Odds ratio for 2 × 2 tables: Mantel-Haenszel estimator, profilelikelihood and presence of surrogate responses

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Buddhananda Banerjee

And

Prof. Atanu Biswas

Applied Statistics Unit
Indian Statistical Institute
Kolkata 700108

buddhananda_r@isical.ac.in, atanu@isical.ac.in

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Buddhananda Banerjee and Atanu Biswas
Applied Statistics Unit, Indian Statistical Institute
203 B. T. Road, Kolkata – 700 108, India
emails: buddhananda_r@isical.ac.in, atanu@isical.ac.in

Abstract: Use of surrogate outcome to improve the inference in biomedical problems is an area of growing interest. Here consider a set up where both the true and surrogate endpoints are binary and we observe all the surrogate endpoints along with a few true endpoints. In a two treatment set up we study the surrogate-augmented Mantel-Haenszel estimator based on observations from different groups when the group effect is present. We compare Mantel-Haenszel estimator with the one obtained by maximizing profile likelihood in surrogate augmented set up. We observe that the performance of these estimators are very close.

Keywords: Log-odds ratio, Mantel-Haenszel estimator, profile likelihood, surrogate end-point, true end-point.

1 Introduction

Many clinical outcomes are such that the response variables are often difficult or highly expensive to measure, or the responses are delayed where short term measures are needed for inferential and administrative purposes. So to evaluate the effects of treatments or exposures on the true endpoint in medical studies, a closely related variable are used as a surrogate response. For example, damage to the heart muscle due to myocardial infraction can be accurately assessed by arterioscintography. As it is an expensive procedure, peak cardiac enzyme level in the blood stream, which is more easily obtainable, being used as surrogate measure of heart vascular damage [1]. Often observed value of response variable in the middle of experiment is considered

as surrogate endpoint. High dose interferon-α is used for patients with age related macular degeneration (ARMD) who progressively loose their vision. Observations are taken after six months and one year for surrogate and true endpoints respectively [2]. CD4 cell count is used as surrogate for HIV patients where the survival time is true one.

A statistical definition and validation criteria of surrogate endpoint were first introduced by Prentice (1989) [3]. Begg and Leung (2000) [4] proposed that measure of concordance can be possible validation criteria for discrete random variables. In the present paper we are interested in inferential problems using properly validated surrogate endpoints where we assume that the validation is done a-priori. Day and Duffy (1996) [5] focused on the use of surrogate for the true endpoint in clinical or preservation trial to shorten the duration of trial and to increase the power. Freedman et al. (1992) [6] supplemented these criteria with the so-called *proportion explained* by an intermediate endpoint for binary outcome variable which has been extended by Lin et al. (1997) [7] to failure time endpoints. Pepe (1992) [8] considered semi-parametric model to estimate regression coefficients of covariates when surrogate data are present and showed its consistency. Chen (2000) [9] developed a robust imputation method in the same set up. Chen et al. (2007) [10] developed a method on two sample empirical likelihood that simultaneously combines the estimating equations from the validation and non-validation samples where no distributional association between surrogate and covariates has been assumed. Molenberghs et al. (2001) [11] introduced the situation where the surrogate is binary and the true endpoint is continuous, or vice versa. In addition, they considered the case of ordinal endpoints. In a recent study Banerjee and Biswas (2011) [12] studied the estimation of the difference in success probabilities in the two treatment set up in the presence of surrogate responses.

In this paper we consider the two treatment problem. Assume that the response variable is binary for true as well as surrogate endpoints. Surrogate responses are quickly and easily available than the true ones. Here we compare treatment effects in terms of log-odds ratio when large numbers of surrogate endpoints are available along with moderate numbers of true and surrogate paired observations when observations

are available from multiple tables. Estimate the common odds ratio for multiple tables is a well studied problem [13-17]. We propose a methodology to obtain Mantel-Haenszel (MH) [18-19] and profile likelihood (PMLE) [20] based estimators in the surrogate augmented framework. We established asymptotic normality of the estimators. Our extensive simulation study also shows remarkable closeness in the behaviour of the two surrogate augmented estimators - MH and PMLE.

Rest of the article is as follows. Section 2 describes the data structure of multiple tables in the presence of surrogate endpoints. In Section 3 we discuss the MH estimator and the PMLE without surrogate. Imputation with surrogate data is described in Section 4. Section 5 studies the MH estimator and the PMLE in the presence of surrogate data. Simulation results are reported in Section 6 to show the closeness of the estimators and Section 7 concludes.

2 Data structure

We consider a set up of two treatment binary end-points with binary surrogates. Begg and Leung (2000) [4] pointed out that, for binary endpoints, the probability of concordance is an indicator of association between true and surrogate endpoints. Suppose n_A and n_B patients are allotted to treatments A and B, respectively; but we get only m_A and m_B true end-points along with all surrogate endpoints within the stipulated time frame or cost limit, where $m_t << n_t$, $t = A, B$. Let Z be an indicator variable such that $Z = 1$ or 0 according as the treatment A or B is allocated to a patient. Denote true and surrogate endpoints for treatment t by Y_t and W_t, $t = A, B$. All these endpoints are either 1 or 0 for success or failure, respectively. We denote $p_t = P(Y_t = 1)$ as the success probability by the true endpoints for treatment t. Furthermore, let us denote

$$P(W_t = 1|Y_t = 1) = \pi_{t1} \quad \text{and} \quad P(W_t = 0|Y_t = 0) = \pi_{t0}, \tag{2.1}$$

which are the *sensitivity* and *specificity* of the 2×2 table for treatment t where the true and surrogate responses are in the two margins. Consequently, the success probabilities

by the surrogate responses for the treatment t be,

$$r_t = P(W_t = 1) = (1 - \pi_{t0}) + (\pi_{t1} + \pi_{t0} - 1)p_t.$$

The data corresponding to treatment t can be represented in a table as follows.

True↓ Surrogate→	$W_t = 1$	$W_t = 0$	Total
$Y_t = 1$	m_{t11}	m_{t10}	Y_{tT}
$Y_t = 0$	m_{t01}	m_{t00}	$m_t - Y_{tT}$
Total	W_{tT}	$m_t - W_{tT}$	m_t

where $Y_{tT} = \sum_{j=1}^{m_t} Y_{t,j}$ and $W_{tT} = \sum_{j=1}^{m_t} W_{t,j}$; also we denote $W_{tS} = \sum_{j=m_t+1}^{n_t} W_{t,j}$. If any marginal is found to be zero, it is customary to add 0.5 to each of the marginals. Banerjee and Biswas (2011) [12] considered a similar set up.

3 Multiple tables: MH estimator and PMLE

Suppose there are k 2×2 tables. If the ith table has the cell frequencies Y_{Ai}, $n_{Ai} - Y_{Ai}$, Y_{Bi} and $n_{Bi} - Y_{Bi}$, $i = 1, \cdots, k$, the MH-estimator is given by

$$\widehat{\psi}_{MH}^{(C)} = \frac{\sum_{i=1}^{k} \left(\frac{n_{Ai}n_{Bi}}{N_i}\right) \widehat{q}_{Ai}^{(C)} \widehat{p}_{Bi}^{(C)} \widehat{\psi}_i^{(C)}}{\sum_{i=1}^{k} \left(\frac{n_{Ai}n_{Bi}}{N_i}\right) \widehat{q}_{Ai}^{(C)} \widehat{p}_{Bi}^{(C)}} = \frac{\sum_{i=1}^{k} Y_{Ai}(n_{Bi} - Y_{Bi})/N_i}{\sum_{i=1}^{k} Y_{Bi}(n_{Ai} - Y_{Ai})/N_i} = \frac{\sum_{i=1}^{k} R_i}{\sum_{i=1}^{k} S_i}, \qquad (3.1)$$

with $N_i = n_{Ai} + n_{Bi}$ and $R_i = Y_{Ai}(n_{Bi} - Y_{Bi})/N_i$, $S_i = Y_{Bi}(n_{Ai} - Y_{Ai})/N_i$, and $\widehat{\psi}_i^{(C)} = \widehat{p}_{Ai}^{(C)} \widehat{q}_{Bi}^{(C)} / (\widehat{q}_{Ai}^{(C)} \widehat{p}_{Bi}^{(C)})$ is the estimate of odds ratio ψ for the ith table, where $p_{ti}^{(C)} = n_t^{-1} \sum_{j=0}^{n_t} Y_{ti,j} = 1 - q_{ti}^{(C)}$ and $Y_{ti} = \sum_{j=0}^{n_t} Y_{ti,j}$, for $t = A, B$. Here (C) stands for the completely available data.

As an alternative, maximization of profile likelihood can also be done for estimating common odds ratio across the k tables (see Bohning et al. [18]). Consider the likelihood

$$L(\mathbf{p}_A, \mathbf{p}_B) = \prod_{i=1}^{k} \binom{n_{Ai}}{Y_{Ai}} p_{Ai}^{Y_{Ai}} (1 - p_{Ai})^{n_{Ai} - Y_{Ai}} \binom{n_{Bi}}{Y_{Bi}} p_{Bi}^{Y_{Bi}} (1 - p_{Bi})^{n_{Bi} - Y_{Bi}} \qquad (3.2)$$

where $\mathbf{p}_A = (p_{A1}, p_{A2}, \cdots, p_{Ak})$, $\mathbf{p}_B = (p_{B1}, p_{B2}, \cdots, p_{Bk})$. Now denote $\theta_{Ai} = p_{Ai}/(1 - p_{Ai})$, $\theta_{Bi} = p_{Bi}/(1 - p_{Bi})$ and assume that $\psi = \theta_{Ai}/\theta_{Bi}$, for $i = 1, \cdots, k$. Replacing $\theta_{Ai} = \psi\theta_{Bi}$ in the log-likelihood and taking partial derivative with respect to θ_{Bi} and

equating to zero we get the feasible solution of θ_{Bi} as a function of ψ. Thus, the profile log-likelihood is a function of unknown parameter ψ only. Differentiating the profile log-likelihood with respect to ψ and equating it to zero we get an iterative solution for ψ as $\psi = \phi(\psi)$. The iteration becomes faster by adding some specified common term to both sides of the iterative equation. See Bohning et al. ([18], p. 123) for details. Let us denote this estimator by $\widehat{\psi}^{(C)}_{PMLE}$.

4 Surrogate augmented estimate

Whenever a true endpoint of jth individual $Y_{t,j}$ is unavailable we replace it by the estimated value of $\widehat{P}_t(W_{t,j}) = P(Y_{t,j} = 1|W_{t,j})$ with the help of observed surrogate endpoint, where the relationship between Y_t and W_t is estimated from the 2×2 table on m_t paired data on (Y_t, W_t). The total number of successes by t (that is $\sum_{j=1}^{n_t} Y_{t,j}$) is approximated by

$$\widehat{\mathbf{Y}}_t = Y_{tT} + \sum_{j=1}^{n_t - m_t} \widehat{P}(Y_{t,m_t+j} = 1|W_{t,m_t+j}) = Y_{tT} + \sum_{j=1}^{n_t - m_t} \widehat{P}_t(W_{t,m_t+j}). \qquad (4.1)$$

Among the $n_t - m_t$ unavailable true responses the number of successes by surrogates is W_{tS} and the number of failures by surrogates is $(n_t - m_t - W_{tS})$. Clearly there could be successes from the true end-points among these W_{tS} surrogate-successes or among the $(n_t - m_t - W_{tS})$ surrogate-failures. We assume that these are proportionate to $P(Y_t = 1|W_t = 1)$ and $P(Y_t = 1|W_t = 0)$, respectively. It can be easily shown that, by our model assumption,

$$P(Y_t = 1|W_t = 1) = \frac{\pi_{t1} p_t}{r_t} = P_{t1}, \quad P(Y_t = 1|W_t = 0) = 1 - \frac{\pi_{t0}(1 - p_t)}{1 - r_t} = P_{t0}.$$

Clearly, we can estimate these P_{t1} and P_{t0} only from the 2×2 data on (Y_t, W_t) on the m_t available pairs, the these estimates are

$$\widehat{P}_{t1} = \frac{m_{t11}}{W_{tT}}, \quad \widehat{P}_{t0} = \frac{m_{t10}}{m_t - W_{tT}}.$$

which are maximum likelihood estimates of corresponding probabilities. Hence, by effective use of surrogate end-points to obtain the conditional expectation of true end-point when it is not available but the surrogate one is available, we approximate the

total number of successes for treatments t as

$$\widehat{\mathbf{Y}}_{\mathbf{t}} \;=\; Y_{tT} + \frac{m_{t11}}{W_{tT}} W_{tS} + \frac{m_{t10}}{m_t - W_{tT}} (n_t - m_t - W_{tS}),$$

Here we assume that W_{tT} is away from 0 or m_t for all practical purposes. One has to define $\widehat{\mathbf{Y}}_t$ and suitably when $W_{tT} = 0$. Now onwards we will denote $\widehat{p}_t^{(S)} = \widehat{\mathbf{Y}}_t / n_t = 1 - \widehat{q}_t^{(S)}$. Here (S) stands for surrogate augmented estimator. The estimates based on only the available true responses is $\widehat{p}_t^{(T)} = Y_{tT}/m_t = 1 - \widehat{q}_t^{(T)}$, $t = A, B$, where (T) stands for the estimators based on true endpoints only. In practice we may get $\widehat{p}_t^{(T)}$ or $\widehat{p}_t^{(S)}$; but $\widehat{p}_t^{(C)}$ is only hypothetical which could be obtained only if we could observe all the true responses.

5 Surrogate end-points for multiple tables

5.1 Mantel-Haenszel estimator

Consider k groups under experiment with moderate sizes of true observations $\{(m_{Ai}, m_{Bi}),\ i = 1, \cdots, k\}$ and obtain MH estimator of ψ, which is assumed to be constant across the groups and ψ being the common value of ψ_is, $i = 1, \cdots, k$. Denote $M_i = m_{Ai} + m_{Bi}$, the available true response size for the ith group and total number of sample sizes for the same are $N_i = n_{Ai} + n_{Bi}$ where $i = 1, \cdots, k$, and the MH estimator is

$$\widehat{\psi}_{MH}^{(E)} = \frac{\sum_{i=1}^k \mu_i^{(E)} \widehat{q}_{Ai}^{(E)} \widehat{p}_{Bi}^{(E)} \widehat{\psi}_i^{(E)}}{\sum_{i=1}^k \mu_i^{(E)} \widehat{q}_{Ai}^{(E)} \widehat{p}_{Bi}^{(E)}} \sim \frac{\sum_{i=1}^k \mu_i^{(E)} q_{Ai} p_{Bi} \widehat{\psi}_i^{(E)}}{\sum_{i=1}^k \mu_i^{(E)} q_{Ai} p_{Bi}}.$$

where $\widehat{\psi}_i^{(E)} = \widehat{p}_{Ai}^{(E)} \widehat{q}_{Bi}^{(E)} / (\widehat{q}_{Ai}^{(E)} \widehat{p}_{Bi}^{(E)})$ and $\mu_i^{(C)} = \left(\frac{n_{Ai} n_{Bi}}{N_i}\right) = \mu_i^{(S)}$ whereas $\mu_i^{(T)} = \left(\frac{m_{Ai} m_{Bi}}{M_i}\right)$. The estimators $\widehat{p}_t^{(C)}$, $\widehat{p}_t^{(S)}$ and $\widehat{p}_t^{(T)}$ are already defined in Sections 3 and 4 respectively. Note that $\widehat{p}_{ti}^{(E)} \to p_{ti}$ almost surely for all i and $E = C, T, S$ for $t = A, B$.

Under the equality of odds ratios across the k groups, $\widehat{\psi}_i^{(E)}$ is asymptotically $N(\psi, \psi^2/\omega_i^{(E)})$ with $\omega_i^{(E)} = Var(\log \widehat{\psi}_i^{(E)})^{-1}$. Consequently, for $E = C, T, S$

$$\widehat{\psi}_{MH}^{(E)} \overset{a}{\sim} N\left(\psi, \frac{\psi^2 \sum_i \left(\mu_i^{(E)} q_{Ai} p_{Bi}\right)^2 / \omega_i^{(E)}}{\left(\sum_i \mu_i^{(E)} q_{Ai} p_{Bi}\right)^2}\right). \tag{5.1}$$

5.2 Surrogate-augmented profile likelihood based estimation

The iterative solution for ψ by profile likelihood method is already discussed in Section 4. Unlike the Mantel-Haenszel estimator profile likelihood based estimator is not easy to compute; in some cases it becomes almost intractable. Using the available true endpoint data, $\widehat{\psi}^{(T)}_{PMLE}$ can be obtained by replacing n_{Ai}, n_{Bi} by m_{Ai}, m_{Bi} in the likelihood (3.2).

For the surrogate-augmented case we replace Y_{ti} by $\widehat{\mathbf{Y}}_{ti}$ in $\widehat{\psi}^{(C)}_{PMLE}$, as well as $\widehat{p}^{(S)}_{Ai}(\psi)$s and $\widehat{p}^{(S)}_{Bi}(\psi)$s are also used to obtain new estimator $\widehat{\psi}^{(S)}_{PMLE}$, which also follows a normal distribution. We have the following remarks.

Remark 1. The iterative solution for our surrogate-augmented PMLE, denoted by $\widehat{\psi}^{(S)}_{PMLE}$ gives our surrogate-augmented MH estimator $\widehat{\psi}^{(S)}_{MH}$ at the first iteration if we start with the initial value of $\psi = 1$. This can be easily shown following the derivations of Appendix A.3 of [18], p. 172-173, by replacing their $x_i^{(E)}$, x_i^C, $n_i^{(E)}$, n_i^C by $\widehat{\mathbf{Y}}_{Ai}$, $\widehat{\mathbf{Y}}_{Bi}$, n_{Ai}, n_{Bi}.

Remark 2. However, our numerical computations (not reported here for the sake of brevity) shows remarkable closeness in the performances of $\widehat{\psi}^{(S)}_{MH}$ and $\widehat{\psi}^{(S)}_{PMLE}$.

6 Simulations

We have done extensive simulation studies for different combination of p_{Ai} and p_{Bi} such that common odds ratio ψ is fixed. We performed it for different number of group, k, from 3 to 50 (shown in the Tables 1-3). Number of true endpoint is chosen at random number around 80 as $m_{ti} \sim 80 + Bin(5, 0.6)$. Total sample sizes are taken within 130-350. For simplicity we kept $\pi_{t1} = 0.9$ and $\pi_{t0} = 0.8$ for $t = A, B$. For each of the above parameter combination we carried out 10,000 iterations.

We observed remarkably close results for the MH estimator and the PMLE. Table 1(a) shows absolute difference between MH estimator and PMLE in the surrogate-

augmented situation, that is $|\widehat{\psi}^{(S)}_{MH} - \widehat{\psi}^{(S)}_{PMLE}|$ when $\psi = 1.1$ whereas Table 1(b) shows $|Var(\widehat{\psi}^{(S)}_{MH}) - Var(\widehat{\psi}^{(S)}_{PMLE})|$. Both are very close to zero. This, along with asymptotic normality of each estimator, reflect the closeness of the performances of $\widehat{\psi}^{(S)}_{MH}$ and $\widehat{\psi}^{(S)}_{PMLE}$.

We obtain substantial gain in MH estimate and the PMLE when surrogate is used. We provide $\mathcal{E}_{S|T} = Var(\widehat{\psi}^{(T)}_{M})/Var(\widehat{\psi}^{(S)}_{M})$ for $M = MH, PMLE$ in Table 2. The values of $\mathcal{E}_{S|T}$, the ratio of the variance based on only true responses to the variance in the surrogate-augmented situation, show that we can have 20% - 57% gain by using surrogate responses for the given parameter combinations. Thus we can have substantial gain in using surrogate responses when all the true responses can not be observed. Use of surrogate provides increases efficiency to a good extent. Table 3 provides $\mathcal{E}_{C|S} = Var(\widehat{\psi}^{(C)}_{M})/Var(\widehat{\psi}^{(S)}_{M})$-values for $M = MH, PMLE$, which gives an idea of the efficiency achieved by using the surrogate responses to the maximum efficiency that could be achieved if all the true responses were available. In Tables 2 and 3, $\mathcal{E}_{S|T}$ and $\mathcal{E}_{C|S}$ are same for both MH and PMLE up to the reported two decimal places.

7 Concluding remarks

The basic idea of the present paper is to illustrate how the efficient use of surrogate data can improve the estimate of odds ratio in a 2×2 set up. Since odds ratio is a very important measure which is extensively used by the practitioners, the present methodology has tremendous potential application in the real world. Although this method is shown to be very useful, the results are not surprising. It is expected that an efficient use of surrogate will bring better result, and we tried to provide some sensible method of using surrogate in this context.

Although we illustrated our methodology for binary surrogate data, from the general expression of $\widehat{\mathbf{Y}}_t$ in (4.1) it is clear that our procedure is applicable for any types of surrogates, binary, categorical or continuous.

One interesting part is the result on closeness of MH estimator and PMLE. So far our knowledge goes, there is no study and indication on the closeness of the results from these two widely used approaches for estimating common odds ratio in the pres-

ence of surrogate. The present paper fulfils that gap.

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Table 1(a). Simulated values of $|\widehat{\psi}^{(S)}_{MH} - \widehat{\psi}^{(S)}_{PMLE}|$ (order 10^{-4}).

	$n_{ti} \approx$	130	150	180	200	250	300	350
	3	4.55	4.42	4.28	4.09	3.87	3.70	3.53
	5	5.29	4.93	4.65	4.42	4.20	3.98	3.89
	7	5.20	4.87	4.67	4.54	4.28	3.99	3.83
k	10	5.24	4.99	4.70	4.60	4.29	4.24	4.08
	25	5.30	5.00	4.74	4.66	4.37	4.14	4.12
	40	5.28	5.00	4.74	4.60	4.38	4.22	4.13
	50	5.29	5.03	4.75	4.64	4.36	4.20	4.13

Table 1(b). Simulated values of $|Var(\widehat{\psi}^{(S)}_{MH}) - Var(\widehat{\psi}^{(S)}_{PMLE})|$ (order 10^{-5}).

	$n_{ti} \approx$	130	150	180	200	250	300	350
	3	31.84	29.55	28.37	26.21	22.40	21.57	19.68
	5	21.75	20.90	17.97	16.96	15.18	13.40	13.26
	7	15.04	15.12	12.77	12.35	10.97	9.94	9.49
k	10	11.75	10.49	9.30	8.76	8.07	7.45	6.91
	25	4.59	4.14	3.74	3.62	3.27	3.02	2.84
	40	2.91	2.71	2.44	2.24	2.05	1.95	1.82
	50	2.32	2.16	2.02	1.89	1.64	1.51	1.45

Table 2. Simulated vlues of $\mathcal{E}_{S|T} = Var(\widehat{\psi}_M^{(T)})/Var(\widehat{\psi}_M^{(S)})$ for $M = MH, PMLE$.

	$n_{ti} \approx$	130	150	180	200	250	300	350
	3	1.20	1.28	1.33	1.37	1.47	1.49	1.54
	5	1.21	1.27	1.35	1.36	1.47	1.51	1.56
	7	1.21	1.26	1.34	1.37	1.48	1.51	1.56
k	10	1.21	1.28	1.36	1.39	1.46	1.54	1.53
	25	1.22	1.28	1.31	1.39	1.46	1.53	1.55
	40	1.20	1.27	1.32	1.35	1.48	1.50	1.55
	50	1.21	1.28	1.36	1.40	1.45	1.48	1.57

Table 3. Simulated value of $\mathcal{E}_{C|S} = Var(\widehat{\psi}_M^{(C)})/Var(\widehat{\psi}_M^{(S)})$ for $M = MH, PMLE$.

	$n_{ti} \approx$	130	150	180	200	250	300	350
	3	0.74	0.66	0.58	0.54	0.44	0.38	0.33
	5	0.75	0.68	0.59	0.54	0.47	0.39	0.34
	7	0.76	0.68	0.61	0.54	0.47	0.40	0.36
k	10	0.76	0.69	0.62	0.57	0.47	0.40	0.35
	25	0.76	0.69	0.60	0.57	0.47	0.43	0.36
	40	0.76	0.67	0.59	0.56	0.47	0.40	0.37
	50	0.76	0.69	0.61	0.56	0.47	0.41	0.37