Correction of Verification Bias using Log-linear Models for a Single Binary-scale Diagnostic Tests

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Abstract

In diagnostic medicine, the test that determines the true disease status without an error is referred to as the gold standard. Even when a gold standard exists, it is extremely difficult to verify each patient due to the issues of cost-effectiveness and invasive nature of the procedures. In practice some of the patients with test results are not selected for verification of the disease status which results in verification bias for diagnostic tests. The ability of the diagnostic test to correctly identify the patients with and without the disease can be evaluated by measures such as sensitivity, specificity and predictive values. However, these measures can give biased estimates if we only consider the patients with test results who also underwent the gold standard procedure. The emphasis of this paper is to apply the log-linear model approach to compute the maximum likelihood estimates for sensitivity, specificity and predictive values. We also compare the estimates with Zhou’s results and apply this approach to analyze Hepatic Scintigraph data under the assumption of MNAR. We demonstrated the efficiency of the estimators by using simulation studies.

Keywords: Verification bias; Diagnostic tests; Log-linear models; Missing data

Introduction

Diagnostic testing in medicine is the process of identifying the patients with and without a particular disease. Accuracy of the diagnostic test is the ability of the test to correctly identify the true disease status of the patient [1]. The test or procedure that determines the true disease status without an error is called the gold standard test. However, even with the existence of a gold standard test, verification for the disease status of each patient may not be obtained due to various reasons such as the invasive nature or too costly gold standard test. For example, the Prostate Specific Antigen (PSA) blood test is used as a screening test for diagnosis of prostate Cancer with a ranging cost from $60 to $80. However, the true diagnosis is generally confirmed by invasive procedures such as prostate biopsy with a ranging cost from $1600 to $1800. Thus patients with a high risk or a prostate screening test positive are more likely to be offered the gold standard test than those with low risk or a negative screening test. Furthermore, the inference about the measures of diagnostic accuracy such as sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) may be biased because individuals who are selected for the gold standard test based on the diagnostic test results are not a random sample [2]. Many authors have referred to this bias as, work-up bias [3] or verification bias [4]. Therefore, in the presence of verification bias, the efficiency of a diagnostic test heavily depends only on those patients whose disease status has been verified. In addition if there is a positive association between patient selection for verification and the test results will produce more bias results [5].

When the true disease status is missing among patients who were not selected for verification, the framework of the missing data mechanism proposed by Rubin can be applied for verification bias correction. If the probability of selecting patients for verification is independent of both observed and unobserved data then missingness in the disease status is considered missing completely at random (MCAR). Missingness in the disease status is considered missing at random (MAR) when the probability of selecting patients only depends on the observed data and it is considered missing not at random (MNAR) when the probability depends on unobserved data [6]. This is most likely to occur when there is long time lag between the initial test and verification, when there are multiple investigators at various institutions, when the patient population is very heterogeneous or when the disease process is not well understood.

Begg and Greens [4] proposed a method of verification bias correction for binary diagnostic tests by using Bayes’ theorem under the MAR (i.e. conditional assumption). Zhou [7] derived the maximum likelihood estimators for sensitivity and specificity and their variances under both MAR and MNAR mechanisms. However, under the MNAR assumption, Zhou [7] assumed that two known ratios need to be quantified. Zhou [8] showed that the estimators of PPV and NPV are unbiased and consistent if the probability of selecting patients for disease verification does not depend on the true disease status of the patient (i.e. MAR assumption). Some authors have tried to use multiple imputation methods to correct for verification bias under ignorable missingness [9]. However, the validity of that approach was debated by De Groot et al. [10]. In dealing with multiple diagnostic tests and the presence of covariates, Baker [11] Kosinski and Barnhart [12] suggested regression approaches to deal with the MNAR missing mechanism. However, their models require the use of multiple tests or covariates in order to achieve identifiability. Martinez et al. [13] have tried to address the issue of verification bias in the MNAR setting by using a Bayesian approach with a beta prior distribution. Some authors have tried using Gibbs sampling techniques as a Bayesian approach to correct the verification bias in MNAR estimates [14]. All these available methods require iterative methods to compute the estimates of measures for...
diagnostic accuracy especially under MNAR mechanism. However, by using the log-linear model approach, the explicit solutions for the measures of diagnostic accuracy estimates can be computed by the use of a simple algebraic formula (computationally convenient) under all missing data mechanisms.

In this paper, we provide the log-linear model approach to correct for verification bias in order to compute the estimates of diagnostic measures (i.e. Sensitivity, Specificity, PPV and NPV) under various assumptions of missing data mechanisms. We also confirm by simulations that the estimators are asymptotically unbiased and more efficient than complete cases estimates. In next section, we will show the impact of verification bias by using hypothetical example. The following sections will focus on the method of log-linear models to correct the verification bias for diagnostic measures and comparison with Zhou [7] results. Furthermore, we illustrate the log-linear model approach by application to the Hepatic Scintigraph data.

Impact of Verification Bias

In diagnostic medicine, it is a common practice to refer only patients who are test positives for a gold standard test for disease verification. To illustrate the impact of bias, we considered a hypothetical study of 1000 patients to measure the sensitivity, specificity, PPV and NPV (Tables 1 and 2).

The hypothetical data are summarized in Table 1. If every patient is being referred for verification for the gold standard then the true sensitivity from Table 1 is 0.71. Furthermore, the true specificity, PPV and NPV are 0.87, 0.37 and 0.96 respectively. However, if we consider that only 10% of those who have a test negative result receive the gold standard, then the data are summarized in Table 2. From Table 2, the observed sensitivity, specificity, PPV and NPV are 0.96, 0.4, 0.37 and 0.96 respectively. Overall if positive test results are incorporated the other variables. In terms of λ , the homogenous log-linear model (presence of only two-way interactions) for partially observed one variable is \( \lambda_{ij} = \lambda_i + \lambda_j + \lambda_{ij}(i) + \lambda_{ij}(j) + \lambda_{ij}(i)(j) + \lambda_{ij}(i)(k) \)

\[ \lambda_{ij(k)} = \exp \left( \lambda_i + \lambda_j + \lambda_{ij} + \lambda_{ij}(i) + \lambda_{ij}(j) + \lambda_{ij}(i)(j) + \lambda_{ij}(i)(k) \right) \]

Because this is an over parameterized model, we add the side conditions that the sum of each \( \lambda \) term over each of the indicated subscripts is zero. For computational purposes, it is convenient to use an alternative parameterization of the model. Let \( m_0 \geq 0 \), \( b_j \geq 0 \) and \( \sum b_j = n_{ij} \) such that \( \mu_{ij} = m_0 + \mu_{ij}^* \). In terms of log-linear models \( \mu_{ij} = \exp(\lambda_i + \lambda_j + \lambda_{ij}) - \exp(\lambda_i) - \exp(\lambda_j) - \exp(\lambda_{ij}) \), it is being referred for verification. The detailed derivation can be found in the Appendix.

Taking advantage of the side conditions, we can derive the following expression for \( b_j \):

\[ b_j = -2 \exp(\lambda_{ij}) + 2 \exp(\lambda_i) + 2 \exp(\lambda_j) + 2 \exp(\lambda_{ij}) + 2 \exp(\lambda_{ij}(j)) + 2 \exp(\lambda_{ij}(j)(k)) \]

Table 2: Hypothetical data with unverified cases.

|     | Verified | Unverified | Total  |
|-----|----------|------------|--------|
| -3  | D +      | D −        |        |
| T + | 71       | 120        | 191    |
| T − | 29       | 780        | 809    |
|     |          |            | 1000   |

Table 3: Two way table with one supplementary margin.

|     | Verified | Unverified | Total  |
|-----|----------|------------|--------|
| -3  | D +      | D −        |        |
| T + | 71       | 120        | 191    |
| T − | 3        | 78         | 809    |
|     |          |            | 1000   |
and in general notation the marginal and conditional probabilities can be expressed as:

\[ \pi_{ij} = Pr(I = i, J = j) = \frac{m_{ij}(1 + b_i)}{n_{i+}} \]

\[ \pi_{i+} = Pr(I = i) = \sum_{j=1}^{J} \frac{m_{ij}(1 + b_i)}{n_{i+}} \]

\[ \pi_{+j} = Pr(J = j) = \sum_{i=1}^{I} \frac{m_{ij}(1 + b_i)}{n_{+j}} \]

\[ \pi_{ij} = Pr(I = i | J = j) = \frac{m_{ij}(1 + b_i)}{\sum_{m=1}^{M} m_{mj}(1 + b_j)} \]

\[ \pi_{+j} = Pr(J = j | I = i) = \frac{m_{ij}(1 + b_i)}{\sum_{m=1}^{M} m_{mj}(1 + b_j)} \]

The likelihood ratio statistic with respect to a model fitting the data perfectly is:

\[ G^2 = 2 \left[ n_{i+} \log \left( \frac{n_{i+}}{\hat{m}_{i+}} \right) + \sum_{m=1}^{M} n_{mj} \log \left( \frac{n_{mj}}{\sum_{m=1}^{M} \hat{m}_{mj}} \right) + n_{+j} \log \left( \frac{n_{+j}}{\sum_{j=1}^{J} \hat{m}_{+j}} \right) \right] \]

Models parameter estimates

Baker et al. [17] identified nine different models for the two-way table with three supplementary margins based on the dependence of the missingness on one or the other or its own realization. For Table 3, when \( b_i \) equals to \( \beta_i \) or \( \hat{\beta}_i \), there are three different identifiable models. First and second subscripts to the parameter \( \beta \) correspond to variable I and J respectively. The subscript “.” indicates that parameter is constant over corresponding index. In addition, each model has a unique interpretation. For example, Model \( (\hat{\beta}_i) \) can be interpreted as the missingness in I is constant (MCAR). Similarly, Model \( (\hat{\beta}_j) \) can be interpreted as the missingness in J depends on the realization of I (MAR) and when the missingness in J depends on its own realization, then we consider Model \( \hat{\beta}_j \) to be MNAR.

Assuming Poisson distribution for cell counts, the maximum likelihood estimates for \( m_{ij} \) and \( \hat{\beta} \) can be derived from log-likelihood functions for each model. Detailed derivation of the estimates are provided in Appendix. The likelihood ratio statistics for each model can also be found in the Appendix.

MCAR estimates

\[ \hat{\beta} = \frac{n_{i+1}}{n_{i+1}} \hat{m}_i = \frac{n_{i+1} - n_{i+1} - n_{i+1}}{n_{i+1}} \]

\[ \hat{\beta}_i = \frac{\hat{m}_i(1 + \hat{\beta})}{\sum_i \hat{m}_i(1 + \hat{\beta})} \]

\[ \hat{\beta}_j = \frac{\hat{m}_j(1 + \hat{\beta})}{\sum_j \hat{m}_j(1 + \hat{\beta})} \]

From equation 2, the estimates for Sensitivity and Specificity are

\[ \text{Sensitivity} (\text{MCAR}) = \hat{\delta}_{i+1} = \frac{\hat{m}_{i+}}{\hat{m}_{i+} + \hat{m}_{i+}} \]

\[ \text{Specificity} (\text{MCAR}) = \hat{\delta}_{+j1} = \frac{\hat{m}_{+j}}{\hat{m}_{+j} + \hat{m}_{+j}} \]

Similarly, the estimates for PPV \( (\hat{\pi}_{+j1}) \) and NPV \( (\hat{\pi}_{i+2}) \) can be computed from equation 3.

MAR estimates

\[ \hat{\beta}_i = \frac{n_{i+1}}{m_{i+1}} \hat{m}_i = n_{i+1} \]

\[ \hat{\beta}_j = \frac{\hat{m}_j(1 + \hat{\beta})}{\sum \hat{m}_j(1 + \hat{\beta})} \]

\[ \hat{\beta}_j = \frac{\hat{m}_j(1 + \hat{\beta})}{\sum \hat{m}_j(1 + \hat{\beta})} \]

From equation 4 the estimates of the Sensitivity and Specificity can be obtained as follows

\[ \text{Sensitivity} (\text{MAR}) = \hat{\delta}_{i+1} = \frac{\hat{m}_{i+}}{\hat{m}_{i+} + \hat{m}_{i+}} \]

\[ \text{Specificity} (\text{MAR}) = \hat{\delta}_{+j1} = \frac{\hat{m}_{+j}}{\hat{m}_{+j} + \hat{m}_{+j}} \]

can be obtained. Similarly, from equation 5 the estimates of PPV \( (\hat{\pi}_{+j1}) \) and NPV \( (\hat{\pi}_{i+2}) \) can be computed.

MNAR estimates

\[ \sum_i \hat{m}_i(1 + \hat{\beta}_i) \]

\[ \sum_j \hat{m}_j(1 + \hat{\beta}_j) \]

\[ \hat{\beta}_i = \frac{\hat{m}_i(1 + \hat{\beta}_i)}{\sum \hat{m}_i(1 + \hat{\beta}_i)} \]

\[ \hat{\beta}_j = \frac{\hat{m}_j(1 + \hat{\beta}_j)}{\sum \hat{m}_j(1 + \hat{\beta}_j)} \]

For Model \( (\hat{\beta}_i) \), equation 8 provides the estimates of Sensitivity and Specificity as follows

\[ \text{Sensitivity} (\text{MNAR}) = \hat{\delta}_{i+1} = \frac{\hat{m}_{i+}}{\hat{m}_{i+} + \hat{m}_{i+}} \]

\[ \text{Specificity} (\text{MNAR}) = \hat{\delta}_{+j1} = \frac{\hat{m}_{+j}}{\hat{m}_{+j} + \hat{m}_{+j}} \]

while equation 9 provides the estimates of PPV \( (\hat{\pi}_{+j1}) \) and NPV \( (\hat{\pi}_{i+2}) \).

Inference about diagnostic measures

In this section, the multivariate delta method is used to draw the
inferences about the diagnostic measures for Model ($\beta_1$) (MAR). A similar method can be used for Model ($\beta_2$) (MCAR) and Model ($\beta_3$) (MNAR). To derive the asymptotic variance of the estimates, we have

$$\sqrt{\text{Var}(\hat{x}_{ij})} \sim N(0,1).$$

However, to ensure better normal approximation, we derived the asymptotic distribution of

$$\logit(\hat{x}_{ij}) = \logit(\pi_{ij}) = \logit(\pi_{ij}(1-\pi_{ij})) .$$

By using multivariate delta method for Model ($\beta_2$), we have

$$\logit(\hat{x}_{ij}) \sim N(\logit(\pi_{ij}), C^T I_1 C) \tag{10}$$

where $C = \left[ \frac{\partial \logit(\pi_{ij})}{\partial \pi_{ij}}, \frac{\partial \logit(\pi_{ij})}{\partial \pi_{ij}}, \ldots, \frac{\partial \logit(\pi_{ij})}{\partial \pi_{ij}} \right]$ and $I_1$ is the Fisher information. The detailed derivation of $I_1$ is provided in the Appendix. Therefore, the $100(1-\delta)\%$ confidence interval for $\pi_{ij}$ is

$$\left( \left[ \logit^{-1}(\hat{\pi}_{ij}) - z \sqrt{\text{Var}(\hat{\pi}_{ij})}, \logit^{-1}(\hat{\pi}_{ij}) + z \sqrt{\text{Var}(\hat{\pi}_{ij})} \right] \right).$$

In case of negative estimates for MNAR model, the variances for model parameters (Tables 5-7).

**Simulation Study**

A simulation study was conducted to illustrate the reduction in bias and root mean squared error (RMSE) of the estimators for sensitivity and specificity for MAR model compared to complete case analysis (Table 4).

Two variables "Test Results" and "Disease Status" with different sample sizes (N) were generated from the multinomial distribution with marginal probabilities of $\pi_{11} = 0.5$ and $\pi_{12} = 0.5$ under different sensitivity ($\frac{\pi_{11}}{\pi_{11}+\pi_{12}}$) and specificity ($\frac{\pi_{12}}{\pi_{12}+\pi_{11}}$) values. We cross-classified these variables in a $2 \times 2$ contingency table. This process was repeated 2000 times. In each complete contingency table, we generated missing values in "Disease Status" in such a way that missingness in "Disease Status" depends on the realization of the "Test Results" to ensure the MAR missing mechanism. Table 4 represents the results from our simulation for MAR model when 50% of negative tests and 10% of the positive tests were not verified for the disease. Table 4 shows that correcting for the verification bias using the log-linear model approach will substantially reduce the bias as well as improve the performance of the estimators compared to complete case analysis. We obtained similar results with 10% missigness in T+ with different amounts of missings in T- such as 70%, 60%, 40%, 30% and 20% and/or various marginal probabilities. In addition to this, we carried out an extensive simulation for Model ($\beta_3$) by simulating the MNAR missing mechanism to estimate PPV and NPV. We observed the reduction in bias and RMSE compared to complete case analysis under different amounts of non-ignorable missingness on the disease status.

**Application**

In this section, we will demonstrate the log-linear modeling approach to compute the measures of diagnostic accuracy under various missing mechanisms by using the Hepatic Scintigraph data published by [19]. In the Hepatic Scintigraph data, 650 patients underwent hepatic scintigraphy of which 429 patients had positive scans while 221 patients had negative hepatic scans. Only 263 patients out of 429 and 81 patients out of 221 were referred for status verification using procedures such as liver biopsy, exploratory laparotomy or autopsy within 6 weeks of their scans. Table 5 represents the verified and unverified cases by hepatic scan results. Table 6 shows the Maximum likelihood estimates for model parameters (Tables 5-7).

**Final Remarks**

Verification bias is an extremely common problem in diagnostic medicine. This paper shows that how the log-linear model approach in single binary-scale diagnostic tests correct the verification bias for estimating the diagnostic measures. Log-linear models also reduces
the bias and improves the performance of the estimators compared to complete case analysis. In addition to this, explicit estimates for the measures of diagnostic accuracy under different missing mechanisms can be computed from simple algebraic formula, while other available methods require iterative methods to estimate the measures of diagnostic accuracy. Furthermore, this approach will allow us to test for MCAR assumption for particular data. However, the only way to confirm for MAR or MNAR missing mechanisms is to recollect the missing data. Although in diagnostic medicine due to the issue of cost-effectiveness, we do not have the luxury of getting hold of the missing data. As a result, careful modeling of missing mechanisms to reduce the bias is more an important issue. Therefore, if the data are not MCAR then by using the scientific knowledge about the data we can assume a MAR or MNAR missing mechanism to compute estimates for the measures of diagnostic accuracy with log-linear models.

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Appendix

Log-linear parameterization

Expected counts for all verified cases can be modeled by using equation 1 in the following way:

$$
\mu_{ij} = \exp\{\lambda_i + \lambda_j + \lambda_{ij} + \lambda_{ri} + \lambda_{rij} + \lambda_{rij}(11)\}
$$

Expected counts for all un-verified cases can be modeled as the following way:

$$
\mu_{ij} = \exp\{\lambda_i + \lambda_j + \lambda_{ij} + \lambda_{ri} + \lambda_{rij} + \lambda_{rij}(12)\}
$$

Some of the side conditions (the sum of each $\lambda$-term over each of the indicated subscript is zero) for the log-linear models are

$$
\sum_{k} \lambda_{ij}(k) = 0, \sum_{j} \lambda_{ij}(j) = 0, \sum_{i} \lambda_{ij}(i) = 0, \sum_{k} \lambda_{ijk}(1k) = 0
$$

By using these conditions, we can get

$$
h_j = \frac{\mu_{ij}}{\mu_{ii}} = -2\exp\{\lambda_{ij} + \lambda_{rij}(il) + \lambda_{rij}(j1) + \lambda_{rij}(11)\}
$$

Maximum likelihood (ML) Estimates for Model ($\beta$) (MCAR)

$$
L = \sum_{ij} n_{ij} \log\left(m_{ij}\right) + \sum_{ij} n_{ij} \log\left(m_{ij}\beta\right) - \sum_{i} m_{ij}(1 + \beta)
$$

$$
\frac{\partial L}{\partial \beta} = \sum_{ij} \left(\frac{n_{ij}}{m_{ij}\beta}\right) m_{ij} - \sum_{i} m_{ij}
$$

$$
: 0 = \frac{n_{ii1}}{\mu_{ii}} - \hat{m_i} \text{ However, for completed data } \hat{m_i} = n_{i11} \text{ which provides the ML estimates for } \beta : \hat{\beta} = \frac{n_{i12}}{n_{i11}}
$$

ML estimates for model ($\beta$) can be derived by taking the derivative of $L$ with respect to $\beta$:

$$
\frac{\partial L}{\partial \beta} = \frac{n_{i11}}{m_{i1} \mu_{i1}} \beta - (1 + \beta)
$$

First solving for $\hat{m}_i$

$$
\hat{m}_i = \left(\frac{n_{i11}}{n_{i11}} + \frac{n_{i12}}{m_{ii} \mu_{ii}} \hat{m}_i\right) \left(\frac{n_{i11}}{n_{i11}} + \frac{n_{i12}}{m_{ii} \mu_{ii}} \hat{m}_i\right)
$$

Substituting $\hat{\beta}$ from equation $11$:

$$
\hat{m}_i = \left(\frac{n_{i11}}{n_{i11}} + \frac{n_{i12}}{m_{ii} \mu_{ii}} \hat{m}_i\right) \left(\frac{n_{i11}}{n_{i11}} + \frac{n_{i12}}{m_{ii} \mu_{ii}} \hat{m}_i\right)
$$

Maximum likelihood Estimates for Model ($\beta$) (MAR)

$$
L = \sum_{ij} n_{ij} \log\left(m_{ij}\right) + \sum_{ij} n_{ij} \log\left(m_{ij}\beta\right) - \sum_{i} m_{ij}(1 + \beta)
$$

$$
\frac{\partial L}{\partial \beta} = \frac{n_{i12}}{m_{i1} \mu_{i1}} m_{ij} - \sum_{i} m_{ij}
$$
Therefore, the ML estimates for $\hat{\beta}_j$ are 

\[ : 0 = \frac{n_{i,j+1}}{\hat{m}_i} \cdot \hat{m}_i, \therefore \text{The ML estimates for } \hat{\beta}_j : \hat{\beta}_j = \frac{n_{i,j+1}}{\hat{m}_i}. \]

ML estimates for Model $\beta_j$ can be derived by taking the derivative of $L$ with respect to $\hat{\beta}_j$.

\[ .0 = \frac{n_{i,j+1}}{m_j} + \frac{n_{i+1,j+2}}{\hat{m}_i} (1 + \hat{\beta}_j) \]

\[ .(1 + \hat{\beta}_j) = \frac{n_{i,j+1}}{m_j} + \frac{n_{i+1,j+2}}{\hat{m}_i} \]

\[ .1 + \frac{n_{i+1,j+2}}{\hat{m}_i} \cdot \hat{m}_i = n_{i,j+1} + \frac{n_{i+1,j+2}}{\hat{m}_i} \]

\[ .(\hat{m}_i + n_{i+1,j+2}) \cdot \hat{m}_i = n_{i,j+1} \hat{m}_i + n_{i+1,j} \hat{m}_i \]

\[ .\hat{m}_i (\hat{m}_i + n_{i+1,j+2} - n_{i,1,j}) = n_{i,j+1} \hat{m}_i \]

\[ .\hat{m}_i = n_{i,j+1} \]

**Maximum likelihood Estimates for Model $\beta_j$ (MNAR)**

\[ L = \sum_{i,j} n_{i,j} \log (m_j) + \sum_{i,j} n_{i+1,j} \log \left( \sum_{j} m_j \beta_j \right) - \sum_{i,j} m_j (1 + \beta_j) \]

\[ \frac{\partial L}{\partial \beta_j} = \sum_{i,j} n_{i+1,j} \beta_j \left( m_j - \sum_{j} m_j \right) \]

\[ .0 = \sum_{i,j} \left( \frac{n_{i+1,j}}{\hat{m}_i} \right) \cdot \hat{m}_i \]

\[ .\hat{m}_i = n_{i,j+1} \]

\[ .\hat{m}_i (\hat{m}_i + n_{i+1,j+2} - n_{i,1,j}) = n_{i,j+1} \hat{m}_i \]

\[ .\hat{m}_i = n_{i,j+1} \]

From equation 12, we can guess ML estimates for $\hat{\beta}_j$ by $\sum_{i,j} \hat{m}_i \beta_j = n_{i+1,j+2} \forall \hat{\beta}_j$. ML estimates for Model $\beta_j$ can be derived by taking the derivative of $L$ with respect to $\hat{\beta}_j$.

\[ .0 = \frac{n_{i,j+1}}{m_j} + \frac{n_{i+1,j+2}}{\hat{m}_i} \beta_j - (1 + \hat{\beta}_j) \]

\[ .\hat{m}_i \beta_j = n_{i,j+1} + \frac{n_{i+1,j+2}}{\hat{m}_i} \hat{m}_i \beta_j \]

\[ .\hat{m}_i (1 + \hat{\beta}_j) = n_{i,j+1} + \frac{n_{i+1,j+2}}{\hat{m}_i} \hat{m}_i \beta_j \]

\[ .\hat{m}_i = n_{i,j+1} \]

**Comparison of MAR Estimates with Zhou’s Result**

The estimates for Sensitivity is

\[ \text{Sensitivity(Zhou)} = \frac{(n_{i,j+1} \cdot n_{1,j+1})}{n_{i,j} \cdot (n_{i,j+1} + n_{1,j+1})} \]

\[ = \frac{n_{i,j+1} \cdot n_{1,j+1} \cdot n_{i,j+1} \cdot n_{1,j+1} + n_{i,j+1} \cdot n_{1,j+1} \cdot n_{i,j+1} \cdot n_{1,j+1}}{n_{i,j} \cdot (n_{i,j+1} + n_{1,j+1}) \cdot n_{i,j+1} \cdot n_{1,j+1} + n_{i,j+1} \cdot n_{1,j+1} \cdot n_{i,j+1} \cdot n_{1,j+1}} \]

\[ = \frac{(n_{i,j+1} \cdot n_{1,j+1} \cdot n_{i,j+1} \cdot n_{1,j+1} \cdot n_{i,j+1} \cdot n_{1,j+1})}{n_{i,j} \cdot (n_{i,j+1} + n_{1,j+1}) \cdot n_{i,j+1} \cdot n_{1,j+1} + n_{i,j+1} \cdot n_{1,j+1} \cdot n_{i,j+1} \cdot n_{1,j+1}} \]

From equation 6 the Sensitivity estimates from log-linear model are

\[ \text{Sensitivity(MAR)} = \frac{\hat{m}_i (1 + \hat{\beta}_j)}{\hat{m}_i (1 + \hat{\beta}_j) + \hat{m}_i (1 + \hat{\beta}_j)} \]
Similarly, we can show that the estimates for Specificity from log-linear models are equivalent to \[ \text{Specificity estimates.} \]

**Information Matrices:**

**Model \( (\beta) \)**

\[
\frac{\partial^2 L}{\partial \beta^2} = \frac{n_{1111}}{\beta^2} \\
-E \left( \frac{\partial^2 L}{\partial \beta^2} \right) = E \left( \frac{n_{1112} \beta}{\beta^2} \right) = \frac{m_{1112}}{\beta} \\
-E \left( \frac{\partial^2 L}{\partial \beta \partial m_j} \right) = \frac{1}{m_y} + \frac{\beta}{m_{yz}} \\
-E \left( \frac{\partial^2 L}{\partial \beta \partial m_{ij}} \right) = 1
\]

\[
I = \begin{bmatrix}
-E \left( \frac{\partial^2 L}{\partial m_{111} \partial m_{112}} \right) & -E \left( \frac{\partial^2 L}{\partial m_{111} \partial m_{121}} \right) & -E \left( \frac{\partial^2 L}{\partial m_{111} \partial m_{211}} \right) & -E \left( \frac{\partial^2 L}{\partial m_{111} \partial m_{212}} \right) \\
-E \left( \frac{\partial^2 L}{\partial m_{112} \partial m_{111}} \right) & -E \left( \frac{\partial^2 L}{\partial m_{112} \partial m_{121}} \right) & -E \left( \frac{\partial^2 L}{\partial m_{112} \partial m_{211}} \right) & -E \left( \frac{\partial^2 L}{\partial m_{112} \partial m_{212}} \right) \\
-E \left( \frac{\partial^2 L}{\partial m_{121} \partial m_{111}} \right) & -E \left( \frac{\partial^2 L}{\partial m_{121} \partial m_{121}} \right) & -E \left( \frac{\partial^2 L}{\partial m_{121} \partial m_{211}} \right) & -E \left( \frac{\partial^2 L}{\partial m_{121} \partial m_{212}} \right) \\
-E \left( \frac{\partial^2 L}{\partial m_{211} \partial m_{111}} \right) & -E \left( \frac{\partial^2 L}{\partial m_{211} \partial m_{121}} \right) & -E \left( \frac{\partial^2 L}{\partial m_{211} \partial m_{211}} \right) & -E \left( \frac{\partial^2 L}{\partial m_{211} \partial m_{212}} \right)
\end{bmatrix}
\]

**Model \( (\beta) \)**

\[
-E \left( \frac{\partial^2 L}{\partial \beta^2} \right) = \frac{m_{1111}}{\beta} \\
-E \left( \frac{\partial^2 L}{\partial \beta \partial m_j} \right) = \frac{1}{m_y} + \frac{\beta}{m_{yz}} \\
-E \left( \frac{\partial^2 L}{\partial \beta \partial m_{ij}} \right) = 1
\]
Model Likelihood Ratio Statistics

Model ($\beta$)

\[
-L(\frac{\partial^2 L}{\partial \beta_i^2}) = \sum_{j} \left( \frac{m_{ij}^2}{m \beta_i} \right)
\]

\[
-L(\frac{\partial^2 L}{\partial \beta_i^2}) = \frac{1}{m_i} \left( \frac{\beta_i}{\sum_j m_{ij} \beta_j} \right)
\]

\[
-L(\frac{\partial^2 L}{\partial \beta_i^2}) = \frac{m_i \beta_i}{\sum_j (m_{ij} \beta_j)}
\]

Likelihood Ratio Statistics

Model ($\beta$)

\[
G^2 = 2 \left\{ \sum_{i,j} n_{i,j} \log \left( \frac{n_{i,j}}{m_i \beta_j} \right) + \sum_i n_{i,12} \log \left( \frac{n_{i,12}}{m_i \beta_j} \right) + \sum_i n_{i,21} \log \left( \frac{n_{i,21}}{m_i \beta_j} \right) \right\}
\]

Model($\beta$) $G^2 = 2 \left\{ \sum_{i,j} n_{i,j} \log \left( \frac{n_{i,j}}{m_i \beta_j} \right) + \sum_i n_{i,12} \log \left( \frac{n_{i,12}}{m_i \beta_j} \right) + \sum_i n_{i,21} \log \left( \frac{n_{i,21}}{m_i \beta_j} \right) \right\}$

Model($\beta$) $G^2 = 2 \left\{ \sum_{i,j} n_{i,j} \log \left( \frac{n_{i,j}}{m_i \beta_j} \right) + \sum_i n_{i,12} \log \left( \frac{n_{i,12}}{m_i \beta_j} \right) + \sum_i n_{i,21} \log \left( \frac{n_{i,21}}{m_i \beta_j} \right) \right\}$