Logistic regression with unknown sizes

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Abstract

Binomial data with unknown sizes often appear in biological and medical sciences. The previous methods either use the Poisson approximation or the quasi-likelihood approach. A full likelihood approach is proposed by treating unknown sizes as latent variables. This approach simplifies analysis as maximum likelihood estimation can be applied. It also facilitates us to gain a lot more insights into efficiency loss across models and estimation precision within models. Simulation assesses the performance of the proposed model. An application to the surviving jejunal crypt data is discussed. The proposed method is not only competitive with the previous methods, but also gives an appropriate explanation of the inflated variation of expected sizes.

Keywords: Dose response; Efficiency loss; Mixture model; Overdispersion

1 Introduction

Binomial data with unknown sizes often appear in biological and medical sciences. For example, Margolin et al. (1981) studied how the number of revertant colonies of Salmonella strain TA98 changed with the dosage of a chemical agent quinolin. Bailer and Piegorsch (2000) reviewed a \textit{C. dubia} survival and reproduction toxicity test. Trajstman (1989) presented a data set from an experiment of a \textit{M. bovis} subjected to the decontaminants. Elder (1996) investigated how the times in high heat affect the survival of V79-473 cells.

The jejunal radiation damage is studied extensively in the literature of medical sciences. Some studies concerned the clinical value of some material in protecting jejunal crypts against radiation (e.g., Goel et al. 2003, Salin et al. 2001 and Khan et al. 1997). Other studies investigated radiosensitivity of jejunal crypt stem cells (e.g., Kinashi et al. 1997). There are also studies interested in survival of crypt epithelial cells in the jejunum of mice exposed to different doses of X-rays (e.g., Mason et al. 1999). Table 1 presents a surviving jejunal crypt data set from an experiment done on 126 mice (Kim and Taylor 1994; Elder et al. 1999). In such an experiment, each mouse is exposed to a certain dose of gamma rays, then sacrificed to find out the number of crypts survived. The total number of crypts before the experiment is unknown, since the only way to know this number is to sacrifice the mouse while live mice are required in the experiment.

Let $y_i$ be the number of surviving crypts in mouse $i$. It is appropriate to treat $y_i$ as a binomial random variable with size $n_i$ and surviving probability $p_i$, where $n_i$ is the total number of crypts in mouse $i$. The issue of interest is to investigate how the surviving probability $p_i$ depends on the dose of gamma radiation $x_i$ applied to mouse $i$. If the $n_i$ were known, then one could apply the classical logistic regression (e.g., McCullagh and Nelder 1999). Because $n_i$ is unknown, $y_i$ can also be approximately treated as a Poisson random variable, which is a common approach in the literature. Such a Poisson approximation is crude when $p_i$ is moderately large (e.g., Elder et al. 1999). By putting additional assumptions on the $n_i$, Kim and Taylor (1994) and Elder et al. (1999) developed a quasi-likelihood approach. Kim and Taylor (1994) considered that $E(n_i) = m_i$ and var $(n_i) = m_i$ with $m_i$ known and $> 1$ unknown. Elder et al. (1999) considered estimating $m = E(n_i)$ with var $(n_i) = m(1 + m)$ and $> 0$.

We will assume that each $n_i$ is a Poisson random variable with mean $m_i$ and that the $m_i$ arise as a random sample from a mixing distribution. In particular, a gamma distribution will be used in this article. By doing this, the requirement of prior knowledge about the $E(n_i)$ in Kim and Taylor (1994) is removed. Compared to the quasi-likelihood approach in Elder et al. (1999), our approach simplifies analysis as standard techniques, i.e., maximum likelihood...
Table 1: The jejunal crypt data (dose: the dose of gamma radiation in Gy; count: the surviving number of crypts of a mouse).

| dose | count            |
|------|------------------|
| 6.25 | 76, 96, 73, 81, 87, 77, 75 |
| 6.50 | 75, 80, 67, 86, 70, 78, 88, 76, 54, 58, 76, 69, 61, 70 |
| 6.75 | 66, 51, 48, 47, 45, 59, 49 |
| 7.25 | 66, 51, 48, 42, 47, 36, 76, 40, 37, 45, 38, 40, 35, 27, 35 |
| 7.75 | 19, 18, 25, 19, 19, 18, 21, 18 |
| 8.00 | 19, 24, 19, 16, 12, 14, 19, 11, 21, 19, 14, 16, 13 |
| 8.25 | 19, 19, 19, 16, 12, 13 |
| 8.75 | 19, 19, 19, 18, 18, 14, 19, 11, 21, 19, 14, 16, 13 |
| 9.25 | 6, 3, 5, 6, 4, 6, 3 |
| 9.50 | 1, 4, 5, 5, 3, 6, 3, 5, 5, 1, 4, 3, 4 |

estimation, can be applied. This model also facilitates us to investigate the efficiency loss due to the \( n_1 \) being unknown and being over-dispersed and how one parameter influence estimation precision of the parameters within a model. Therefore, we can gain much more insights into the problem than previous methods.

The proposed method is described in Section 2. Efficiency losses are studied in Section 3. The estimation precision is investigated in Section 4. A simulation study is presented in Section 5. The investigation of the jejunal crypt data is done in Section 6.

2 The proposed method

Suppose that the data consist of \( r \) pairs of \((y_i; x_i), i = 1, 2, \ldots, r\), where \( x_i \) is the covariate associated with observation \( i \), such that \( y_i \sim \text{Bin}(n_i; p_i) \), \( p_i = h(x_i; ) \). Note that \( h^{(1)} \) is a known link function, such as

\[
h(x; ) = \frac{\exp(x^0)}{1 + \exp(x^0)};
\]

When each \( n_i \) is assumed to be a Poisson random variable with mean \( \lambda_i \), it is easily shown that \( y_i \sim \text{Pois} (\lambda_i) \). We will further assume that the \( \lambda_i \) arise as a random sample from a gamma density which can be written as

\[
\lambda_i \sim \text{Gamma}(\alpha_i, \beta_i); \quad \alpha_i \sim \text{Gamma}(0; 1); \quad \beta_i \sim \text{Gamma}(0; 1); \quad \text{and} \quad \text{var}(\lambda_i) = \frac{\alpha_i}{\beta_i};
\]

where \( \alpha_i \) is the shape parameter and \( \beta_i \) is the rate parameter. The mean is \( \lambda_i = \alpha_i \) and the variance is \( \text{var}(\lambda_i) = \frac{\alpha_i}{\beta_i} = \frac{\alpha_i}{\beta_i} \). Note that \( \alpha_i = (\beta_i)^2 \), that is, \( \alpha_i = \text{the squared coefficient of variation} \). With \( (\beta_i; \gamma) \) used to parameterize gamma densities and \( \gamma = (\beta_i; \gamma) \), it is clear that marginally \( y_i \) is a negative binomial random variable (Anscombe 1949) with density

\[
f(y_i; \lambda_i) = \binom{y_i + \lambda_i}{y_i} \frac{\exp(y_i \lambda_i)}{\exp(\lambda_i) + \exp(y_i \lambda_i)} g^{y_i};
\]

The log likelihood is written as

\[
\log f(y_i; \lambda_i) = \sum_{i=1}^{r} \log f(y_i; \lambda_i); \quad i = 1, \ldots, r.
\]

This looks much like, but is not a special case of negative binomial regression. In negative binomial regression, \( y_j \sim \text{Pois}(\lambda_j) \), \( \lambda_j = \gamma_j (\beta_j; ) \), and \( \gamma_j = (\beta_j; ) \) for some function \( \gamma \). In the proposed model, \( y_j \sim \text{Pois}(\lambda_j) \), \( \lambda_j = \gamma_j (\beta_j; ) \), \( \gamma_j = (\beta_j; ) \), and \( \beta_j \) is only a parameter and has nothing to do with \( \beta_j \).

Let \( \hat{} \) be the maximum likelihood estimator (MLE) for \( \beta_j \). Asymptotically, \( \hat{} \) is a multivariate normal random vector
with mean and variance-covariance matrix $I_1^{-1}(\cdot)$ (e.g., Lehmann and Casella 1998, chapter 6), where, with $r$ being the gradient with respect to $r$, $I_r(\cdot)$ is the Fisher information matrix given by

$$I_r(\cdot) = \begin{pmatrix}
\frac{2}{4} & 6^2 & 0 & 3^2 \\
6^2 & \frac{1}{4} & 7 & 0 \\
0 & 7 & \frac{1}{4} & 0 \\
3^2 & 0 & 0 & \frac{1}{4}
\end{pmatrix} \tag{2}
$$

Because of those zero entries in $I_r(\cdot)$, is orthogonal to the pair of $(\cdot)$, There are several consequences (e.g., Cox and Reid 1987). The asymptotic standard errors of $^\circ$ and $^\circ$ are not affected by treating $\theta$ as either known or unknown. The MLEs of $(\cdot)$ and $(\cdot)$ are asymptotically independent. The MLEs of $\theta$ and $\gamma$ given vary only slowly with $\xi$.

3 Efficiency loss

The parameter of interest is $\gamma$. Within the proposed model, the MLE $^\circ\gamma$ is asymptotically fully efficient. If we knew the $n_i$, then a more precise estimation of $\gamma$ is feasible. Two kinds of efficiency losses are of interest: that originated from the $n_1$ being unknown, and that from the over-dispersion among the $n_i$.

If we knew the $n_i$, then the Fisher information matrix of $\gamma$ is

$$I_r(\cdot) = \begin{pmatrix}
X^r & n_1 r \frac{h(x_i; \gamma)}{h(x_i; \gamma)} r^0 \frac{h(x_i; \gamma)}{h(x_i; \gamma)} \\
\frac{n_1 r}{h(x_i; \gamma)} r^{\theta} \frac{h(x_i; \gamma)}{h(x_i; \gamma)} & \frac{n_1 r}{h(x_i; \gamma)} r^{\theta} \frac{h(x_i; \gamma)}{h(x_i; \gamma)} \\
\end{pmatrix}
$$

When the $n_i$ are unknown and arise from a Poisson distribution with mean $\mu$, the Fisher information matrix is

$$I_r(\cdot) = \begin{pmatrix}
\frac{1}{5} & \frac{6}{5} & \frac{1}{5} & \frac{6}{5} \\
\frac{6}{5} & \frac{1}{5} & \frac{6}{5} & \frac{1}{5} \\
\frac{1}{5} & \frac{6}{5} & \frac{1}{5} & \frac{6}{5} \\
\frac{6}{5} & \frac{1}{5} & \frac{6}{5} & \frac{1}{5}
\end{pmatrix} \tag{3}
$$

which is obtained from $I_r(\cdot)$ in (2) by letting $\xi = 1$.

A sensible approach to evaluate the efficiency loss is to average $I_r(\cdot)$ in (2) by treating the $n_i$ as a sample from a Poisson distribution with mean $\mu$, i.e., to consider

$$I_r(\cdot) = E I_r(\cdot) = \begin{pmatrix}
X^r & \frac{n_1 r}{h(x_i; \gamma)} r^0 \frac{h(x_i; \gamma)}{h(x_i; \gamma)} \\
\frac{n_1 r}{h(x_i; \gamma)} r^{\theta} \frac{h(x_i; \gamma)}{h(x_i; \gamma)} & \frac{n_1 r}{h(x_i; \gamma)} r^{\theta} \frac{h(x_i; \gamma)}{h(x_i; \gamma)} \\
\end{pmatrix} \tag{4}
$$

A numeric experiment is used to investigate the efficiency losses, in which there is a single covariate $x$ and the parameter of interest is the slope $r_1$ while the intercept $r_0$ is fixed to be one. A $2^4$ design is considered, i.e.,

$$\begin{array}{c|c|c|c|c}
X_1 & X_2 & X_3 & X_4 \\
\hline
0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 \\
0 & 1 & 1 & 0 \\
0 & 1 & 1 & 1 \\
1 & 0 & 0 & 0 \\
1 & 0 & 1 & 0 \\
1 & 0 & 1 & 1 \\
1 & 1 & 0 & 0 \\
1 & 1 & 0 & 1 \\
1 & 1 & 1 & 0 \\
1 & 1 & 1 & 1
\end{array}
$$

where $X_1$ is the set of integers in [5, 5], and $X_2$ is $\in\{0, 0, 1, 1, 3, 3, 3, 3, 4, 4, 4, 4, 4, 4, 1, 1, 6, 6, 9\}$, a set of 11 normal random variables with mean 0 and variance 25. It is assumed that the number of replications is identical over each $x$ value.

Let $b$ be the ratio of the asymptotic standard deviation of $\gamma_1$ calculated from $I_r(\cdot)$ in (4) and that from $I_r(\cdot)$ in (3). Let $b_1$ be the ratio of the asymptotic standard deviation of $\gamma_1$ calculated from $I_r(\cdot)$ in (3) and that from $I_r(\cdot)$ in (4). This means that $b_1$ is the ratio of the asymptotic standard deviation of $\gamma_1$ calculated from $I_r(\cdot)$ in (4) and that from $I_r(\cdot)$ in (3). Table 2 presents these efficiency loss measures. The ranges of $b_1$ and $b_1$ are given by (0.706; 0.786), (0.732; 0.941) and (0.517; 0.740), respectively.

Figure 1 shows how the efficiency loss measure changes when $\xi$ varies continuously. As $\xi$ increases, the gamma
distribution tends to be degenerated, and the efficiency loss from the over-dispersion among the \( n_1 \) decreases. In the four panels, the efficiency loss is at most 0.621, which indicates that the efficiency loss from the over-dispersion among the \( n_1 \) is small.

Table 2: The efficiency loss measures over 16 settings.

| setting | 1 | 1 | 100 | 25 | 0.706 | 0.837 | 0.591 |
|---------|---|---|-----|----|-------|-------|-------|
| 2       | 2 | 100| 25  |    | 0.747 | 0.859 | 0.642 |
| 3       | 1 | 300| 25  |    | 0.706 | 0.732 | 0.517 |
| 4       | 2 | 300| 25  |    | 0.747 | 0.773 | 0.578 |
| 5       | 1 | 100| 49  |    | 0.706 | 0.890 | 0.629 |
| 6       | 2 | 100| 49  |    | 0.747 | 0.902 | 0.674 |
| 7       | 1 | 300| 49  |    | 0.706 | 0.799 | 0.564 |
| 8       | 2 | 300| 49  |    | 0.747 | 0.828 | 0.618 |
| 9       | 1 | 100| 25  |    | 0.729 | 0.858 | 0.625 |
| 10      | 2 | 100| 25  |    | 0.786 | 0.902 | 0.709 |
| 11      | 1 | 300| 25  |    | 0.729 | 0.765 | 0.558 |
| 12      | 2 | 300| 25  |    | 0.786 | 0.799 | 0.564 |
| 13      | 1 | 100| 49  |    | 0.729 | 0.904 | 0.659 |
| 14      | 2 | 100| 49  |    | 0.786 | 0.941 | 0.740 |
| 15      | 1 | 300| 49  |    | 0.729 | 0.824 | 0.601 |
| 16      | 2 | 300| 49  |    | 0.786 | 0.871 | 0.685 |

4 Estimation precision of \( \mu \) and \( \sigma \)

For a Poisson sample of size \( r \) with mean \( \mu \), the information of \( \mu \) is given by

\[
I_r(\mu) = \sum_{i=1}^{r} h(x_i; \mu) X_i.
\]

When \( r \) increases, the estimation of \( \mu \) becomes less precise. On the contrary, a large \( r \) serves a good purpose for the estimation of \( \sigma \) in a logistic regression model, which can be clearly seen from \( I_r(\sigma) \) in (3).

When the \( n_i \) are unknown and arise from the a Poisson distribution with mean \( \mu \), although \( \mu \) and \( \sigma \) are not orthogonal, we will show that a large \( r \) will lead to a more precise estimation of \( \mu \) but a less precise estimation of \( \sigma \).

To this end, we will partition the asymptotic variance-covariance matrix \( V \), i.e., the inverse matrix of \( I_r(\mu) \) in (3), into a \( 2 \times 2 \) block form, where, \( V = (V_{11}, V_{22}) \), and

\[
V_{11} = \frac{1}{n} \sum_{i=1}^{n} X_i \begin{bmatrix} 1 & \mu(h(x_i; \mu)) \\ \mu(h(x_i; \mu)) & \mu(h(x_i; \mu))^2 \end{bmatrix},
\]

\[
V_{22} = \frac{1}{n} \sum_{i=1}^{n} X_i \begin{bmatrix} \mu(h(x_i; \mu))^2 & 0 \\ 0 & \mu(h(x_i; \mu))^2 \end{bmatrix}.
\]

The diagonal entries of \( V_{11} \) and \( V_{22} \) are nonnegative. The variance of each component in \( \mu \) is a nonincreasing function of \( r \), while that of \( \sigma \) is a nondecreasing function of \( r \).

When the \( n_1 \) are over-dispersed, we also conjecture that a large \( r \) will have the same effects on the estimation of \( \mu \) and \( \sigma \) as those in the simple Poisson model. Figure 2 is a numerical illustration.
Figure 1: The efficiency loss measure \( \gamma \) varies with \( \beta_0 = 1, x \times X_1, (1; \beta) = (1; 100) \) (upper left panel), \( (2; 100) \) (upper right), \( (1; 300) \) (lower left), and \( (2; 300) \) (lower right).

Figure 2: The standard deviations of \( \beta_0 \) and \( \beta_1 \) change with respect to \( \beta_0 = 1, x \times X_1, 10 \) replications at each \( x \), \( (1; \beta) = (1; 25) \) (top panels) and \( (2; 49) \) (bottom panels).
5 Simulation

The simulation with the same 16 settings as the efficiency loss study and 1000 samples is reported in Table 3. The number of replications is 10 over each x value. The bias and mean square error are pretty small. All coverage probabilities of 95% confidence interval achieve their nominal value 0.95.

| setting | bias | mean square error | coverage probability |
|---------|------|------------------|----------------------|
| 1       | 0.005| 0.003            | 0.956                |
| 2       | 0.007| 0.015            | 0.968                |
| 3       | 0.003| 0.002            | 0.947                |
| 4       | 0.008| 0.007            | 0.948                |
| 5       | 0.005| 0.002            | 0.951                |
| 6       | 0.004| 0.013            | 0.927                |
| 7       | 0.002| 0.001            | 0.951                |
| 8       | 0.004| 0.005            | 0.945                |
| 9       | 0.000| 0.003            | 0.949                |
| 10      | 0.014| 0.015            | 0.948                |
| 11      | 0.001| 0.001            | 0.946                |
| 12      | 0.001| 0.007            | 0.952                |
| 13      | 0.001| 0.002            | 0.948                |
| 14      | 0.014| 0.013            | 0.949                |
| 15      | 0.001| 0.001            | 0.947                |
| 16      | 0.004| 0.006            | 0.945                |

6 Example

For the jejunal crypt data in Table 1, it is assumed that the surviving probabilities \( p_i \) satisfy \( \log f_{p_i} = (\underbrace{1 - p_i}) g = 0 + 1 \cdot x_i \) for all i (e.g., Kim and Taylor 1994 and Elder et al. 1999). The R function `optim` is used to maximize the likelihood function in (1). The estimates of \( b \) and \( d \) are stable, but that of \( r \) varies a lot. The estimate \( ^{\hat{}} \) is 3121.834 when its initial value is 20, but becomes 6070.602 when its initial value is 200. The Hessian matrix is found to be nearly singular, which implies that the variance of \( \mu \) is huge.

By the likelihood ratio test, we would like to assume that the \( n_i \) arise from a single Poisson distribution. The results are reported in Table 4, which also shows the estimates and their standard errors using the logistic regression (with \( n_i = 160 \)), the quasi-likelihood approaches in Kim and Taylor (1994) (with \( E (n_i) = 160 \)) and Elder et al. (1999). Our estimates and standard errors are very close to those in Elder et al. (1999). All the estimates of previous methods fall into our 95% confidence intervals: (5207; 8203) for \( \hat{r} \) (1248; 1200) for \( \hat{b} \) and (1034; 2892) for \( \hat{d} \). The standard errors of \( b \) are pretty small, while that of \( r \) is quite large. Elder et al. (1999) conjectured that the variance inflation of \( r \) is due to the data structure, i.e., there is no zero dose. By the estimation precision study in Section 4, we can not only give a more accurate explanation of the large standard error of \( r \), but also explains the small standard errors of \( b \). Since \( ^{\hat{}} \) is as large as 1962, the standard error of \( r \) is large, while those of \( b \) are small.

7 Discussion

One may consider estimating the \( n_i \) and then apply the logistic regression. There is a lot of literature about estimating binomial size \( n \) under the condition that \( p \) is either known or unknown. If \( p \) is unknown, then it is usually treated as a nuisance parameter (e.g., Draper and Guttman, 1971; Caroll and Lombard, 1985). Unlike the studies in the literature,
Table 4: The jejunal crypt data results from the proposed and previous approaches (logistic regression and Kim’s method fix $n_1$ and $E(n_1)$ at 160, respectively; Kim’s and Elder’s quasi-likelihood method of moments estimates come from Elder et al. (1999)).

|                | estimate (standard error) |
|----------------|----------------------------|
| **logistic**   |                            |
| 0              | 7.432 (0.175)              |
| 1              | 1.185 (0.024)              |
| **Kim’s**      |                            |
| 0              | 7.410 (0.191)              |
| 1              | 1.183 (0.026)              |
| **Elder’s**    |                            |
| 0              | 6.727 (0.725)              |
| 1              | 1.126 (0.061)              |
| **proposed**   |                            |
| 0              | 6.705 (0.764)              |
| 1              | 1.124 (0.063)              |

The $p_i$ depend on covariates, and many $n_1$ need to be estimated. Such a two-stage approach also makes analysis unnecessarily more complicated. The proposed approach estimates all parameters in a seamless fashion by treating the means of the $n_1$ as nuisance parameters and integrating them out.

**Appendix: The Fisher information matrix**

Let $\ell (\cdot) = \log f (y; x; \cdot)$ and $\ell (\cdot) = \log (\cdot)$. The first order derivatives are

$$\frac{\partial}{\partial \theta} = \frac{\partial}{\partial \theta} \left( + y \right) + \frac{\partial}{\partial \theta} \left( \log f + h(x; \cdot)g \right) + \frac{\partial y}{\partial h(x; \cdot)};$$

$$\frac{\partial^{\prime}}{\partial \theta} = \frac{y}{h(x; \cdot)} + \frac{y}{h(x; \cdot)} h(x; \cdot);$$

$$\frac{\partial^{\prime \prime}}{\partial \theta} = \frac{y}{h(x; \cdot)} \frac{( + y)h(x; \cdot) g}{h(x; \cdot) + h(x; \cdot) r(h(x; \cdot));}$$

The second order derivatives are

$$\frac{\partial^{\prime}}{\partial \theta} = \frac{\partial^{\prime}}{\partial \theta} \left( + y \right) + \frac{\partial^{\prime}}{\partial \theta} \left( \log f + h(x; \cdot) g \right) + \frac{\partial y}{\partial h(x; \cdot)};$$

$$\frac{\partial^{\prime}}{\partial \theta} = \frac{y}{h(x; \cdot)} + \frac{( + y)h(x; \cdot) g}{h(x; \cdot) + h(x; \cdot) r(h(x; \cdot));}$$

By taking negative expectation with respect to $f (y; x; \cdot)$, one obtains the Fisher information matrix. Note that $E (y) = h(x; \cdot)$. 

7
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