence intervals closest to the nominal.
Table 3: Ames salmonella assay: Simulation results.

|   | PU  | RBIAS | WALD  | IBMSE |
|---|-----|-------|-------|-------|
| $\beta_0$ | 50.95 | -0.62 | 91.77 | 0.17  |
| $\beta_1$ | 49.65 | -0.12 | 93.77 | 0.01  |
| $\beta_0^*$ | 49.43 | -0.05 | 93.63 | 0.00  |
| $\beta_1^*$ | 49.98 | -0.26 | 94.17 | 0.03  |
| $\beta_0^*$ | 51.49 | -1.79 | 91.56 | 0.20  |
| $\beta_1$ | 50.21 | -0.39 | 93.85 | 0.01  |
| $\beta_0^*$ | 49.95 | -0.09 | 93.65 | 0.00  |
| $\beta_1^*$ | 50.14 | -0.30 | 94.14 | 0.01  |
| $\beta_0^*$ | 48.56 | 0.85  | 91.70 | 0.09  |
| $\beta_1^*$ | 49.43 | 0.26  | 93.85 | 0.01  |
| $\beta_0^*$ | 49.71 | 0.14  | 93.74 | 0.00  |
| $\beta_1^*$ | 49.63 | 0.21  | 94.21 | 0.01  |
| $\kappa$ | 71.88 | -22.60 | 81.07 | 20.08 |
| $\kappa^*$ | 55.37 | 1.98  | 90.73 | 0.11  |
| $\kappa^*$ | 53.71 | 3.61  | 89.08 | 0.33  |
| $\kappa^*$ | 48.44 | 11.96 | 91.56 | 3.37  |

5.2 Epileptic seizures data

We consider here the epileptic seizures data on two-week seizure counts for 59 epileptics given by Thall and Vail (1990). The data were analyzed by several authors, including Venables and Ripley (2002, Section 10.4) and Bellio and Sartori (2006, Section 3.3). The number of seizures was recorded for a baseline period of 8 weeks, and then patients were randomly assigned to a treatment group or a control group. Counts were then recorded for four successive two-weeks periods. The response was the number of observed seizures. We analyzed the data by comparing the response before and after the treatment, hence obtaining a set of 59 matched pairs. The only covariates in the linear predictor are then given by the two treatment indicators. We assume a negative binomial model for the response $Y_{ij}, i = 1, \ldots, 59, j = 1, 2$, with mean and variance

$$
\mu_{ij} = \exp(\lambda_i + x_{ij}\beta), \quad V(Y_{ij}) = \mu_{ij} + \kappa\mu_{ij}^2,
$$

where intercepts $\lambda_i$ determine the stratified structure corresponding to each subject, $x_{i1} = (0, 0)$, while $x_{i2} = (1, 0)$ if subject $i$ received the placebo and $x_{i2} = (0, 1)$ if subject $i$ received the treatment. We focus on inference about $\beta = (\beta_1, \beta_2)^T$ and $\kappa$, while the intercepts are treated as nuisance parameters. The methods in this paper estimate anyway the whole vector of parameters. Figure 4 displays the parameter estimates and the corresponding confidence intervals obtained with ML, modified profile likelihood (MPL), mean BC, mean BR and median BR. The modified profile likelihood for this model has been considered in Bellio and Sartori (2006).

We run 10000 replications with covariates fixed at the observed value and true parameters set to the observed ML estimates. We found 1549, 6 and 4 samples out of 10000 where the IWLS algorithm did not reach convergence for ML (and mean BC), mean BR and median BR, respectively. We note that, 2220 samples out of 10000 do not reach convergence using the function glm.nb. Hence, from a computational
Figure 4: Epileptic seizures: points represent the parameter estimates while the vertical lines represent 95% Wald-type confidence intervals.

Table 4: Epileptic seizures: Simulation results.

|       | PU   | RBIAS | WALD  | IBMSE |
|-------|------|-------|-------|-------|
| $\hat{\beta}_1$ | 49.80 | 0.42  | 82.22 | 0.00  |
| $\tilde{\beta}_1$ | 50.15 | -0.16 | 89.63 | 0.00  |
| $\beta^*_1$ | 49.86 | 0.52  | 94.36 | 0.00  |
| $\hat{\beta}_1^*$ | 49.89 | 0.54  | 94.40 | 0.00  |
| $\hat{\beta}_2$ | 49.84 | 0.09  | 82.03 | 0.00  |
| $\tilde{\beta}_2$ | 49.45 | 0.37  | 89.04 | 0.01  |
| $\beta^*_2$ | 50.63 | -0.50 | 94.55 | 0.02  |
| $\hat{\beta}_2^*$ | 50.62 | -0.53 | 94.60 | 0.02  |
| $\hat{\kappa}$ | 100.00 | -79.32 | 0.39  | 3671.91 |
| $\kappa^*$ | 93.47 | -40.99 | 40.34 | 286.52 |
| $\kappa^!$ | 48.78 | 3.99  | 81.44 | 1.10  |
| $\kappa^!$ | 48.81 | 3.89  | 82.15 | 1.08  |

From a point of view, the implementation in brnb is more stable than that in glm.nb. On the other hand, it turns out that mean and median BR methods present negligible numerical problems with respect to ML. This is justifiable by the fact that ML tends to significantly underestimate the dispersion parameter producing estimates that are close to boundary of the parameter space. This is in line with the results in Table 11.
1. The results for mean and median BR are based on samples in which the algorithm converges for both methods, while the 1549 non-convergence samples are discarded for ML and mean BC.

Table 4 displays the results for the parameters $\beta$ and $\kappa$. For the regression coefficients, all the approaches are almost equivalent in terms of PU and RBIAS, although it should be kept in mind that the results for $\hat{\beta}$ and $\hat{\beta}$ are based only on roughly 85% of the samples. Concerning the dispersion parameter, mean and median BR outperform ML in terms of all measures. The results are particularly bad for ML. We also see how largely the mean squared error of $\hat{\kappa}$ is affected by the huge bias in the estimator. We note that, in this extreme scenario, mean BC behaves similarly to ML. In addition, both mean and median BR show empirical coverages of Wald-type confidence intervals remarkably close to the 95% nominal value, while coverages for ML and mean BC are quite far from the nominal level.

Although not of direct interest in the present example, both mean and median BR provide improved estimates also of the nuisance parameters. The simulation results for these are presented in Figure 5. Once again, we can appreciate the improved performance of mean and median BR by looking at the coverages of 95% Wald-type confidence intervals which are closest to the nominal value.

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Figure 5: Epileptic seizures: Simulation results for estimators of the nuisance parameters: ML (black solid line), mean BC (green dotted line), mean BR (red dashed line), and median BR (blue dot-dash line).

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**Appendix**

**Quantities involved in $A^*(\theta)$ and $A^\dagger(\theta)$**

Let $\text{diag}\{e_1, \ldots, e_n\}$ denote a diagonal matrix having $(e_1, \ldots, e_n)$ as its main diagonal. Let, in addition, $1_n$ be a $n$-vector of ones and $I_n$ the identity matrix of order $n$.

In order to give the expressions of matrix quantities appearing in (*3*), we will use the index $s$, $s = 1, \ldots, p$ for elements of $\beta$ and the subscript $\phi$ for the $\phi$ parameter. For simplicity, the argument $\theta$ will be omitted. We get

$$P_{\beta_s} + Q_{\beta_s} = \begin{bmatrix} X^\top X_s D^{-1} D' W X & 0_p \\ 0_p^\top & 0 \end{bmatrix},$$
where \( X_s^D \) denotes the diagonal matrix with elements of the \( s \)th column of the matrix \( X \) as its main diagonal and \( D' = \text{diag}\{d'_1, \ldots, d'_n\} \). Moreover, letting \( R = P_\phi + Q_\phi \), we have
\[
R = \begin{bmatrix} R_{\beta\beta} & R_{\beta\phi} \\ R_{\phi\beta} & R_{\phi\phi} \end{bmatrix},
\]
with
\[
R_{\beta\beta} = \kappa'(\phi)X^TD^2\Omega M^2V^{-2}X,
R_{\beta\phi} = R_{\phi\beta}^T
= \kappa'(\phi)X^TD\Omega\{M(\kappa M + I_n)\}^{-1}\{E_1 - ME_2 - M^3(\kappa M + I_n)^{-1}\}1_n,
R_{\phi\phi} = \kappa'(\phi)\sum_{i=1}^{n} m_i \left\{ -2E(S_{3i}) + \frac{2\kappa^2\mu_i^3 + 9\kappa\mu_i^2 + 6\mu_i}{\kappa^3(\kappa\mu_i + 1)^2} - \frac{6}{\kappa^4} \log(\kappa\mu_i + 1) \right. \\
\left. + 2E(S_{1i}S_{2i}) - \frac{2\mu_i}{\kappa\mu_i + 1}E(S_{2i}Y_i) - \frac{2(\kappa\mu_i - (\kappa\mu_i + 1)\log(\kappa\mu_i + 1))}{\kappa^2(\kappa\mu_i + 1)}E(S_{2i}) \right\}
+ i_{\kappa\kappa}\kappa'(\phi)\kappa''(\phi),
\]
where \( \Omega = \text{diag}\{m_1, \ldots, m_n\} \), \( M = \text{diag}\{\mu_1, \ldots, \mu_n\} \), \( V = \text{diag}\{V(Y_1), \ldots, V(Y_n)\} \), \( S_{ai} = \sum_{j=0}^{n} j_a/(\kappa j + 1)^a \), \( a = 1, 2, 3 \), \( E_1 = \text{diag}\{E(S_{21}Y_1), \ldots, E(S_{2n}Y_n)\} \) and \( E_2 = \text{diag}\{E(S_{21}), \ldots, E(S_{2n})\} \).

In order to give the expressions for the additional quantities \( u \) and \( S_{\phi\phi} \) appearing in \([4]\), we denote by \([C]_r\) the \( r \)-th column of a matrix \( C \) and by \( i_{\beta\beta}^s \) the \((s, s)\) element of \( i_{\beta\beta}^{-1} \). Let, in addition, \( v_i = V(Y_i) \) and \( v'_i = dV(Y_i)/d\mu_i = 1 + 2\kappa\mu_i \). Then, \( u = (u_1, \ldots, u_p)^T \) with
\[
u_s = [(X^TWX)^{-1}]_s^T X^T \begin{bmatrix} h_{s,1} \{d_1v'_1/(6v_1) - d'_1/(2d_1)\} \\
\vdots \\
h_{s,n} \{d_nv'_n/(6v_n) - d'_n/(2d_n)\} \end{bmatrix}.
\]

In the above expression, \( h_{s,i} \) is the \( i \)-th diagonal element of \( XG_sX^TW \), with \( G_s = [i_{\beta\beta}^{-1}]_s[i_{\beta\beta}^s]_s/(i_{\beta\beta}^{s,s})_s \).

Finally,
\[
S_{\phi\phi} = \kappa'(\phi)\sum_{i=1}^{n} m_i \left\{ -\frac{2}{3}E(S_{3i}) + \frac{1}{3}\frac{2\kappa^2\mu_i^3 + 9\kappa\mu_i^2 + 6\mu_i}{\kappa^3(\kappa\mu_i + 1)^2} - \frac{2}{\kappa^4} \log(\kappa\mu_i + 1) \right. \\
\left. + \frac{1}{2}E(S_{1i}S_{2i}) - \frac{1}{2}E(S_{2i}Y_i) - \frac{1}{2}(\kappa\mu_i - (\kappa\mu_i + 1)\log(\kappa\mu_i + 1))E(S_{2i}) \right\}
+ i_{\kappa\kappa}\kappa'(\phi)\kappa''(\phi).
\]
Supplementary Material for Accurate inference in negative binomial regression

1 introduction

The current report reproduces the numerical results and figures in the main text. The outputs have been produced using R (R Core Team 2020) and the brnb function available in the forked brglm2 R package (Kosmidis 2020) on GitHub (https://github.com/eulogepagui/brglm2).

The code chunk below checks and loads the R packages that are used for the reproduction of numerical results in the main text.

```r
library("MASS")
library("survival")
library("ggplot2")
library("gridExtra")
library("cowplot")
```

We also provide code to reproduce all model fits and simulation results in the main text. The R scripts to carry out the simulation experiments, and the results from those are provided in the brnb_code_results.zip archive. res_dir is the directory where the contents of the archive are and needs to be set appropriately.

```r
res_dir <- "brnb_code_results"
```

2 Simulation studies

This section provides the R code that reproduces the numerical results of Section 4 of the paper.

The following code chunk uses the image file intercept_simulation_results.rda to reproduce the reported computational diagnostics in Table 1 of the main text.

```r
load(paste(res_dir, "intercept_simulation_results.rda", sep = "/"))
```

ComputationDiagnostic

```r
## 0.5 0.75 1 1.5 2 0.5 0.75 1 1.5 2
## A1 535 214 108 43 17 18 3 0 0 0
## A2 163 85 42 17 12 6 3 0 3 1
## A3 2 1 0 0 0 0 0 0 2 1
## A4 0 0 0 0 0 0 0 0 0 0
## A1 36 6 0 0 0 0 0 0 0 0
## A2 16 0 1 0 0 0 0 0 0 0
## A3 2 0 0 0 0 0 0 0 0 0
## A4 0 0 0 0 0 0 0 0 0 0
```

The code chunk below prepares the data for producing Figure 1 in the main text.
Figure 1 is the result of

```r
## Relative bias; probability of underestimation and coverages
p1 <- ggplot(dataggplot,aes(x = kappa, y = rbias)) +
  geom_hline(aes(yintercept = 0), col = "grey") +
  geom_line(aes(linetype=methods,colour=methods ))+
  geom_point(aes(shape=methods,colour=methods) ) +
  labs(x = ",", y = "RBIAS") +
  facet_grid(mu2 ~ n4, labeller = label_parsed )+
  scale_colour_manual(values=c("blue","red", "black"))+
  scale_linetype_manual(values = c("dotted","dotted","dotted"))+
  scale_x_discrete("",limits=factor(c(1:5)), breaks=c(1:5),
  labels=c(0.5,0.75,1,1.5,2))+
  theme_bw()+
  theme(legend.position = "",strip.background = element_blank(),
  axis.ticks.x=element_blank(),axis.text.x = element_blank(),
  plot.margin=unit(c(0,0,-0.1,0.03), "cm")
)
p2 <- ggplot(dataggplot,aes(x = kappa, y = pu)) +
  geom_hline(aes(yintercept = 50), col = "grey") +
  geom_line(aes(linetype=methods,colour=methods ))+
  geom_point(aes(shape=methods,colour=methods) ) +
  labs(x = ",", y = "PU") +
  facet_grid(mu2 ~ n4, labeller = label_parsed )+
  scale_colour_manual(values=c("blue","red", "black"))+
  scale_linetype_manual(values = c("dotted","dotted","dotted"))+
  scale_x_discrete("",limits=factor(c(1:5)), breaks=c(1:5),
  labels=c(0.5,0.75,1,1.5,2))+
  theme_bw()+
  theme(legend.position = "",strip.background = element_blank(),
  strip.text.x = element_blank(),
  strip.text.y = element_blank(),
  strip.text.size = element_blank(),
  strip.text.direction = "vertical")
```

17
The code chunk below prepares the data and ggplot objects for producing Figure 2, Figure 3, Figure 4, Figure 5, Figure 6 in the main text.

```r
load(paste(res_dir, "covariates_simulation_results.rda", sep="/"))
coef <- rep(rep(1:6,each=3),20)
measures <- as.factor(rep(rep(c(1,2,3,4),each=18),5))
levels(measures) <- c("RBIAS","PU","WALD","IBMSE")
methods <- rep(c("ml","br","mbr"),120)
values <- rep(1:5,each=72)
dataggplot <- data.frame(yvalues,methods,values,measures,coef)
dataggplot2 <- data.frame(yvalues2,methods,values,measures,coef)
hline_dat <- data.frame(measures=c("RBIAS","PU","WALD","IBMSE"),
threshold=c(0, 50, 95, 0))
## n = 40 ##
p0.5 <- ggplot(subset(dataggplot,(values==2 & coef!=6)),aes(x = coef, y = yvalues)) +
ggplot2 <- data.frame(yvalues2,methods,values,measures,coef)
dataggplot2 <- data.frame(yvalues2,methods,values,measures,coef)
hline_dat <- data.frame(measures=c("RBIAS","PU","WALD","IBMSE"),
threshold=c(0, 50, 95, 0))
```
Figure 6: Estimated relative bias (RBIAS), probability of under estimation (PU) and coverage probability of 95% Wald-type confidence intervals (WALD) for the intercept $\beta = \log \mu$. Results for ML (black squares), mean BR (blue circles) and median BR (red triangles).
expression(beta[5])) +
theme_minimal() +
theme(legend.position = "none",
  plot.title = element_text(hjust = 0.5),
  axis.text.x = element_blank(),
  axis.ticks.x = element_blank(),
  plot.margin = unit(c(0,0,-0.1,0.03), "cm")
)

p0.75 <- ggplot(subset(dataggplot,(avalues==3 & coef!=6)),aes(x = coef, y = yvalues)) +
  geom_hline(data=hline_dat, aes(yintercept=threshold), col = "grey") +
  geom_line(aes(linetype=methods,colour=methods)) +
  geom_point(aes(shape=methods,colour=methods)) +
  labs(x = "", y = "n = 40") +
  facet_wrap(~ measures, scales = "free_y", labeller = label_parsed) +
  scale_colour_manual(values=c("blue","red", "black")) +
  scale_linetype_manual(values = c("dotted","dotted","dotted")) +
  scale_x_continuous("", labels=c(expression(beta[1]),expression(beta[2]),
    expression(beta[3]),expression(beta[4]),
    expression(beta[5]))) +
theme_minimal() +
theme(legend.position = "none",
  plot.title = element_text(hjust = 0.5),
  axis.text.x = element_blank(),
  axis.ticks.x = element_blank(),
  plot.margin = unit(c(0,0,-0.1,0.03), "cm")
)

p1 <- ggplot(subset(dataggplot,(avalues==4 & coef!=6)),aes(x = coef, y = yvalues)) +
  geom_hline(data=hline_dat, aes(yintercept=threshold), col = "grey") +
  geom_line(aes(linetype=methods,colour=methods)) +
  geom_point(aes(shape=methods,colour=methods)) +
  labs(x = "", y = "n = 40") +
  facet_wrap(~ measures, scales = "free_y", labeller = label_parsed) +
  scale_colour_manual(values=c("blue","red", "black")) +
  scale_linetype_manual(values = c("dotted","dotted","dotted")) +
  scale_x_continuous("", labels=c(expression(beta[1]),expression(beta[2]),
    expression(beta[3]),expression(beta[4]),
    expression(beta[5]))) +
theme_minimal() +
theme(legend.position = "none",
  plot.title = element_text(hjust = 0.5),
  axis.text.x = element_blank(),
  axis.ticks.x = element_blank(),
  plot.margin = unit(c(0,0,-0.1,0.03), "cm")
)

p1.5 <- ggplot(subset(dataggplot,(avalues==5 & coef!=6)),aes(x = coef, y = yvalues)) +
  geom_hline(data=hline_dat, aes(yintercept=threshold), col = "grey") +
  geom_line(aes(linetype=methods,colour=methods)) +
  geom_point(aes(shape=methods,colour=methods)) +
  labs(x = "", y = "n = 40") +
  facet_wrap(~ measures, scales = "free_y", labeller = label_parsed) +
  scale_colour_manual(values=c("blue","red", "black")) +
  scale_linetype_manual(values = c("dotted","dotted","dotted")) +
  scale_x_continuous("", labels=c(expression(beta[1]),expression(beta[2]),
    expression(beta[3]),expression(beta[4]),
    expression(beta[5]))) +
theme_minimal() +
theme(legend.position = "none",

20
plot.title = element_text(hjust = 0.5),
axis.text.x = element_blank(),
axis.ticks.x=element_blank(),
plot.margin=unit(c(0,0,-0.1,0.03), "cm")

pk <- ggplot(subset(dataggplot,(avalues!=1 & coef==6)),aes(x = avalues, y = yvalues)) +
  geom_hline(data=hline_dat, aes(yintercept=threshold), col = "grey") +
  geom_line(aes(linetype=methods,colour=methods )) +
  labs(x = "", y = "n = 40") +
  facet_wrap(~ measures ,scales = "free_y",labeller = label_parsed)+
  scale_colour_manual(values=c("blue","red", "black"))+
  scale_linetype_manual(values = c("dotted","dotted","dotted")) +
  scale_x_continuous()+
  theme_minimal() +
  theme(legend.position = "none")

##n=80 ##

p2_0.5 <- ggplot(subset(dataggplot2,(avalues==2 & coef!=6)),aes(x = coef, y = yvalues2)) +
  geom_hline(data=hline_dat, aes(yintercept=threshold), col = "grey") +
  geom_line(aes(linetype=methods,colour=methods )) +
  labs(x = "", y = "n = 80") +
  facet_wrap(~ measures ,scales = "free_y",labeller = label_parsed)+
  scale_colour_manual(values=c("blue","red", "black"))+
  scale_linetype_manual(values = c("dotted","dotted","dotted")) +
  scale_x_continuous("",
    labels=c(expression(beta[1]),expression(beta[2]),
    expression(beta[3]),expression(beta[4]),
    expression(beta[5])))+
  theme_minimal() +
  theme(legend.position = "none",
    plot.title = element_text(hjust = 0.5),
    plot.margin=unit(c(-0.1,0,-0.1,0.03), "cm"))

p2_0.75 <- ggplot(subset(dataggplot2,(avalues==3 & coef!=6)),aes(x = coef, y = yvalues2)) +
  geom_hline(data=hline_dat, aes(yintercept=threshold), col = "grey") +
  geom_line(aes(linetype=methods,colour=methods )) +
  labs(x = "", y = "n = 80") +
  facet_wrap(~ measures ,scales = "free_y",labeller = label_parsed)+
  scale_colour_manual(values=c("blue","red", "black"))+
  scale_linetype_manual(values = c("dotted","dotted","dotted")) +
  scale_x_continuous("",
    labels=c(expression(beta[1]),expression(beta[2]),
    expression(beta[3]),expression(beta[4]),
    expression(beta[5])))+
  theme_minimal() +
  theme(legend.position = "none",
    plot.title = element_text(hjust = 0.5),
    plot.margin=unit(c(-0.1,0,-0.1,0.03), "cm"))

p2_1 <- ggplot(subset(dataggplot2,(avalues==4 & coef!=6)),aes(x = coef, y = yvalues2)) +
  geom_hline(data=hline_dat, aes(yintercept=threshold), col = "grey") +
  geom_line(aes(linetype=methods,colour=methods )) +
  geom_point(aes(shape=methods,colour=methods)) +
  legend.position = "none"
Figure 2 is the result of
```
ggrid.arrange(p0.5,p2_0.5)
```

Figure 3 is the result of
```
ggrid.arrange(p0.75,p2_0.75)
```

Figure 4 is the result of
```
ggrid.arrange(p1,p2_1)
```

Figure 5 is the result of
```
ggrid.arrange(p1.5,p2_1.5)
```

Figure 6 is the result of
Figure 7: Estimation of regression parameters $\beta = (\beta_1, \beta_2, \beta_3, \beta_4, \beta_5)$ with $\kappa = 0.5, n = 40, 80$. Simulation results for ML (black squares), mean BR (blue circles) and median BR (red triangles).
Figure 8: Estimation of regression parameters $\beta = (\beta_1, \beta_2, \beta_3, \beta_4, \beta_5)$ with $\kappa = 0.75, n = 40, 80$. Simulation results for ML (black squares), mean BR (blue circles) and median BR (red triangles).
Figure 9: Estimation of regression parameters $\beta = (\beta_1,\beta_2,\beta_3,\beta_4,\beta_5)$ with $\kappa = 1$, $n = 40, 80$. Simulation results for ML (black squares), mean BR (blue circles) and median BR (red triangles).
Figure 10: Estimation of regression parameters $\beta = (\beta_1, \beta_2, \beta_3, \beta_4, \beta_5)$ with $\kappa = 1.5, n = 40, 80$. Simulation results for ML (black squares), mean BR (blue circles) and median BR (red triangles).
Figure 11: Estimation of dispersion parameter $\kappa$ with $n = 40, 80$. Simulation results for ML (black squares), mean BR (blue circles) and median BR (red triangles).

grid.arrange(pk,p2_k)

3 Ames salmonella data

This section provides the R code that reproduces the numerical results of Section 5.1 of the paper. The code chunk below reproduces the results in Table 2 and illustrates the use of the brnb function.

```
source(paste(res_dir, "brnb.R", sep = "/"))
freq <- c(15,16,16,27,33,20,
          21,18,26,41,38,20,
          29,21,33,60,41,42)
dose <- rep(c(0,10,33,100,333,1000),3)
observation <- rep(1:3,each=6)
salmonella <- data.frame(freq,dose,observation)
fitmle <- brnb(freq~dose+log(dose+10),link="log",transformation ="identity",
               type = "ML", data = salmonella)
```
```r
fitmeanBR <- brnb(freq~dose+log(dose+10), link="log", transformation ="identity",
    type = "AS_mean", data = salmonella)
fitmedianBR <- brnb(freq~dose+log(dose+10), link="log", transformation ="identity",
    type = "AS_median", data = salmonella)
fitmeanBC <- brnb(freq~dose+log(dose+10), link="log", transformation ="identity",
    type = "correction", data = salmonella)
res <- round(cbind(coef(fitmle,"f"),sqrt(diag(vcov(fitmle,"f")));
    coef(fitmeanBC,"f"),sqrt(diag(vcov(fitmeanBC,"f")));
    coef(fitmeanBR,"f"),sqrt(diag(vcov(fitmeanBR,"f")));
    coef(fitmedianBR,"f"),sqrt(diag(vcov(fitmedianBR,"f"))))),5)
dimnames(res) <- list(c("beta0","beta1","beta2","kappa"),
    c("mle","semle","meanBC","semeanBC",
    "meanBR","semeanBR","medianBR","semedianBR"))
res
## mle semle meanBC semeanBC meanBR semeanBR medianBR semedianBR
## beta0  2.19763 0.32459 2.20982 0.34817 2.21551 0.35153 2.21139 0.35918
## beta1 -0.00098 0.00039 -0.00096 0.00042 -0.00096 0.00042 -0.00096 0.00043
## beta2  0.31251 0.08790 0.31051 0.09466 0.30916 0.09563 0.30909 0.09780
## kappa  0.04877 0.02815 0.06264 0.03276 0.06473 0.03345 0.06922 0.03501
```

The following code chunk uses the image file `salmonella_simulation_results.rda` to reproduce the results in Table 3 in the main text.

`salmonella_simulation_results.rda` results by running the script `brnb_salmonella_functions.R` which is available in the supplementary code archive.

```r
load(paste(res_dir, "salmonella_simulation_results.rda", sep = "/"))
table3
## PU RBIAS WALD IBMSE
## beta0_mle  50.96 -0.62 91.77 0.17
## beta0_meanBC  49.65 -0.12 93.77 0.01
## beta0_meanBR  49.43 -0.05 93.63 0.00
## beta0_medianBR  49.98 -0.26 94.17 0.03
## beta1_mle  51.49 -1.79 91.56 0.20
## beta1_meanBC  50.21 -0.39 93.85 0.01
## beta1_meanBR  49.95 -0.09 93.65 0.00
## beta1_medianBR  51.49 -1.79 91.56 0.20
## beta2_mle  48.56 0.85 91.70 0.09
## beta2_meanBC  49.43 0.26 93.85 0.01
## beta2_meanBR  49.71 0.14 93.74 0.00
## beta2_medianBR  49.63 0.21 94.21 0.01
## kappa_mle  71.88 -22.60 81.07 20.08
## kappa_meanBC  55.37 1.98 90.73 0.11
## kappa_meanBR  53.71 3.61 89.08 0.33
## kappa_medianBR  48.44 11.96 91.56 3.37
```

### 4 Epileptic seizures data

This section provides the R code that reproduces the numerical results of Section 5.2 of the paper. The code chunk below reproduces the results Figure 7 and illustrates again the use of the `brnb` function.
source(paste(res_dir, "nb.r", sep = "/"))
epil2 <- epil[epil$period == 1, ]
epil2$period[epil2$period == 1] <- rep(0, 59); epil2$y <- epil2$base; epil$"time" <- 1;
epil2$"time" <- 4
epil2 <- rbind(epil, epil2)
epil2$pred <- unclass(epil2$trt) * (epil2$period > 0); epil2$subject <- factor(epil2$subject)
epil3 <- aggregate(epil2, list(epil2$subject, epil2$period > 0),
  function(x) if(is.numeric(x)) sum(x) else x[1])
epil3$pred <- factor(epil3$pred,
  labels = c("base", "placebo", "drug"))
contrasts(epil3$pred) <- structure(contr.sdif(3),
  dimnames = list(NULL, c("placebo-base", "drug-placebo")))
# mle with glm.nb
epil3.mle(glm.nb) <- glm.nb(y ~ -1 + factor(subject) + factor(pred), data = epil3)
# mle
epil3.mle <- brnb(y ~ -i + factor(subject) + factor(pred), data = epil3,type="ML")
# meanBR
epil3.br <- brnb(y ~ -i + factor(subject) + factor(pred), data = epil3,type="AS_mean",
  start = coef(epil3.mle,"full" ))
# medianBR
epil3.mbr <- brnb(y ~ -i + factor(subject) + factor(pred), data = epil3,type="AS_median",
  start = coef(epil3.mle,"full" ))
# meanBR
epil3.bc <- brnb(y ~ -i + factor(subject) + factor(pred), data = epil3,type="correction",
  start = coef(epil3.mle,"full" ))
# modified profile likelihood
epil3.mpl <- nb.MPL(y ~ -1 + pred+strata(subject), strata = epil3$subject, data = epil3,
  obj.mle = epil3.mle.glm.nb, hessian = TRUE)
ml.est <- coef(epil3.mle,"full")[-c(1:59)]
ml.se <- sqrt(diag(vcov(epil3.mle,"full")))[-c(1:59)]
ml.ciu <- ml.est+qnorm(0.975)*ml.se
ml.cil <- ml.est-qnorm(0.975)*ml.se
bc.est <- coef(epil3.bc,"full")[-c(1:59)]
bc.se <- sqrt(diag(vcov(epil3.bc,"full")))[-c(1:59)]
bc.ciu <- bc.est+qnorm(0.975)*bc.se
bc.cil <- bc.est-qnorm(0.975)*bc.se
br.est <- coef(epil3.br,"full")[-c(1:59)]
br.se <- sqrt(diag(vcov(epil3.br,"full")))[-c(1:59)]
br.ciu <- br.est+qnorm(0.975)*br.se
br.cil <- br.est-qnorm(0.975)*br.se
mbr.est <- coef(epil3.mbr,"full")[-c(1:59)]
mbr.se <- sqrt(diag(vcov(epil3.mbr,"full")))[-c(1:59)]
mbr.ciu <- mbr.est+qnorm(0.975)*mbr.se
mbr.cil <- mbr.est-qnorm(0.975)*mbr.se
mpl.est <- epil3.mpl$coef
mpl.est[3] <- exp(-epil3.mpl$coef[3])
mpl.se <- epil3.mpl$se
mpl.se[3] <- mpl.se[3]*exp(-epil3.mpl$coef[3])
mpl.ciu <- mpl.est+qnorm(0.975)*mpl.se
mpl.cil <- mpl.est-qnorm(0.975)*mpl.se

Figure 7 is the results of
Figure 12: Epileptic seizures: points represent the parameter estimates while the vertical lines represent 95% Wald-type confidence intervals.

The following code chunk uses the image file epileptic_simulation_results.rda to reproduce the results in Table 4 and Figure 8 in the main text.
epileptic_simulation_results.rda results by running the script
brnb_epileptic_functions.R which is available in the supplementary code archive.
Table 4 is the result of

```
load(paste(res_dir, "epileptic_simulation_results.rda", sep = "/"))
table4
## PU RBIAS WALD IBMSE
## beta1_mle 49.80 0.42 82.22 0.00
## beta1_meanBC 50.15 -0.16 89.63 0.00
## beta1_meanBR 49.86 0.52 94.36 0.00
## beta2_medianBR 49.89 0.54 94.40 0.00
## beta2_mle 49.84 0.09 82.03 0.00
## beta2_meanBC 49.45 0.37 89.04 0.01
## beta2_meanBR 50.63 -0.50 94.55 0.02
## beta2_medianBR 50.62 -0.53 94.60 0.02
## kappa_mle 100.00 -79.32 0.39 3671.91
## kappa_meanBC 93.47 -40.99 40.34 286.52
## kappa_meanBR 48.78 3.99 81.44 1.10
## kappa_medianBR 48.81 3.89 82.15 1.08
```

The code chunk below prepares the data for producing Figure 8 in the main text..

```
yvalues=c(rbias_nuis,pu_nuis,cov_nuis,ibmse_nuis)
methods=rep(rep(c("1","2","3","4"),each=59),4)
measures= as.factor(rep(c(1,2,3,4),each=236))
levels(measures)=c("RBIAS","PU","WALD","IBMSE")
xvalues = rep(rep(1:59,4),4)
dataggplot = data.frame(yvalues,methods,xvalues,measures)
hline_dat=data.frame(measures=c("RBIAS" , "PU", "WALD", "IBMSE"),
threshold=c(0, 50, 95, 0))

Figure 8 is the results of

```
ggplot(dataggplot,aes(x = xvalues, y = yvalues)) +
  geom_hline(data=hline_dat, aes(yintercept=threshold), col = "grey") +
  geom_line(aes(linetype=methods,colour=methods ))+
  ggtitle("") +
  labs(x = "", y = "") +
  facet_wrap(~measures ,scales = "free_y",labeller = label_parsed,nrow=4)+
  scale_colour_manual(values=c("black","green", "red","blue")) +
  scale_linetype_manual(values = c("solid","dotted","dashed","dotdash")) +
  scale_x_discrete(expression(paste("Nuisance parameters"," (",lambda, ")")),
  limits=c(1:59), breaks=c(1:59),labels=c(1:59)) +
  theme_bw()+
  theme(legend.position = "none",
  plot.title = element_text(hjust = 0.5),
  strip.background = element_blank(),text = element_text(),
  axis.text.x = element_blank(),
  plot.margin = margin(-0.5, 0.5, 0, 0, "cm"))
```
Figure 13: Epileptic seizures: Simulation results for estimators of the nuisance parameters: ML (black solid line), mean BC (green dotted line), mean BR (red dashed line), and median BR (blue dotdash line).