Double-mixing semiparametric logistic regression with unknown sizes

Wei Zhang

Department of Statistics, University of California, Riverside, CA , 92521
wxz118@yahoo.com

Abstract

Binomial data with unknown sizes often appear in biological and medical sciences and are usually overdispersed. All previous methods used parametric models and only considered overdispersion due to the variation of sizes. The proposed semiparametric model considers overdispersion due to the variation of sizes and that of probabilities. By doing this, it can include variations caused by observations, missing covariates, and random measurement errors in covariates. An Expectation Conditional Maximization algorithm is provided to stabilize the loglikelihood optimization. Selecting the number of support points of the mixing distributions and the bootstrap methods are also discussed. Simulation is done to evaluate the performance of the proposed model. Two real examples are used to illustrate the proposed model.

Keywords: Bioassay; Dose response; Quantal response

1 Introduction

The study about the binomial data with unknown sizes can be dated back to Wadley (1949), which made a fictitious experimental data set. In the experiment, fruits were infested with fruit-fly larvae and exposed to low temperature with varying days. Some of the larvae would die from low temperature. The number of fruit-flies that were seen to emerge was counted, but the initial larvae number was not known.

A lot of real binomial data with unknown sizes appeared in the literature. For example, Morton (1981) presented a data set about the disinfestation of wheat. Margolin et al. (1981) studied the effects of quinoline on the number of revertant colonies of Salmonella strain TA98. Elder (1996) investigated the relationship between the survival of V79-473 cells and their times in the high heat. Bailer and Piegorsch (2000) took the effect of nitrofen on the offspring of C. dubia as an example.

Let $y_i$ denote a binomial random variable with size $n_i$ unknown and probability $p_i$, and $x_i$ denote a vector of covariates of length $\rho$, $i = 1, 2, \ldots, r$. The issue of interest is to investigate the relationship between the covariates $x_i$ and the probabilities $p_i$. If overdispersion exists, there will be three cases: overdispersion due to only the variability of $n_i$, or due to both of them (Elder et al. 1999).

The binomial data with unknown sizes are usually approximated by Poisson distributions (e.g. Wadley 1949 and Margolin et al. 1981). However, such an approximation is not reasonable for moderate sizes or probabilities (e.g. Elder et al. 1999). Anscombe (1949) considered overdispersion due to the $n_i$ and provided a parametric model based on the negative binomial distribution. Baker et al. (1980) treated $y_i$ in the control group as a Poisson random variable with mean $m$ and that in the treatment group with mean $mp_i$, where a probit dose-response relationship is assumed. Trajstman (1989) modified the method of Baker et al. (1980) to allow a logistic dose-response relation and incorporated overdispersion by assuming a scaled Poisson variance-mean relationship. Based on Baker et al. (1980), Morgan and Smith (1992) used a full negative-binomial distribution and incorporated extra Poisson variation. Kim and Taylor (1994) and Elder et al. (1999) developed a quasi-likelihood approach by regarding $y_i$ as a binomial random variable. Kim and Taylor (1994) assumed that $E(n_i) = m_i$ and $\text{var}(n_i) = m_i\nu$ with $m_i$ known and $\nu \geq 1$ unknown. Elder et al. (1999) estimated $m = E(n_i)$ with $\text{var}(n_i) = m(1 + \nu m)$ and $\nu \geq 0$. All previous methods used parametric models and only considered overdispersion due to the variation of $n_i$. 

We propose a semiparametric model to incorporate overdispersion due to the variability of \( n_i \) and \( p_i \). The \( n_i \) are assumed to be Poisson distributed with means from an unspecified mixing distribution. With the mean of \( n_i \) being a random variable, overdispersion due to the variation of \( n_i \) is taken into account. It is assumed that \( p_i = p(\eta + x_i'\beta) \), where the \( \eta \) are further assumed to follow another unspecified mixing distribution. With \( \eta \) being a random variable, we include variations caused by observations, missing covariates, and random measurement errors in covariates (Follmann and Lambert 1989).

Section 2 is the method part, and includes the proposed model, the Expectation Conditional Maximization (ECM) algorithm, how to select the number of support points, and the bootstrap methods. A simulation study is presented in Section 3. Two real examples of bioassay are investigated in Section 4.

2 Methods

2.1 A model

In the proposed model, a logistic link is assumed, and its inverse is

\[
p_i = p(\eta + x_i'\beta) = \frac{\exp(\eta + x_i'\beta)}{1 + \exp(\eta + x_i'\beta)}.
\]

The unknown size \( n_i \) is assumed to be a Poisson random variable with mean \( \xi_i \). It can be easily shown that \( y_i | \xi_i, \eta \sim \text{Pois}(\xi_i p(\eta + x_i'\beta)) \). The nuisance parameters \( \xi_i \) and \( \eta \) are further assumed to follow mixing distributions \( G \) and \( H \), respectively. Since the parameter of interest \( \beta \) is in an Euclidean space of dimension \( \varrho \), a semiparametric model arises when \( G \) and \( H \) are nonparametric. The density of a single observation \((y, x)\) is

\[
f(y; x, \beta, G, H) = \int \int f(y; x, \beta, \lambda, \alpha)dG(\lambda)dH(\alpha),
\]

where \( f(y; x, \beta, \lambda, \alpha) \) is a Poisson density with mean \( \lambda p(\alpha + x'\beta) \), i.e.,

\[
f(y; x, \beta, \lambda, \alpha) = \exp\{-\lambda p(\alpha + x'\beta)\}\{\lambda p(\alpha + x'\beta)\}^y/y!,
\]

\( y = 0, 1, \ldots \).

The log likelihood can be written as

\[
\ell(\beta, G, H) = \sum_{i=1}^{r} \log f(y_i; x_i, \beta, G, H).
\]  

2.2 An ECM algorithm

Since any distribution can be approximated by a discrete distribution, we assume \( G \) and \( H \) are discrete distributions. First, we consider that \( G \) and \( H \) have a fixed number of support points \( K_1 \) and \( K_2 \), which will be allowed to change in Section 2.3. Let \( G = \sum_{j=1}^{K_1} \rho_j \delta(\lambda_j) \) and \( H = \sum_{m=1}^{K_2} \pi_m \delta(\alpha_m) \), where \( \sum_{j=1}^{K_1} \rho_j = 1, \sum_{m=1}^{K_2} \pi_m = 1, \rho_j \geq 0, \pi_m \geq 0 \), \( \delta \) is the indicator function, \( \lambda_j \in (0, \infty) \), and \( \alpha_m \in \mathcal{R} \). Let \( \rho = (\rho_1, \rho_2, \ldots, \rho_{K_1})', \lambda = (\lambda_1, \lambda_2, \ldots, \lambda_{K_1})', \pi = (\pi_1, \pi_2, \ldots, \pi_{K_2})', \alpha = (\alpha_1, \alpha_2, \ldots, \alpha_{K_2})', \) and \( \theta = (\beta, \rho, \lambda, \pi, \alpha) \). The log likelihood becomes

\[
\ell(\theta) = \sum_{i=1}^{r} \log \left\{ \sum_{j=1}^{K_1} \sum_{m=1}^{K_2} \rho_j \pi_m f(y_i; x_i, \beta, \lambda_j, \alpha_m) \right\}.
\]  

Since direct maximization of \( \ell(\theta) \) in (2) is extremely difficult, an EM algorithm may be considered. However, the M-step in the EM algorithm may be computationally unreliable because of so many parameters.

The ECM algorithm (Meng and Rubin 1993, McLachlan and Peel 2000, p148) is promising. The ECM algorithm simplifies the M-step by replacing the complicated M-step with five computationally simpler and stabler CM-steps.
The expected conditional complete log likelihood to be maximized is
for a single datum \((x, y, z_1, z_2)\) is
\[
\prod_{j=1}^{K_1} \prod_{m=1}^{K_2} \left[ \rho_j \pi_m f(y; x, \beta, \lambda_j, \alpha_m) \right]^{z_{1j} z_{2m}}.
\]
The joint complete log likelihood is
\[
\ell_c(\theta) = \sum_{i=1}^{r} \sum_{j=1}^{K_1} \sum_{m=1}^{K_2} z_{1ij} z_{2jm} \left[ \log \rho_j + \log \pi_m + \log \left( f(y; x, \beta, \lambda_j, \alpha_m) \right) \right].
\]
The expected conditional complete log likelihood to be maximized is
\[
W(\theta; \theta^{(0)}) = E_{\theta^{(0)}} \left\{ \ell_c(\theta) | y_1, y_2, \ldots, y_r \right\}.
\]
In the E-step, the conditional expectation of \(z_{1ij} z_{2jm}\) is calculated, i.e., for \(i = 1, 2, \ldots, r, j = 1, 2, \ldots, K_1, m = 1, 2, \ldots, K_2\),
\[
e_{ijm}^{(0)} = E_{\theta^{(0)}} \left( z_{1ij} z_{2jm} | y_1, y_2, \ldots, y_r \right) = \frac{\rho_j^{(0)} \pi_m^{(0)} f(y_i; x, \beta^{(0)}, \lambda_j^{(0)}, \alpha_m^{(0)})}{\sum_{h_1=1}^{K_1} \sum_{h_2=1}^{K_2} \rho_{h_1}^{(0)} \pi_{h_2}^{(0)} f(y_i; x, \beta^{(0)}, \lambda_{h_1}^{(0)}, \alpha_{h_2}^{(0)})}.
\]
In the CM-step, the expected conditional complete log likelihood
\[
W(\theta; \theta^{(0)}) = \sum_{i=1}^{r} \sum_{j=1}^{K_1} \sum_{m=1}^{K_2} e_{ijm}^{(0)} \log \rho_j + \sum_{i=1}^{r} \sum_{j=1}^{K_1} \sum_{m=1}^{K_2} e_{ijm}^{(0)} \log \pi_m +
\sum_{i=1}^{r} \sum_{j=1}^{K_1} \sum_{m=1}^{K_2} e_{ijm}^{(0)} \log f(y_i; x, \beta, \lambda_j, \alpha_m)
\]
\[
= \text{constant} + \sum_{i=1}^{r} \sum_{j=1}^{K_1} \sum_{m=1}^{K_2} e_{ijm}^{(0)} \log \rho_j + \sum_{i=1}^{r} \sum_{j=1}^{K_1} \sum_{m=1}^{K_2} e_{ijm}^{(0)} \log \pi_m +
\sum_{i=1}^{r} \sum_{j=1}^{K_1} \sum_{m=1}^{K_2} e_{ijm}^{(0)} \{ y_i \log \lambda_j + y_i \log p(\alpha_m + x'_i \beta) - \lambda_j p(\alpha_m + x'_i \beta) \}
\]
is maximized over \(\rho, \pi, \lambda, \alpha\) and \(\beta\) sequentially. Because \(\rho, \pi\) and \((\lambda, \alpha, \beta)\) are in \(T_1(\rho), T_2(\pi)\) and \(T_3(\lambda, \alpha, \beta)\) separately, their maximum likelihood estimators (MLEs) can be found individually. The MLE for \(\rho\) is
\[
\rho_j^{(1)} = r^{-1} \sum_{i=1}^{r} \sum_{m=1}^{K_2} e_{ijm}^{(0)}, j = 1, 2, \ldots, K_1.
\]\[\hline\]
The MLE for \(\pi\) is
\[
\pi_m^{(1)} = r^{-1} \sum_{i=1}^{r} \sum_{j=1}^{K_1} e_{ijm}^{(0)}, m = 1, 2, \ldots, K_2.
\]
We will maximize $T_3(\lambda, \alpha, \beta)$ over $\lambda$, $\alpha$ and $\beta$ sequentially. The conditional MLE for $\lambda$ given $\alpha = \alpha^{(0)}$ and $\beta = \beta^{(0)}$ is

$$
\lambda_{j}^{(1)} = \frac{\sum_{i=1}^{r} \sum_{m=1}^{K_2} e_{ijm}^{(0)} y_i}{\sum_{i=1}^{r} \sum_{m=1}^{K_2} e_{ijm}^{(0)} p(\alpha_m^{(0)} + \beta^0)}, \quad j = 1, 2, \ldots, K_1.
$$

(5)

There are no simple analytic forms for the conditional MLEs of $\alpha$ and $\beta$. The conditional MLE for $\alpha$ given $\lambda = \lambda^{(1)}$ and $\beta = \beta^{(0)}$ is

$$
\alpha_m^{(1)} = \arg\max_{\alpha_m \in \mathbb{R}} \sum_{i=1}^{r} \sum_{j=1}^{K_1} e_{ijm}^{(0)} \left\{ y_i \log \lambda_j + y_i \log p(\alpha_m + \beta^0) - \lambda_j p(\alpha_m + \beta^0) \right\},
$$

(6)

for $m = 1, 2, \ldots, K_2$. The conditional MLE for $\beta$ given $\lambda = \lambda^{(1)}$ and $\alpha = \alpha^{(1)}$ is

$$
\beta^{(1)} = \arg\max_{\beta \in \mathbb{R}^{p}} T_3(\lambda^{(1)}, \alpha^{(1)}, \beta).
$$

(7)

The function $\text{optim}$ in R can be used to get the MLEs of $\alpha$ and $\beta$ in equations (6) and (7).

### 2.3 Selecting the number of support points

The maximized log likelihood $\ell(\hat{\theta})$ can be increased by increasing the number of support points of $G$ or $H$. We propose to choose the number of support points by minimizing the BIC (e.g., Wang et al. 1996) to obtain a reasonable and parsimonious fit to the data, i.e.,

$$
(K_1, K_2) = \arg\min_{(K_1, K_2) \in \{1, 2, \ldots\}^2} \left\{ -2\ell(\hat{\theta}) + \log(r) \left[ 2(K_1 + K_2) - 2 + p \right] \right\}.
$$

Forward model selection is used. For a fixed $K_1$, if the BIC stops to decrease for larger $K_2$, the models with greater $K_2$ will not be considered for this $K_1$. The strategy is the same for $K_2$ fixed and $K_1$ changed. From all the models considered, the one with the minimum BIC is chosen.

### 2.4 The bootstrap method

The confidence intervals for the regression coefficients $\beta$ can be got by the bootstrap method. The nonparametric bootstrap method may be applied for a random design, in which one can sample the pairs $(y_i, x_i)$. For a fixed design, a parametric bootstrap method is recommended. A resample of size $r$ is generated as follows,

$$
y_i^* \sim f(y; \hat{x}, \hat{\beta}, \hat{\lambda}_i, \hat{\alpha}_i), i = 1, 2, \ldots, r,
$$

where $\lambda_i$ and $\alpha_i$ are random variables drawn from the estimated mixing distributions $\hat{G}$ and $\hat{H}$, respectively, where

$$
\hat{G} = \sum_{j=1}^{K_1} \rho_j \delta(\hat{\lambda}_j) \quad \text{and} \quad \hat{H} = \sum_{m=1}^{K_2} \pi_m \delta(\hat{\alpha}_m).
$$

### 3 Simulation

In the simulation, the parameter setting takes a $2^3$ design,

$$
\beta \times G \times H = \{(-2, 3) \times \{G_1, G_2\} \times \{H_1, H_2\}\}.
$$
where \( G_1 = 0.1\delta(100) + 0.8\delta(200) + 0.1\delta(300), G_2 = 0.5\delta(10) + 0.5\delta(50), H_1 = 0.3\delta(-2)+0.3\delta(0.4)+0.4\delta(3), \) and \( H_2 = 0.25\delta(-2) + 0.75\delta(1.5). \) There is a single covariate \( x \) in the simulation. For each integer \( x \) in \([-5, 5]\), 10 values of \( y \) are drawn independently from a Possion distribution with mean \( \lambda p(\alpha + x\beta) \), where \( \lambda \) and \( \alpha \) are random variables drawn from \( G \) and \( H \). So the sample size \( r \) is 110.

For each parameter setting, 200 samples are drawn. Table 1 presents the simulation results. The bias, standard deviation and mean square error of \( \beta \) are small, and each \( \beta \) falls into its 95\% quantile interval, with 2.5\% and 97.5\% quantiles as endpoints.

Table 1: Simulation results: sd stands for standard deviation, qi for 95\% quantile intervals and mse for mean square error.

| setting | beta | G | H | bias | sd     | qi       | mse   |
|---------|------|---|---|------|--------|----------|-------|
| 1       | -2   | \( G_1 \) | \( H_1 \) | -0.00 | 0.08   | (-2.15, -1.86) | 0.01  |
| 2       | -2   | \( G_1 \) | \( H_2 \) | -0.01 | 0.09   | (-2.17, -1.85) | 0.01  |
| 3       | -2   | \( G_2 \) | \( H_1 \) | -0.11 | 0.32   | (-2.77, -1.62) | 0.12  |
| 4       | -2   | \( G_2 \) | \( H_2 \) | -0.07 | 0.24   | (-2.69, -1.68) | 0.06  |
| 5       | 3    | \( G_1 \) | \( H_1 \) | 0.00  | 0.16   | (2.72, 3.27)    | 0.02  |
| 6       | 3    | \( G_1 \) | \( H_2 \) | 0.02  | 0.16   | (2.72, 3.33)    | 0.02  |
| 7       | 3    | \( G_2 \) | \( H_1 \) | 0.17  | 0.68   | (2.20, 4.50)    | 0.49  |
| 8       | 3    | \( G_2 \) | \( H_2 \) | 0.03  | 0.45   | (2.36, 4.23)    | 0.20  |

4 Example

4.1 M. Bovis data

Table 2 is part of Table 1 of Trajstman (1989), and also appeared in Morgan and Smith (1992). One of the decontaminants, HPC or oxalic acid, with a specific concentration was applied on a group of M. bovis cells, which were then placed on the culture plates for colony formation. After 12 weeks (at stationarity), the number of M. bovis colonies were counted, which is equal to the number of surviving M. bovis cells.

An ANOVA model is fitted with a separate factor for each level of the decontaminants. Let \( x_j \) denote a factor for the concentration level \( j \) of the decontaminants. It is assumed that the \( p_i \) satisfy that

\[
\log \left\{ \frac{p_i}{1-p_i} \right\} = \eta + \sum_{j=1}^{11} \beta_j x_{ij}, \quad i = 1, 2, \ldots, 129, \tag{8}
\]

where \( \eta \) is the control effect and \( \beta_j \) is the effect difference between dose \( j \) and the control one, \( j = 1, 2, \ldots, 11 \).

From Table 2 the case in which \( \hat{G} \) and \( \hat{H} \) with 2 support points has the minimum BIC. Therefore, the MLEs of \( G \) and \( H \) are \( \hat{G} = 0.04\delta(12.41) + 0.96\delta(99.32), \) and \( \hat{H} = 0.82\delta(-0.03) + 0.18\delta(0.63), \) respectively.

Table 2 presents the estimated regression coefficients, their bootstrap standard errors and 95\% confidence intervals from 200 bootstrap resamples. The MLEs \( \hat{\beta}_0 \) and \( \hat{\beta}_9 \) violate the monotonic dose-response relationship, i.e., the larger dose do not produce stronger effects here. This finding is consistent with the monotonicity violation of their sample means in Table 2. Nine out of eleven confidence intervals do not include 0, so the corresponding doses have significantly stronger negative effects than the control one. Two exceptions are those of \( \hat{\beta}_6 \) and \( \hat{\beta}_{11} \). An explanation is that the Oxalic acid dose 0.005 is too small to take any different effect on the M. Bovis cells from the control one. The estimates of \( \beta \) in Table 2 cannot be compared to those of Trajstman (1989) and Morgan and Smith (1992), because they used a simple linear model in (8). Figure 2 presents the responses \( y \), the sample means \( \bar{y} \) and the fitted values \( \hat{y} \). The model seems fit well.
Table 2: The *M. bovis* cell survival data.

| % weight/volume | No. of *M. bovis* colonies at stationarity | sample mean |
|-----------------|-------------------------------------------|-------------|
| control experiment (no decontaminant) |                                            |             |
| 52              | 80                                        | 55          |
| 44              | 51                                        | 34          |
| 37              | 46                                        | 37          |
| 46              | 56                                        | 46          |
| 64              | 51                                        | 67          |
| 67              | 40                                        |             |
| [HPC] decontaminant: HPC                  |                                            |             |
| 0.75            | 2                                         | 4           |
| 0.375           | 11                                        | 12          |
| 0.1875          | 16                                        | 6           |
| 0.09375         | 33                                        | 46          |
| 0.075           | 30                                        | 27          |
| 0.0075          | 53                                        | 62          |
| 0.00075         | 3                                         | 42          |
| [Oxalic acid] decontaminant: oxalic acid |                                            |             |
| 5               | 14                                        | 6           |
| 0.5             | 27                                        | 33          |
| 0.05            | 33                                        | 26          |
| 0.005           | 36                                        | 54          |

Figure 1: The response $y$, sample mean $\bar{y}$ and fitted value $\hat{y}$. 

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Table 3: The BIC for the estimated mixing distributions.

| $K_1 \setminus K_2$ | 1   | 2   | 3   | 4   |
|---------------------|-----|-----|-----|-----|
| 1                   | 1061.1 | 991.3 | 977.6 | 985.1 |
| 2                   | 998.0  | 976.9 | 978.3 | 988.9 |
| 3                   | 977.0  | 978.7 | 994.3 |      |
| 4                   | 984.2  | 988.5 |      |      |

Table 4: The estimated regression coefficients, bootstrapped standard error, and 95% confidence interval for the $M$. Bovis data.

| dose  | $\beta$       | MLE | se  | 95% ci                |
|-------|---------------|-----|-----|-----------------------|
|       | $\beta_1$    | -2.74 | 0.55 | (-4.29, -2.36)        |
|       | $\beta_2$    | -1.86 | 0.51 | (-3.38, -1.55)        |
|       | $\beta_3$    | -1.25 | 0.48 | (-2.59, -0.96)        |
|       | $\beta_4$    | -0.98 | 0.45 | (-2.12, -0.69)        |
|       | $\beta_5$    | -0.72 | 0.42 | (-1.72, -0.48)        |
|       | $\beta_6$    | -0.04 | 0.49 | (-0.25, 1.38)         |
|       | $\beta_7$    | -0.35 | 0.38 | (-1.14, -0.07)        |
| Oxalic acid | $\beta_8$    | -2.30 | 0.53 | (-3.63, -1.96)        |
|       | $\beta_9$    | -0.84 | 0.45 | (-1.99, -0.55)        |
|       | $\beta_{10}$ | -0.90 | 0.41 | (-2.11, -0.68)        |
|       | $\beta_{11}$ | -0.28 | 0.38 | (-0.97, 0.08)         |

4.2 Jejunal crypt data

The jejunal crypt data are referred to Table 1 of Elder et al. (1999), which are also studied by Kim and Taylor (1994). There are 126 live mice divided into groups, not all of equal sizes. The treatment consists of exposing each group of mice to a certain dose of gamma rays, and then killing them to find out the number of surviving crypts. The total number of crypts in each mouse is unknown, because the experiment needs live mice. It is assumed that the surviving probabilities $p_i$ satisfy that

\[
\log \left\{ \frac{p_i}{1 - p_i} \right\} = \eta + \beta x_i, \quad i = 1, 2, \ldots, 126,
\]

where $x_i$ is the gamma dose.

The BIC are 724.2 for $K_1 = K_2 = 1$, 733.9 for $K_1 = 2$, $K_2 = 1$ and $K_1 = 1$, $K_2 = 2$. Thus, the estimated $\hat{G}$ is degenerated at $\hat{\alpha} = 6.705$, and $\hat{H}$ at $\hat{\lambda} = 196.1$. We draw 200 bootstrap resamples. Table 4 presents the estimation results of the proposed model and the previous ones. The bootstrap standard error of $\beta$ is quite small and its 95% confidence interval is $(-1.225, -1.029)$. All listed estimates of $\beta$ lie in our confidence interval. Since this interval does not cover 0, the $\beta$ in the proposed model is significant at the significance level of 0.05.

5 Discussion

We propose a flexible semiparametric model to incorporate overdispersion due to the variation of $n_i$ and $p_i$. The regression coefficients are estimated with the nuisance parameters, the mixing distributions in a seamless fashion. Although a logistic dose-response relation is assumed, it can be extended to other links very easily. When one runs
Table 5: Jejunal crypt data results from the proposed and previous approaches (logistic regression and Kim’s method fix $n_i$ and $E(n_i)$ at 160, respectively; Kim’s and Elder’s quasi-likelihood method of moments estimates come from Elder et al. (1999)).

|          | logistic | Kim’s   | Elder’s  | proposed |
|----------|----------|---------|----------|----------|
| $\alpha$ | 7.432 (0.175) | 7.410 (0.191) | 6.727 (0.725) | 6.705    |
| $\beta$  | -1.185 (0.024) | -1.183 (0.026) | -1.126 (0.061) | -1.124 (0.044) |
| $\lambda$| —        | —       | 194.7 (43.4) | 196.1    |

the ECM algorithm, a Poisson regression is suggested to run first to obtain a good initial value of $\beta$.

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