

**ADMISSIBLE, CONSISTENT MULTIPLE TESTING  
WITH APPLICATIONS**

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## **ABSTRACT OF THE DISSERTATION**

### **Admissible, consistent multiple testing with applications**

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For multivariate normal models and exponential family models a multiple testing step-wise method is offered that is both admissible and consistent. The method is readily adaptable to selecting variables in linear regression models where it is akin to the forward selection method plus a screening stage plus a sign compatibility stage. The method is also adaptable to testing the local odds ratios in contingency tables in which the categories are ordered. Examples and simulations are included.

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# Chapter 1

## Introduction

Multiple testing in general linear models is a long standing statistical practice. The subject has been given great impetus over the last two decades with applications arising in fields where the numbers of hypotheses to be tested can be extremely large (namely thousands). Such applications are needed in microarrays, astronomy, mutual fund evaluations, proteomics, disclosure risk, cytometry, imaging and others. Traditional methods, usually classified as single step methods, are deemed too conservative, particularly when the number of hypotheses to be tested is very large. To compensate, stepwise procedures were introduced, which enable more rejection of hypotheses. See, for example, Dudoit and Van Der Laan (2008) and Lehmann and Romano (2005) for description and some properties of single step and stepwise procedures. Many stepwise procedures are based on P-values derived from the marginal distributions of relevant test statistics that test an individual hypothesis. Oftentimes, these and other multiple testing procedures (MTPs) are focused on controlling some type of error rate, namely, the familywise error rate (FWER), weak or strong, or the false discovery rate (FDR). Oftentimes the error rate controlling procedures seek to have good average power.

While focusing on error rate control of the overall procedure, sometimes the properties of the ensuing tests of each individual hypothesis is not given enough attention. The resulting test for an individual hypothesis resulting from an MTP (especially a stepwise MTP) can be complicated. Nevertheless, examining the properties of the individual tests can be important. In fact, a decision theory approach to multiple testing, focusing on individual tests, can suggest procedures that do well when evaluated by the expected number of type I errors and expected numbers of type II errors. This represents another way to evaluate MTPs. See Dudoit and Van Der Laan (2008) where

attention is given to type I and type II errors as well as to error rate controlling procedures.

Before going further, a few examples are helpful.

Example 1 (multivariate normal): given  $X \sim N(\boldsymbol{\mu}, \sigma^2 \Sigma)$ , where  $\boldsymbol{\mu}$  is unknown  $n \times 1$  vector,  $\Sigma$  is a known positive definite matrix,  $\sigma^2$  is either known or can be estimated by  $s^2$ . We intend to test hypothesis  $H_i : \mu_i = 0$  vs  $K_i : \mu_i \neq 0$ ,  $i = 1, \dots, n$ . Here the total number of hypotheses is  $n$ .

If the matrix  $\Sigma$  is diagonal, then test statistics ( $X_i$ ) for individual hypothesis are independent. Otherwise these test statistics are dependent.

Example 2 (independent binomial models): given a  $2 \times C$  contingency table  $\mathbf{X}$  from independent binomial model, where the  $C$  categories are ordered in some sense, we intend to test whether the adjacent binomial parameters are equal or not, i.e.,  $X_i \sim \text{Binomial}(n_i, p_i)$ ,  $i = 1, \dots, C$ ; we want to test  $H_i : p_i = p_{(i+1)}$  vs  $K_i : p_i \neq p_{(i+1)}$ ,  $i = 1, \dots, (C - 1)$ . Here the total number of hypotheses is  $(C - 1)$ .

In example 2, the test statistics for individual hypothesis are most likely dependent.

Example 3 (pairwise comparison) : Instead of comparing adjacent binomial parameters, in the situation that the  $C$  categories are not ordered, it might be of interest to compare any two of the categories. So now there are a total of  $C(C - 1)/2$  hypotheses. And there are logical constraints on the true hypotheses. Decision results of testing for this case might or might not need to observe those logical constraints.

In general, we have  $m$  hypotheses to be tested of which  $m_0$  hypotheses are true. Let  $R$  be the number of hypotheses rejected, following table summarizes the testing result.

	Declared non-significant	Declared significant	Total
true null hypotheses	$U$	$V$	$m_0$
non-true null hypotheses	$T$	$S$	$m - m_0$
Total	$m - R$	$R$	$m$

The family-wise error rate(FWER) is the probability of rejecting at least one null hypothesis that is true null, i.e., FWER is  $P(V \geq 1)$ , and false discovery rate (FDR) is  $E[V/\max(R, 1)]$ .

A MTP which controls FWER at level  $\alpha$  when  $m_0 = m$  is said to control weak FWER. If FWER is controlled at level  $\alpha$  regardless of  $m_0$ , it is called strong FWER control. Weak FWER control is not very appealing. When we say FWER control, we implicitly mean strong FWER control.

Most popular stepwise methods often intend to achieve more power while controlling FWER(weak or strong) or FDR at predefined level.

A multiple testing procedure is a closure testing procedure (Marcus et al., 1976) if it works in following way:

Start with a family of hypotheses  $F_0 = \{H_1, \dots, H_m\}$ , let  $I_m = \{1, \dots, m\}$  be the index of hypotheses. First construct a set of hypotheses through intersection of set  $F_0$ , i.e.,  $F_1 = \{\bigcap_{k \in I} H_k : I \subseteq I_m\}$ . Let  $F_{1i} = \{\bigcap_{k \in I} H_k : \{i\} \subseteq I \subseteq I_m\}$ . Clearly  $F_{1i}$  is a subset of  $F_1$ . The testing has two steps. Step 1, for each intersection hypothesis in  $F_1$ , perform an individual test at level  $\alpha$ . Step 2, for each hypothesis  $H_i$  in  $F_0$ , reject it if at step 1 all hypotheses in  $F_{1i}$  are rejected. The decision made at step 2 is the final decision for each hypothesis in  $F_0$ .

It turns out that all testing procedures that control FWER are either closure testing procedures, or shortcuts to closure testing procedures.

Note that the tests at step 2 of a closure testing are induced from testing at step 1.



Although the individual testing at step 1 can be simple, the test at step 2 can get quite complicated, i.e., the individual test induced from a MTP procedure could be complex.

In a series of papers, Cohen and Sackrowitz (2005a), (2005b), (2007), (2008) and Cohen, Kolassa, and Sackrowitz (2007) have shown that many of the standard stepwise procedures under a wide variety of assumptions, often turn out to be inadmissible for a variety of risk functions that involve both expected type I and expected type II errors. Specifically, for popular step-down MTPs, in multivariate normal model, under typical conditions, it is shown that there exists other MTP whose individual test has smaller type I and type II error.

For exponential family models the inadmissibility is often shown to follow because in testing an individual hypothesis, relevant acceptance sections are not intervals. This represents a disturbing practical shortcoming of many of the usual procedures.

In response to the inadmissibility property and the fact that many stepwise procedures are based on the marginal distributions of test statistics, even when they are statistically dependent, Cohen, Sackrowitz and Xu (CSX) (2009) recommend a new MTP method called maximum residual down (MRD). MRD takes correlation into account and is admissible ( in exponential family models ) for a risk function that focuses on expected type I and type II errors.

However, for some models the MRD method is not consistent. See Chapter 2 for a formal definition of consistency. Informally, consistent means that the probability of correctly testing each hypothesis tends to 1 as the sample size tends to infinity and as critical values tend to infinity at a certain rate.

In this thesis we introduce a modification of MRD which offers a procedure that is admissible and consistent. The modification, discussed in Chapter 3, adds a screening

stage and sign stage to MRD. Call the new procedure MRDSS. The method is applicable to exponential family models, and to other models as well, if sample sizes are large.

Variable selection in the linear regression context is a special multiple testing problem. We will apply the method to selection of variable models in regression. MRD is shown to be equivalent to a forward method in this context. Modification to MRD will be accordingly a modification of forward method.

In another problem we also apply the method to testing all local odds ratios in an  $R \times C$  contingency table.

For the selection of variables model, the MRD method is shown to be equivalent to some forward method of selecting variables. See Miller (2002) for a discussion of forward methods. Both MRD and the forward method are stepwise methods based on what we define as residuals. Forward methods and hence MRD are typically not consistent. See, for example, An and Gu (1985). We show that MRDSS, and thus a modification of the forward methods, is admissible and consistent under modest and typical conditions on the critical values and design matrix. The computational feasibility of MRDSS in the selection of variables model is the same as forward selection, i.e, it is feasible for very large problem.

MRDSS can be extended to other exponential family models. In this thesis, we extend MRDSS to multiple testing of odds ratios in  $2 \times 2$  subtables of  $R \times C$  tables, in which the categories are ordered in some sense. Following table is an example.

	Worse	Same	Slight Better	Better	Cured
Dose 1	$x_{11}$	$x_{12}$	$x_{13}$	$x_{14}$	$x_{15}$
Dose 2	$x_{21}$	$x_{22}$	$x_{23}$	$x_{24}$	$x_{25}$
...					
Dose r	$x_{r1}$	$x_{r2}$	$x_{r3}$	$x_{r4}$	$x_{r5}$

This problem was discussed in Shaffer (1986). The accept region of usual stepwise procedures are not convex, which render them inadmissible. See Chen, Cohen, and Sackrowitz (2009b) for examples. A new methodology, which is an application of MRDSS, is given for this problem.

In the next Chapter we state the problem for multivariate normal model, including definitions and other preliminaries. Stepwise methods, including step-down, step-up and MRD, are described in this chapter. Extension of MRD to MRDSS is given in Chapter 3 for the multivariate normal model, and the connection between MRD and forward selection is described. Admissibility and consistency of usual step-down, step-up, MRD and MRDSS are investigated. In Chapter 4, MRDSS is applied to test of local odds ratios in contingency table with ordered categories. We use either a Poisson model or multinomial model, conditioned on row and column sums. The new methodology is demonstrated with two examples, one for the simple  $2 \times C$  case, one for the more general  $R \times C$  case. Chapter 5 discuss computational related issues, mainly the MRDSS method in testing of local odds ratios and the choosing of critical values. In Chapter 6, a simulation study to compare MRDSS versus step-down method is given for testing of local odds ratios.

## Chapter 2

### Models, definitions and preliminaries

We start with a very general multiple testing problem. Let  $\mathbf{X}$  be a random vector that is distributed as  $f(\mathbf{X}|\boldsymbol{\theta})$ , where  $\boldsymbol{\theta}$  is unknown  $M \times 1$  vector parameters. We intend to test  $H_i : \theta_i = 0$  vs  $K_i : \theta_i \neq 0$ ,  $i = 1, \dots, m$ , where  $m \leq M$ . The distribution function  $f$  usually belongs to a family of distribution, and indexed by  $\boldsymbol{\theta}$ . In this thesis, we assume the family (of distributions) is one class of exponential family, and  $\boldsymbol{\theta}$  are natural parameters of the exponential family.

#### 2.1 Models and definitions

The first model posed has a random sample of  $M \times 1$  vectors,  $\mathbf{X}_\alpha$ ,  $\alpha = 1, \dots, n$ , from a multivariate normal distribution whose mean vector is  $\boldsymbol{\mu}$  and whose covariance matrix is  $\Gamma$ . Sometimes  $\Gamma$  is known and sometimes  $\Gamma = \sigma^2 \Sigma$  where  $\Sigma$  is known and  $\sigma^2$  is unknown. In the later case,  $s^2 = \sum_{\alpha=1}^n (\mathbf{X}_\alpha - \bar{\mathbf{X}})' \Sigma^{-1} (\mathbf{X}_\alpha - \bar{\mathbf{X}}) / M(n-1)$  is an unbiased estimator of  $\sigma^2$ , which is independent of  $\bar{\mathbf{X}} = \sum_{\alpha=1}^n \mathbf{X}_\alpha / n$ . For the first model the density of  $\bar{\mathbf{X}}$  is

$$\begin{aligned} f_{\bar{\mathbf{X}}}(\bar{\mathbf{x}} | \boldsymbol{\mu}, \Sigma) &= (n^{1/2} / (2\pi)^{M/2} |\Gamma|^{1/2}) \exp \{ -n/2 (\bar{\mathbf{x}} - \boldsymbol{\mu})' \Gamma^{-1} (\bar{\mathbf{x}} - \boldsymbol{\mu}) \} \\ &= \beta(\boldsymbol{\mu}, \Gamma) h(\bar{\mathbf{x}}) \exp n \bar{\mathbf{x}}' \Gamma^{-1} \boldsymbol{\mu} \end{aligned} \quad (2.1.1)$$

We wish to test  $H_i : \mu_i = 0$  vs  $K_i : \mu_i \neq 0$ ,  $i = 1, 2, \dots, M$ .

The general linear model has  $\mathbf{Y} = A\boldsymbol{\beta} + \boldsymbol{\epsilon}$  where  $\mathbf{Y}$  is an  $n \times 1$  vector which is multivariate normal with mean vector  $A\boldsymbol{\beta}$  and covariance matrix  $\sigma^2 I$ .  $A = (\mathbf{a}_1, \dots, \mathbf{a}_M)$  is an  $n \times M$  fixed design matrix and  $\boldsymbol{\beta}$  is an  $M \times 1$  vector of parameters. If  $A$  has rank  $M$ , then  $\hat{\boldsymbol{\beta}} = (A'A)^{-1} A' \mathbf{Y} \sim N(\boldsymbol{\beta}, \sigma^2 S^{-1})$  where  $S^{-1} = (A'A)^{-1}$ . An unbiased

estimator of  $\sigma^2$  is  $s^2 = \text{MSE} = \text{SSE}/(n - M)$ , and  $s^2$  is independent of  $\hat{\boldsymbol{\beta}}$ . Thus this general linear model reduces to our multivariate normal model with  $\Gamma = \sigma^2 S^{-1}$ . We wish to test  $H_i : \beta_i = 0$  vs  $K_i : \beta_i \neq 0, i = 1, 2, \dots, M$ .

Another model considered is an exponential family model. Suppose  $Z_i, i = 1, 2, \dots, Q$  are independent and have a one dimensional exponential family distribution with natural parameter  $\omega_i$ , i.e., the joint density of  $\mathbf{Z} = (Z_1, \dots, Z_Q)'$  is

$$f_{\mathbf{Z}}(\mathbf{z} | \boldsymbol{\omega}) = \beta(\boldsymbol{\omega})h(\mathbf{z})e^{\mathbf{z}'\boldsymbol{\omega}}$$

where  $\boldsymbol{\omega} = (\omega_1, \dots, \omega_Q)'$ . Let  $G$  be a full rank  $M \times Q$  matrix of constants,  $M < Q$ , and let  $B = \begin{pmatrix} G \\ F \end{pmatrix}$ , where the rows of  $F$  are orthogonal to the rows of  $G$  and  $B$  has rank  $Q$ . Now let  $\boldsymbol{\theta} = B\boldsymbol{\omega}$  and note

$$\mathbf{z}'\boldsymbol{\omega} = \mathbf{z}'(B'B^{-1})B^{-1}\boldsymbol{\theta} = \mathbf{z}'B'(BB')^{-1}\boldsymbol{\theta}$$

If we let  $\mathbf{X} = B\mathbf{Z}$ , we find the density of  $\mathbf{X}$  is

$$f_{\mathbf{X}}(\mathbf{x} | \boldsymbol{\theta}) = \beta^*(\boldsymbol{\theta})h^*(\mathbf{x})e^{\mathbf{x}'\Sigma^{-1}\boldsymbol{\theta}} \quad (2.1.2)$$

where  $\Sigma = BB'$ . Further note that  $\Sigma = \begin{pmatrix} GG' & 0 \\ 0 & FF' \end{pmatrix}$  and

$$\Sigma^{-1} = \begin{pmatrix} (GG')^{-1} & 0 \\ 0 & (FF')^{-1} \end{pmatrix}.$$

We wish to test  $H_i : \theta_i = 0$  vs  $K_i : \theta_i \neq 0, i = 1, \dots, M$ .

## 2.2 Risk function

Multiple testing procedures are evaluated by considering expected type I error and expected type II error for each individual hypothesis. Let  $\mathbf{X}$  represent all the data. An MTP  $\Phi(\mathbf{x}) = (\phi_1(\mathbf{x}), \dots, \phi_M(\mathbf{x}))'$  where  $\phi_i(\mathbf{x})$  is a test function for testing  $H_i$  vs  $K_i, i = 1, \dots, M$  is inadmissible, if there exists another MTP such that for each testing

problem, the expected type I and type II errors are less than or equal to those of  $\Phi(\mathbf{x})$  and for at least one type of error and some parameter points strictly less.

Such an evaluation is based on an  $M \times 1$  vector risk function where the  $i$ th component is the typical risk function for testing an individual hypothesis. This vector risk function is least stringent in the sense that if a procedure is inadmissible for the vector risk function it would be inadmissible for any risk that is a monotone function of the expected number of type I and expected number of type II errors.

### 2.3 Consistency

Consistency is defined in An and Gu (1985) and in Bunea, Wegkamp, and Auguste (2006). Let  $I_0 \subseteq \{1, \dots, M\} \stackrel{def}{=} I_M$ , be the non-zero components of  $\boldsymbol{\mu}$ . An estimator  $\hat{I}$  of  $I_0$  is called consistent if  $\lim_{n \rightarrow \infty} P\{\hat{I} = I_0\} = 1$ . If  $M_0 \leq M$  is the number of indices in  $I_0$  then  $\hat{I}$  is consistent if and only if the MTP leads to  $M_0$  rejections, none of which are erroneous.

If the critical values are to be compared to test statistics as opposed to the P-value determined by the statistics, then consistency is possible only if certain critical values tend to infinity at a certain rate.

### 2.4 Stepwise procedures for multiple testing

Most popular MTPs that control FWER or FDR are stepwise procedures. Those MTPs are defined in terms of a set of critical values which determine acceptances or rejections at various steps. Stepwise MTPs are more powerful than one-step MTPs in most situations. For the purpose of illustration, we use the problem of testing  $H_i : \mu_i = 0$  vs  $K_i : \mu_i \neq 0$ ,  $i = 1, \dots, M$ .

### 2.4.1 Standard step-down or step-up

Let  $p_1, \dots, p_M$  denote the P-value of the individual test of hypothesis  $H_1, \dots, H_M$ , respectively. Let  $p_{(1)}, \dots, p_{(M)}$  denote the ordered P-values, and  $H_{(1)}, \dots, H_{(M)}$  the corresponding hypotheses. Given a sequence of critical P-values  $\alpha_1 < \alpha_2 < \dots < \alpha_M$ , a step-down procedure is defined as follows:

(1) If  $p_{(1)} < \alpha_1$ , reject  $H_{(1)}$  and continue to next step, otherwise stop and accept all hypotheses.

(2) If  $p_{(2)} < \alpha_2$ , reject  $H_{(2)}$  and continue to next step, otherwise stop and accept all remaining hypotheses.

(3) In general, at step  $k$ , if  $p_{(k)} < \alpha_k$ , reject  $H_{(k)}$  and continue to next step, otherwise stop and accept all remaining hypotheses.

(4) at last step, step  $M$ , if  $p_{(M)} < \alpha_M$ , reject  $H_{(M)}$ , otherwise accept  $H_{(M)}$ .

Let  $i_0 = \min\{i : 1 \leq i \leq M, p_{(i)} \geq \alpha_i\}$ , then the step-down method rejects  $H_{(1)}, \dots, H_{(i_0-1)}$ .

Note that one can define the step-down method equivalently through a sequence of critical values for test statistics, instead of critical P-values.

If the sequence of critical P-values is chosen to be  $\alpha_i = \alpha/(M - i + 1)$  (Holm, 1979), then FWER is strongly controlled at  $\alpha$ .

While step-down procedures start with the individual most significant hypothesis, i.e, hypothesis with the smallest P-value, the step-up procedures work the opposite way, i.e., start with the individual least significant hypothesis ( the hypothesis with maximal P-values).

Given a sequence of critical P-values  $\alpha_1 < \alpha_2 < \dots < \alpha_M$ , step-up method perform testing in following way:

(1) If  $p_{(M)} \geq \alpha_M$ , accept  $H_{(M)}$  and continue to next step, otherwise stop and reject all hypotheses.

(2) If  $p_{(M-1)} \geq \alpha_{(M-1)}$ , accept  $H_{(M-1)}$  and continue to next step, otherwise stop

and reject all remaining hypotheses.

(3) In general, at step  $k$ , if  $p_{(M-k+1)} \geq \alpha_{(M-k+1)}$ , accept  $H_{(M-k+1)}$  and continue to next step, otherwise stop and reject all remaining hypotheses.

(4) at last step, step  $M$ , if  $p_{(1)} \geq \alpha_1$ , accept  $H_{(1)}$ , otherwise reject  $H_{(1)}$ .

Let  $i_1 = \max\{i : 1 \leq i \leq M, p_{(i)} < \alpha_i\}$ , then the step-up method rejects  $H_{(1)}, \dots, H_{(i)}$ .

If the sequence of critical P-values is chosen to be  $\alpha_i = \alpha/(M - i + 1)$  (Hochberg, 1988), then under assumption of independent or positive regression dependence on the set (Sarkar and Chang, 1997), FWER is strongly controlled at  $\alpha$  for step-up procedures.

If the sequence of critical P-values is chosen to be  $\alpha_i = i\alpha/M$  (Benjamini and Hochberg, 1995), then under assumption of independent or positive regression dependence on the set, step-up procedure controls FDR at  $\alpha$ .

Except through the change of critical values, the stepwise procedures in above do not take dependence into consideration at all steps. For example, suppose all hypotheses are dependent. Suppose at step 1, hypothesis  $H_1$  is rejected ( or accepted), this should affect the significance level of remain hypotheses, or their P-values. But in the above step-down/up procedures, the same set of P-values are used throughout all the steps.

The standard stepwise methods described above only need the P-value of individual hypothesis to perform multiple testing, which means they can be easily applied in a wide range of situations. The computation effort usually is small. However, the other side of this advantage is that because standard stepwise methods only utilize the P-values determined from marginal distribution of individual test statistics, intuitively, they will be less powerful than stepwise methods that take dependence into consideration in every steps.

#### 2.4.2 MRD for multivariate normal model

Cohen, Sackrowitz, and Xu (2009) proposed a new stepdown procedure, called maximum residual down (MRD). MRD takes dependent into consideration in every step.

We start with the multivariate normal model with  $\Gamma = \Sigma = (\sigma_{ij})$  known and



nonsingular.

Let  $\mathbf{X} = (X_1, \dots, X_M)'$ ,  $\mathbf{X}^{(i_1, \dots, i_r)}$  be a subvector of  $\mathbf{X}$  consisting of all components except  $X_{i_1}, \dots, X_{i_r}$ .  $\Sigma_{(i_1, \dots, i_r)}$  is the  $(M-r) \times (M-r)$  covariance matrix of  $\mathbf{X}^{(i_1, \dots, i_r)}$ , for any  $j \neq i_1, \dots, i_r$ ,  $\boldsymbol{\sigma}_j^{(i_1, \dots, i_r)}$  is the  $(M-r-1) \times 1$  vector of covariances between  $X_j$  and all variables except  $X_{i_1}, \dots, X_{i_r}$  and  $X_j$ .

$$\sigma_{(j|i_1, \dots, i_r)}^2 = \sigma_{jj} - \boldsymbol{\sigma}_j^{(i_1, \dots, i_r)'} \Sigma_{(i_1, \dots, i_r, j)}^{-1} \boldsymbol{\sigma}_j^{(i_1, \dots, i_r)} \quad (2.4.1)$$

is the conditional variance of  $X_j$ , given all variables except  $X_{i_1}, \dots, X_{i_r}, X_j$ .

Now define the  $j$ th normalized residual at step  $m$  to be

$$U_{mj}(\mathbf{X}^{(i_1, \dots, i_{m-1})}) = \frac{X_j - \boldsymbol{\sigma}_j^{(i_1, \dots, i_{m-1})'} \Sigma_{(i_1, \dots, i_{m-1}, j)}^{-1} \mathbf{X}^{(i_1, \dots, i_{m-1}, j)}}{[\sigma_{(j|i_1, \dots, i_{m-1})}^2]^{1/2}} \quad (2.4.2)$$

$m = 1, \dots, M$ . At step  $m$ , we let  $\mathbf{U}_m$  be the  $(M-m+1) \times 1$  vector of  $U_{mj}$ 's. We note that if  $D_m$  is the diagonal matrix of the terms in (2.4.1), then

$$\mathbf{U}_m = D_m^{1/2} \Sigma_{(i_1, \dots, i_{m-1})}^{-1} \mathbf{X}^{(i_1, \dots, i_{m-1})}$$

Let  $C_1 > C_2 > \dots > C_M > 0$  be a given set of constants. Then MRD is determined as follows:

At step 1, consider  $U_{1j}(\mathbf{X})$ ,  $j \in 1, \dots, M$ . Let  $j_1 = j_1(\mathbf{X})$  be such that  $|U_{1j_1}(\mathbf{X})| = \max_j |U_{1j}(\mathbf{X})|$ . If  $|U_{1j_1}(\mathbf{X})| < C_1$ , stop and accept all  $H_i$ . Otherwise reject  $H_{1j_1}$  and continue to step 2.

At step 2, consider the  $(M-1)$  functions  $U_{2j}(\mathbf{X}^{(j_1)})$ ,  $j \in \{1, \dots, M\} \setminus \{j_1\}$ . Let  $j_2 = j_2(\mathbf{X}^{(j_1)})$  be such that  $|U_{2j_2}(\mathbf{X}^{(j_1)})| = \max \{|U_{2j}(\mathbf{X}^{(j_1)})| : j \in 1, \dots, M \setminus \{j_1\}\}$ . If  $|U_{j_2}| < C_2$  stop and accept all remaining null hypotheses. Otherwise reject  $H_{j_2}$  and continue to step 3.

In general, at step  $m$ ,  $m = 1, \dots, M$ , consider  $M-m+1$  functions  $U_{mj}(\mathbf{X}^{(j_1, \dots, j_{m-1})})$ ,  $j \in \{1, \dots, M\} \setminus \{j_1, \dots, j_{m-1}\}$ . Let  $j_m = j_m(\mathbf{X}^{(j_1, \dots, j_{m-1})})$  be such that

$$|U_{mj_m}| = \max \left\{ |U_{mj}(\mathbf{X}^{(j_1, \dots, j_{m-1})})| : j \in 1, \dots, M \setminus \{j_1, \dots, j_{m-1}\} \right\}.$$

If  $|U_{mj_m}| < C_m$ , stop and accept all remaining null hypotheses. Otherwise reject  $H_{j_m}$  and continue to step  $m + 1$  ( unless  $m = M$ , in which case, stop).

For the multivariate normal model where  $\Gamma = \sigma^2\Sigma$  and  $\sigma^2$  is unknown, a modification of  $U_{mj}$  is called for. The denominator of  $U_{mj}$  would be multiplied by some estimator of  $\sigma^2$ . It could be  $s = \sqrt{s^2}$ , mentioned in Section 2 or it could be another estimator of  $\sigma^2$ , say  $V$  which would be an unbiased estimator of  $\sigma^2$  when  $\boldsymbol{\mu} = \mathbf{0}$ . This latter estimation was used by CSX(2009).

The general linear model discussed in detail in Section 2 is a special case of the the multivariate normal model with  $\Gamma = \sigma^2\Sigma$ . The matchups are familiar, i.e.,  $\mathbf{X}$  is replaced by  $\hat{\boldsymbol{\beta}}$ ,  $\boldsymbol{\mu}$  is replaced by  $\boldsymbol{\beta}$ ,  $\sigma^2\Sigma$  is replaced by  $\sigma^2S^{-1}$  and  $\sigma^2$  would be estimated by MSE or simply by  $\mathbf{y}'\mathbf{y}/n$ .

In the event  $\Sigma$  is unknown but enough replications on  $\mathbf{X}$  are available,  $\Sigma$  could be estimated by a maximum likelihood estimator, say  $\hat{\Sigma}$ , and  $\hat{\Sigma}$  would replace  $\Sigma$  in the definition of  $U_{mj}$ . Should the number of replications, i.e. , sample size, be large, the optimality properties of MRDSS should be asymptotically true.

It has been shown that MRD is admissible. For the problem of test treatment vs control, MRD performs favorably to step-up/step-down methods in simulations in terms of total number of errors.

## Chapter 3

### Extension of MRD to MRDSS

The MTP for the multivariate normal model, called maximum residual down (MRD), has many desirable properties including admissibility. However, on some occasions, the test result of MRD can be counterintuitive. For example, in the multivariate normal model,  $\mathbf{X} \sim N(\boldsymbol{\mu}, \Sigma)$  with  $\Sigma$  known, we intend to test  $H_i : \mu_i = 0$  vs  $K_i : \mu_i \neq 0$ ,  $i = 1, \dots, M$ . One could construct a special  $\Sigma$ , such that even if  $X_1 = 0$ , MRD will still reject  $H_1$ . Also, one could construct another special  $\Sigma$ , such that even if  $|X_1|/\sqrt{\sigma_{11}}$  is very large, for typical constant critical values, MRD will accept  $H_1$ . This calls for some modifications or extensions of MRD. Here we give one such extension of MRD. The new MTP includes three stages, MRD stage, screen and sign stages. The MRD procedure followed by a screening stage and a sign stage is called MRDSS.

#### 3.1 MRDSS in multivariate normal model

MRDSS starts with MRD stage, which is described in Chapter 2.

To add a screening stage to MRD, let  $C_U > C_L > 0$  be two additional constants. Typically  $C_L \leq C_M < C_U$ . Note that  $C_1 > C_2 > \dots > C_M$  are the set of critical values used in MRD stage. After MRD is done, each hypothesis is temporarily accepted or rejected.

Let  $H_{j_1}, \dots, H_{j_p}$  be those hypotheses that are rejected. Should any

$$|X_{j_i}|/\sqrt{\sigma_{j_i j_i}} < C_L,$$

$i = 1, \dots, p$ , then reverse the reject decision to an accept decision.

For those hypotheses that MRD accepted, say,  $H_{j_{p+1}}, \dots, H_{j_M}$ , reject any for which

$$|X_{j_i}|/\sqrt{\sigma_{j_i j_i}} > C_U,$$

$i = p + 1, \dots, M$ .

Note that the screen stage eliminates the counterintuitive situation that is discussed in the begin of this chapter. However, when MRD rejects a hypothesis, say  $H_j$  at step  $m^*$ , which means  $|U_{m^*j}|$  is maximum among all remaining residuals, and  $|U_{m^*j}| > C_{m^*}$ , the sign of  $U_{m^*j}$  could be positive or negative, which is not necessarily the same as the sign of  $X_j$ . This is counterintuitive in some sense. When MRD rejects  $H_j$ , roughly saying, under some assumptions, we have evidence that  $\mu_j$  is nonzero with the same sign of  $U_{m^*j}$ . However, when the two signs are not the same, the direct evidence (  $X_i$  ) does not agree with the one from MRD. Sign stage will handle this situation.

To add a sign stage, we need to slightly modify the MRD stage : record the sign of  $U_{m_{j_m}}$  whenever it rejects  $H_{j_m}$ . Hence each hypothesis that is rejected by MRD stage will have a sign : + or -. The sign stage considers only those hypotheses rejected by MRD, i.e.,  $H_{j_1}, \dots, H_{j_p}$ , and such that  $C_L < |X_{j_i}|/\sqrt{\sigma_{j_i j_i}} < C_U$ ,  $i = 1, \dots, p$ . Then switch those to accept whenever the sign of  $X_{j_i}$  is different from the sign of  $U_{m^*j_i}$  where  $m^*$  is the step when  $H_{j_i}$  was rejected by MRD.

Remark : The screen stage following MRD involves  $|X_i|$ ,  $i = 1, \dots, M$ . The sign stage involves the sign of  $U_{m^*i}$  and the sign of  $X_i$ .

Remark: Sign stage only makes sense in the two-side hypothesis testing. It is related to the direction of rejection. Later on, we will give a general definition of sign.

We will illustrate MRDSS in the following example:

Example 3.1

Let  $\mathbf{X} = (X_1, X_2, X_3, X_4)'$  be such that  $\mathbf{X} \sim N(\boldsymbol{\mu}, \Sigma)$  where

$$\Sigma = \begin{pmatrix} 2 & 1 & 1 & 1 \\ 1 & 2 & 1 & 1 \\ 1 & 1 & 2 & 1 \\ 1 & 1 & 1 & 2 \end{pmatrix}.$$

We wish to test  $H_i : \mu_i = 0$  vs  $K_i : \mu_i \neq 0$ ,  $i = 1, \dots, 4$ .

For the purpose of demonstrating the application of MRDSS we will let  $C_1 = 2.3, C_2 = 2.0, C_3 = 1.7, C_4 = 1.4, C_L = .6$ , and  $C_U = 3.6$ . Now suppose we observe  $X_1 = 1, X_2 = 5, X_3 = 4.7$  and  $X_4 = 5.3$ .

First we apply MRD. At step 1 the residuals are :

$$\begin{aligned} U_{11} &= \left[ X_1 - (1, 1, 1) \begin{pmatrix} 2 & 1 & 1 \\ 1 & 2 & 1 \\ 1 & 1 & 2 \end{pmatrix}^{-1} (X_2, X_3, X_4)' \right] / \left[ 2 - (1, 1, 1) \begin{pmatrix} 2 & 1 & 1 \\ 1 & 2 & 1 \\ 1 & 1 & 2 \end{pmatrix}^{-1} \begin{pmatrix} 1 \\ 1 \\ 1 \end{pmatrix} \right]^{1/2} \\ &= [X_1 - (X_2 + X_3 + X_4)/4](\frac{4}{5})^{1/2} = -2.46 \\ U_{12} &= [X_2 - (X_1 + X_3 + X_4)/4](\frac{4}{5})^{1/2} = 2.01 \\ U_{13} &= [X_3 - (X_1 + X_2 + X_4)/4](\frac{4}{5})^{1/2} = 1.68 \\ U_{14} &= [X_4 - (X_1 + X_2 + X_3)/4](\frac{4}{5})^{1/2} = 2.35 \end{aligned} \tag{3.1.1}$$

Since  $|U_{11}|$  is the largest and  $|U_{11}| > 2.3 = C_1$ , MRD rejects  $H_1$  and goes to the next step. Now with  $X_1$  eliminated,

$$\begin{aligned} U_{22} &= \left[ X_2 - (1, 1) \begin{pmatrix} 2 & 1 \\ 1 & 2 \end{pmatrix}^{-1} (X_3, X_4)' \right] / \left[ 2 - (1, 1) \begin{pmatrix} 2 & 1 \\ 1 & 2 \end{pmatrix}^{-1} \begin{pmatrix} 1 \\ 1 \end{pmatrix} \right]^{1/2} \\ &= [X_2 - (X_3 + X_4)/3]/(\frac{3}{4})^{1/2} = 1.44 \\ U_{23} &= [X_3 - (X_2 + X_4)/3]/(\frac{3}{4})^{1/2} = 1.10 \\ U_{24} &= [X_4 - (X_2 + X_3)/3]/(\frac{3}{4})^{1/2} = 1.79 \end{aligned}$$

Since  $|U_{22}|, |U_{23}|$  and  $|U_{24}|$  are all less than  $C_2 = 2.0$ , MRD stops and accepts  $H_2, H_3$ , and  $H_4$ .

Next we do the screen stage by comparing each  $|X_i/\sqrt{2}|$  to  $C_L = .6$  and  $C_U = 3.6$ . We see that  $C_L < |X_i/\sqrt{2}| < C_U$  for  $i = 1, 2, 3$  but  $|X_4/\sqrt{2}| = 3.75 > 3.6 = C_U$ . Thus the MRD decision to accept  $H_4$  is reversed to reject  $H_4$ .

Lastly we perform the sign stage. This applies only to hypotheses  $H_i$  that were rejected by MRD and for which  $C_L < |X_i/\sqrt{2}| < C_U$ . In this example only  $H_1$  falls into this category. Upon examination we see that  $H_1$  was rejected at the first step of MRD stage with  $U_{11} = -2.46$  while  $X_1/\sqrt{2} = .707$ . Since these signs are opposite we reverse the MRD decision to reject  $H_1$ .

In conclusion MRDSS will accept  $H_1, H_2, H_3$  and reject  $H_4$ .

### 3.2 MRDSS in exponential family models

There are many models involving distributions that belong to the exponential family. For example, hypothesis testing problems involving binomial parameters, Poisson parameters, parameters of exponential distributions, and odds ratios or local odds ratios in contingency tables. Invariably the models and questions can be transformed to the general model given in (2.1.2) in Chapter 2.

For the models dealing with  $M$  contrasts among binomial parameters or Poisson parameters, residuals of the type  $U_{mj}$  given in (2.4.2) can be formed with  $\sigma_{(j \cdot i_1, \dots, i_{m-1})}$  replaced by some function of the remaining  $M - m$  variables in  $\Sigma^{-1}\mathbf{X}$ .

More general extensions of MRD could involve different types of residuals and different types of tests based on the “new” type of residuals. A residual can be based on the coefficient multiplying the parameters to be tested, in the expression in the exponent of the multivariate exponential family density. Also the screen stage and sign stage can be more generally defined.

For contingency table models the role of the residuals and the entire MRDSS procedure will be discussed in next Chapter.

### 3.3 Properties of MRDSS

We will discuss the properties of MRDSS for the multivariate normal model. For exponential family models, the conclusion will follow similarly.

MRDSS can be thought of a family of multiple testing procedures that are parameterized by the critical values  $C_1, \dots, C_M$  and  $C_L$  and  $C_U$ . The MRD stage of MRDSS takes dependent into consideration in every steps. We will prove that MRDSS is admissible, just like MRD. Due to the screen stage, MRDSS is also consistency.

#### 3.3.1 Admissibility of MRDSS

Consider the setup where  $\mathbf{X}$ , defined in Section 2, has density (2.1.2) and we wish to test  $H_i : \theta_i = 0$  vs  $K_i : \theta_i \neq 0$ . Let  $\psi_i(\mathbf{X})$  be a test function for  $H_i$  vs  $K_i$ . Let  $\mathbf{W} = \Sigma^{-1}\mathbf{X}$ . A lemma concerning admissibility of any single test, say  $\psi_i(\mathbf{X})$ , is as follows:

**Lemma 3.3.1.** *A necessary and sufficient condition for  $\psi_i(\mathbf{X}) = \psi_i^*(\mathbf{W})$  to be admissible is that for almost every fixed  $\{W_j, j = 1, \dots, Q; j \neq i\}$ , the acceptance section of the test is convex in  $W_i$ .*

*Proof.* See Matthes and Truax (1967) □

Next we define

*PROPERTY L:* A test is said to have *Property L* if there exists three points  $\mathbf{x}, \mathbf{x}^* = \mathbf{x} + r_1\mathbf{g}, \mathbf{x}^{**} = \mathbf{x} + r_2\mathbf{g}$ , with  $0 < r_1 < r_2$ , such that  $\mathbf{x}$  and  $\mathbf{x}^{**}$  are accept points and

$\mathbf{x}^*$  is a reject point when testing  $H_1$  vs  $K_1$ .

Note that a procedure has *Property L* (for a set of positive measure) if and only if it is inadmissible by virtue of Lemma 3.3.1.

**Theorem 3.3.2.** *The MTP  $\Phi_{MRDSS}(\mathbf{X})$  is admissible for the vector risk function.*

*Proof.* The proof is by contrapositive. That is, we will assume that  $\Psi_1$  of the MRDSS has *Property L* and then show that this is impossible. That is, we assume that for  $\psi_1$  there exists 3 sample points  $\mathbf{x}$ ,  $\mathbf{x}^*$  and  $\mathbf{x}^{**}$  for which we accept, reject, accept (ARA) in that order with  $\mathbf{x}^* = \mathbf{x} + r_1\mathbf{g}$ ,  $\mathbf{x}^{**} = \mathbf{x} + r_2\mathbf{g}$ ,  $0 < r_1 < r_2$ , we must show this leads to a contradiction.

We will consider every possible way that the three stages of  $\psi_1$  might yield an ARA sequence for the points  $\mathbf{x}$ ,  $\mathbf{x}^*$  and  $\mathbf{x}^{**}$  as defined before. Note that MRD is admissible so that the sequence ARA is impossible at stage 1. The other 7 possible (first stage) test results for MRD are AAA, AAR, RAA, ARR, RAR, RRA and RRR. Recall that screening (stage 2) can, potentially, reverse any stage 1 decision. However, the sign stage (stage 3) is applicable only when the stage 1 action was to Reject and no change was made at stage 2. As an example of the reasoning used to identify the possible paths suppose stage 1 results in the sequence AAR. By definition stage 3 cannot impact the first two actions. Thus the only two paths possible, beginning with AAR, are  $\text{AAR} \rightarrow \text{ARR} \rightarrow \text{ARA}$  and  $\text{AAR} \rightarrow \text{ARA} \rightarrow \text{ARA}$ . Following these rules we find that there are 18 paths ( listed in table 3.3.1 ) that must be studied. We will show that each of these paths leads to contradiction.

Note that the fourth row in each cell of table 3.3.1 indicates how  $|X_i|$  relates to the screen stage. This will help in showing that each of the 18 cases cannot happen.

At this point we note a fact.



F1: Consider  $\mathbf{x}, \mathbf{x}^* = \mathbf{x} + r_1 \mathbf{g}, \mathbf{x}^{**} = \mathbf{x} + r_2 \mathbf{g}$ , with  $0 < r_1 < r_2$ . Then  $|x_1^*| \leq \max(|x_1|, |x_1^{**}|)$ .

Now for the 18 cases listed in table 3.3.1. Cases 1, 2, 7, 9 and 15 violate F1 as seen from the fourth row of the cells in table 3.3.1.

Case 3: From table 3.3.1 we see that a sign change occurred at  $\mathbf{x}^{**}$  when both  $\mathbf{x}_1^{**}$  and  $U_{m^*1}(\mathbf{x}^{**})$  were positive. This contradicts the sign stage rule.

Case 4: Cannot occur since MRD is admissible.

Case 5: From table 3.3.1 we see that at  $\mathbf{x}^{**}$  the screen stage took a reject to an accept implying  $|x_1^{**}| < C_L$ . But  $|x_1^*| > C_L$  implying  $x_1^* < 0$ . But MRD is *ARR* implying  $U_{m^*1}(\mathbf{x}^*) > 0$ . Hence MRDSS being *ARA* is contradicted at  $\mathbf{x}^*$ .

Case 6: From the first row in this cell we see that  $U_{m^*1}(\mathbf{x}^{**}) > 0$  From the sign change at  $\mathbf{x}^{**}$ , we find  $x_1^{**} < 0$  which implies  $x_1^* < 0$ . But this violates the sign rule.

Case 8: From the fourth row we find  $x_1^* < 0$  which implies  $x_1 < 0$ . Since MRD is *RAA*,  $U_{m^*1}(\mathbf{x}) < 0$ . However from row 3 we have a sign change, implying a contradiction.

Case 10: Again both  $U_{m^*1}(\mathbf{x}) < 0$  and  $x_1 < 0$  contradicting a sign change.

Case 11: Both  $x_1^{**}$  and  $U_{m^*1}(\mathbf{x}^{**})$  are positive, contradicting a sign change.

Case 12: Same reasoning as Case 11.

Case 13: From the fourth row  $x_1^* > 0$  and between  $C_U$  and  $C_L$ . From the first row

$U_{m^*1}(\mathbf{x}) < 0$ . This contradicts row 3 at  $\mathbf{x}^*$ .

Case 14: From the first row  $U_{m^*1}(\mathbf{x}^*) < 0$ ,  $U_{m^*1}(\mathbf{x}) < 0$ . Since there is a sign change at  $x_1$  that implies  $x_1 > 0$ ,  $x_1^* > 0$ , and  $x_1^{**} > 0$ . From row 2,  $x_1^{**} < C_U$ . Hence  $C_L < x_1 < C_U$  and also  $C_L < x_1^* < C_U$ . In particular  $x_1^* > 0$ . This contradicts the sign change rule at  $\mathbf{x}^*$ .

Case 16: Note that a sign action took place at  $\mathbf{x}$  and at  $\mathbf{x}^{**}$ . Applying F1, we have  $C_L < |x_1^*| < C_U$ . Now if  $x_1 < 0$  that implies  $U_{m^*1}(\mathbf{x}) > 0$  which in turn implies  $U_{m^*1}(\mathbf{x}^*) > 0$  and  $U_{m^*1}(\mathbf{x}^{**}) > 0$ . Since there is a sign change at  $\mathbf{x}^{**}$  then we have  $x_1^{**} < 0$  which means  $x_1^* < 0$  and a sign change should have occurred at  $\mathbf{x}^*$ . This is a contradiction. Now if  $x_1 > 0$ , similar reasoning leads to a contradiction at  $\mathbf{x}^*$ .

Case 17: From the first two rows we conclude  $C_L < |x_1^*|$  and  $|x_1^{**}| < C_L$  implying  $x_1^* < 0$  and therefore  $x_1 < 0$ . The sign stage at  $\mathbf{x}$  implies  $U_{m^*1}(\mathbf{x}) > 0$  and therefore  $U_{m^*1}(\mathbf{x}^*) > 0$ . But  $|x_1| < C_U$  and  $|x_1^{**}| < C_L$  implies  $|x_1^*| < C_U$ . Hence we have  $C_L < |x_1^*| < C_U$  and  $x_1^* < 0$  and  $U_{m^*1}(\mathbf{x}^*) > 0$ . This contradicts the sign stage at  $\mathbf{x}^*$ .

Case 18: From the first two rows we have  $|x_1| < C_L$  and  $|x_1^*| > C_L$  so  $x_1^* > 0$  implying  $x_1^{**} > 0$ . Since there is a sign action at  $\mathbf{x}^{**}$ ,  $|x_1^{**}| < C_U$  and  $U_{m^*1}(\mathbf{x}^{**}) < 0$  implying  $U_{m^*1}(\mathbf{x}^*) < 0$ . Hence  $x_1^* > 0$ ,  $x_1^{**} > 0$ ,  $C_L < x_1^* < x_1^{**} < C_U$ , implies there should have been a sign action at  $\mathbf{x}^*$ . This is a contradiction.  $\square$

Suppose in MRDSS that the MRD portion is replaced by another admissible MTP. Then the other admissible MTP supplemented by a screen and sign stage will retain the admissibility property. This means that Theorem 3.3.2 can be applied to a large class of MTPs. In fact we have corollary 3.3.3 below.

Let  $\Sigma$  be positive definite and let  $\mathbf{g}_i$  be the  $i$ -th column of  $\Sigma$ . Then define the class of MTPs with:

*PROPERTY N*: Suppose  $\Psi(\mathbf{X})$  is an MTP with individual test functions  $\Psi_i(\mathbf{X})$ . Suppose  $\Psi_i(\mathbf{X})$ , for every  $i$ , is such that the acceptance section along the line  $\mathbf{x} + r\mathbf{g}_i$  is an interval. Then the MTP is said to have *Property N*. It is noted in the Appendix that *Property N* is necessary and sufficient for an MTP to be admissible.

**Corollary 3.3.3.** *Any MTP with Property N, supplemented by a screen stage and sign stage is admissible.*

*Proof.* In the proof for Theorem 3.3.2 the value of  $U_{m^*1}$  was never used. That is, only the sign of  $U_{m^*1}$  was used. Therefore if we take an admissible procedure with *Property N* and use the definition of sign given after the corollary, the entire proof can be replicated.  $\square$

The more general version of MRDSS involves functions  $W_{mj}(\mathbf{X})$  analogous to  $U_{mj}$  and statistics  $T_j(\mathbf{X})$  analogous to  $|X_j|$ . The  $W_{mj}(\mathbf{X})$  have the properties of  $U_{mj}(\mathbf{X})$  for suitably defined  $\mathbf{g}_j$ ,  $j = 1, \dots, M$ , required for admissibility. The  $W_{mj}$ 's and  $T_j$ 's are used as follows:

For the MRD stage we must first decide which of the  $M$  hypotheses is eligible for rejection at the first step. Toward this end we associate each  $W_{1j}$ ,  $j = 1, \dots, M$  with its corresponding two sided P-value, say  $P(W_{1j})$ .  $P(W_{1j})$  represents the probability, under the global null hypothesis that all  $\theta_j = 0$ , of observing  $W_{1j}$  or something more extreme than  $W_{1j}$ . Then the hypothesis eligible to be rejected first is the hypothesis related to  $\min_{1 \leq j \leq M} P(W_{1j})$  or  $\max_{1 \leq j \leq M} (1 - P(W_{1j}))$ . Similarly define  $P(W_{mj})$  and assume that  $1 - P(W_{mj})$  is decreasing and then increasing as are the  $W_{mj}$  so that MRD will be admissible.

At step  $m$ , the hypothesis eligible to be rejected corresponds to the min of those  $M - (m - 1)$  remaining P-values computed under the global null of  $M - (m - 1)$  parameters equaling 0. Now let  $j^*$  be the index for which  $W_{mj}$  has the minimum P-value.

To decide whether MRD rejects  $H_{j^*}$  at a given step consider two sets of constants:

$$C_{1a} < C_{2a} < \cdots < C_{Ma} < 0, \text{ and, } C_{1b} > C_{2b} > \cdots > C_{Mb} > 0$$

with  $C_{ja} < C_{jb}$ ,  $j = 1, \dots, M$ . Proceed stepwise as in MRD except that at step  $m$ , reject  $H_{j^*}$  if  $W_{mj^*} < C_{ja}$  or  $W_{mj^*} > C_{jb}$ . For the screening stage, let  $C_{Ua} < C_{La} \leq C_{Lb} < C_{Ub}$ . Then if MRD accepted  $H_j$ , switch to reject if  $T_j < C_{Ua}$  or  $T_j > C_{Ub}$ . If MRD rejected  $H_j$ , switch to accept if  $C_{La} < T_j < C_{Lb}$ , otherwise make no change. Finally for the sign stage, suppose  $H_j$  is rejected at step  $m^*$ , switch the reject to a final accept if either

- (i)  $W_{m^*j} > C_{m^*b}$ , there was no change at the screen stage, and  $T_j < C_{La}$  or
- (ii)  $W_{m^*j} < C_{m^*a}$ , there was no change at the screen stage, and  $T_j > C_{Lb}$ .

In CCS(2009) MRDSS is determined where  $W_{mj}$  and  $T_j$  are Fisher exact test statistics for  $2 \times C$  tables and  $W_{mj}$  and  $T_j$  are related to Pearson Chi-square statistics for  $R \times C$  tables.

### 3.3.2 Consistency of MRDSS

Suppose in general we have a random sample  $\mathbf{X}_\alpha, \alpha = 1, \dots, n$ , where the distribution of  $\mathbf{X}_\alpha$  depends on  $\boldsymbol{\nu}$  and we wish to test  $H_i : \nu_i = 0$  vs  $K_i : \nu_i \neq 0$ ,  $i = 1, \dots, M$ . Assume test statistics  $(T_{ni}(\mathbf{x}) - ET_{ni}(\mathbf{x}))/\sigma_{T_{ni}}$  converges in law to a standard normal where  $ET_{ni}(\mathbf{x})/\sigma_{T_{ni}} \rightarrow 0$  as  $n \rightarrow \infty$  under  $H_i$  and  $ET_{ni}(\mathbf{x})/\sigma_{T_{ni}} = O(\sqrt{n})$  under  $K_i$ . Also assume  $C_L$  and  $C_U$  tend to  $\infty$  in such a way that  $C_L = o(\sqrt{n})$  and  $C_U = o(\sqrt{n})$ . Then we have

**Theorem 3.3.4.** *Under the above assumptions  $\Phi_{MRDSS}(x)$  is consistent.*

*Proof.* See Chen, Cohen, and Sackrowitz (2009a). □

From the proof, it should be clear that the screen stage ensures the consistency of MRDSS.

### 3.3.3 Connection between MRD/MRDSS and forward selection

For this section we assume the general linear model described in Section 2 with  $\sigma^2$  known. We test  $H_i : \beta_i = 0$  vs  $K_i : \beta_i \neq 0$ ,  $i = 1, \dots, M$ . Let  $C_1 > C_2 > \dots > C_M > 0$  be a given set of constants.

Recall  $A = (\mathbf{a}_1, \dots, \mathbf{a}_n)$  and let  $A$  be partitioned as  $(A_1, A_2)$  where  $A_1$  is  $n \times (m-1)$  and  $A_2$  is  $n \times (M-m+1)$ . Let  $V = R(A)$  be the linear space spanned by the columns of  $A$  and  $V_1 = R(A_1)$  be the linear space spanned by the columns of  $A_1$ . Furthermore, let  $P_V$  be the projection matrix for space  $V$  and let  $P_1$  be the projection matrix for space  $V_1$ . Let  $V_2 = V \cap V_1^\perp = R(A_{2.1})$ , where  $A_{2.1} = A_2 - P_1 A_2 = (\mathbf{a}_{2.1m}, \dots, \mathbf{a}_{2.1M})$ . Finally let  $P_2$  denote the projection matrix for  $V_2$  so that  $P_V = P_1 + P_2$ .

Forward selection methods are studied in Miller (2002) and many other texts studying linear regression. They are methods that select fixed variables to enter a linear regression model in steps. In the first step one considers the random variables  $(\mathbf{a}'_i \mathbf{y}) / \sigma \|\mathbf{a}_i\|$ ,  $i = 1, \dots, M$ . The forward method selects the fixed variable  $\mathbf{a}_{i_1}$  provided that

$$U_{1i_1} = \max_{1 \leq i \leq M} (|\mathbf{a}'_i \mathbf{y}| / \sigma \|\mathbf{a}_i\|) > C_1. \quad (3.3.1)$$

If  $U_{1i_1} \leq C_1$ , no variables are chosen and the procedure stops. Now assume  $(m-1)$  variables have been selected. Without loss of generality say they are  $(\mathbf{a}_1, \dots, \mathbf{a}_{m-1}) = A_1$ . Then at stage  $m$ , the method selects  $\mathbf{a}_{i_m}$  provided

$$U_{mi_m} = \max_{m \leq j \leq M} (|\mathbf{a}'_{2.1j} \mathbf{y}| / \sigma \|\mathbf{a}_{2.1j}\|) > C_m. \quad (3.3.2)$$

If  $U_{mi_m} \leq C_m$ , the procedure stops. Thus at step  $m$ , the forward method is tantamount to rejecting  $H_{i_m} : \beta_{i_m} = 0$  by virtue of (3.3.2).

Note that the vector of components  $\mathbf{a}'_{2.1j} \mathbf{y}$  in (3.3.2) can be written as  $A'_{2.1} \mathbf{y}$ .

Now recall MRD applied to  $\hat{\boldsymbol{\beta}} \sim N(\boldsymbol{\beta}, \sigma^2 S^{-1})$ . At step one the numerator of the residual is proportional to  $S\hat{\boldsymbol{\beta}} = A'\mathbf{y}$ , which is the vector of components in the expression in the numerator in (3.3.1). At step  $m$ , assuming  $H_i : \beta_i = 0, i = 1, \dots, m-1$  have been rejected, MRD deletes the first  $m-1$  rows and first  $m-1$  columns of  $S^{-1}$  and considers  $\hat{\boldsymbol{\beta}}_2 \sim N(\boldsymbol{\beta}_2, \Lambda_{22})$  where  $\boldsymbol{\beta}_2 = (\beta_m, \dots, \beta_M)'$  and  $S^{-1} = \begin{pmatrix} \Lambda_{11} & \Lambda_{12} \\ \Lambda_{21} & \Lambda_{22} \end{pmatrix}$ , with  $\Lambda_{11}$   $(m-1) \times (m-1)$  and  $\Lambda_{22}$   $(M-m+1) \times (M-m+1)$ . The residuals  $\mathbf{U}_m$  at this step are proportional to  $\Lambda_{22}^{-1}\hat{\boldsymbol{\beta}}_2$ . That is,

$$\mathbf{U}_m \propto \Lambda_{22}^{-1}\hat{\boldsymbol{\beta}}_2. \quad (3.3.3)$$

However, note

$$A_1\hat{\boldsymbol{\beta}}_1 + A_2\hat{\boldsymbol{\beta}}_2 = A\hat{\boldsymbol{\beta}} = P_V\mathbf{y}. \quad (3.3.4)$$

Multiply both sides of (5.4) by  $P_2$  to get

$$A_{2\cdot 1}\hat{\boldsymbol{\beta}}_2 = P_2P_V\mathbf{y} = P_2\mathbf{y}. \quad (3.3.5)$$

Since  $\Lambda_{22}^{-1} = A_2'A_2 - A_2'P_1A_2 = A_{2\cdot 1}'A_{2\cdot 1}$ , we find using (3.3.3) and (3.3.5) that

$$\mathbf{U}_m \propto A_{2\cdot 1}'P_2\mathbf{y} = A_{2\cdot 1}'\mathbf{y}. \quad (3.3.6)$$

Note that the components of (3.3.6) are  $(\mathbf{a}'_{2\cdot 1}\mathbf{y})$ , the unnormalized terms in the expression (3.3.2). Thus we have proved

**Theorem 3.3.5.** *For the assumption of the general linear regression model, the forward selection method is equivalent to MRD.*

REMARK : Whereas the forward method and MRD are oftentimes not consistent procedures, MRDSS and thus the forward method plus screening, plus sign is consistent. It is interesting to note that Christensen (1987) p.288, claims that the precise screening step we recommend is an improvement on the forward method.

The backward method starts by assuming a linear regression model with  $M$  parameters. At step 1, one can decide that  $\beta_{i_1} = 0$  if  $T_{i_1} = \min_{1 \leq i \leq M} T_i(\hat{\boldsymbol{\beta}}) = \min_{1 \leq i \leq M} (|\hat{\beta}_i|/\sigma_{\hat{\beta}_i}) \leq C_m$ . Otherwise the procedure stops and no variables are eliminated.

At stage  $m$ , assuming without loss of generality that variables  $\mathbf{a}_1, \dots, \mathbf{a}_{m-1}$  have been eliminated, one considers residuals of the form

$$(\hat{\beta}_j - \boldsymbol{\lambda}_j^{(1, \dots, m-1)} \Lambda_{11(m-1)}^{-1} (\hat{\beta}_1, \dots, \hat{\beta}_{m-1})') / \lambda_{j \cdot (1, \dots, m-1)}^{1/2} \quad (3.3.7)$$

where  $\boldsymbol{\lambda}_j^{(1, \dots, m-1)}$  are the elements in the  $j^{\text{th}}$  row of  $S^{-1}$  that represent the covariance of  $\hat{\beta}_j$  and  $(\hat{\beta}_1, \dots, \hat{\beta}_{m-1})'$ ;  $\Lambda_{11(m-1)}^{-1}$  represents the covariance matrix of  $(\hat{\beta}_1, \dots, \hat{\beta}_{m-1})'$  and  $\lambda_{j \cdot (1, \dots, m-1)}$  is the conditional variance of  $\hat{\beta}_j$  given  $\hat{\beta}_1, \dots, \hat{\beta}_{m-1}$ .

If  $\min_{m \leq j \leq M}$  of the terms in (3.3.7)  $\leq C_{M-m+1}$ , and the index is  $i_m$  then decide  $\beta_{i_m} = 0$  and continue. Otherwise stop.

REMARK : The backward method is consistent under mild conditions (see An and Gu, 1985). Nevertheless the backward method is akin in some sense to the step-up method of multiple testing. They are identical at the first step. As previously mentioned step-up methods are often inadmissible in normal and exponential family models and it can be shown that the backward method would sometimes be inadmissible for a risk function whose components are expected number of type I errors and expected number of type II errors.

### 3.4 Discussion

The MRD procedure is admissible and takes correlation into consider in every stage. However, it is not consistent. MRDSS retains the two favorable properties and, in addition, it is consistent due to the screen stage. In MRDSS, the screen stage is after the MRD stage. If we put the screen stage as the first stage, followed by MRD stage and sign stage, we get a new procedure. It will work as follows:

(1) screen stage : compare individual test statistics to  $C_L$  and  $C_U$ . Accept those hypotheses whose test statistics are less than  $C_L$ , and reject those hypotheses whose test statistics are greater than  $C_U$ . Let  $I_0$  denote the index of hypotheses that are accepted, and  $I_1$  the index of the hypotheses that are rejected.

(2) For those hypotheses with test statistics falling between  $C_L$  and  $C_U$ , i.e, for all  $H_i$  , where  $i \notin I_0 \cup I_1$ , play MRD, under the condition that  $H_j : j \in I_0$  are true and  $H_{j'} : j' \in I_1$  are not true.

(3) Play sign stage as before.

Call this procedure as screen+MRD+sign. The difference between this MTP and MRDSS lies in the order of MRD stage and screen stage. However, this difference makes it hard to tell whether it is admissible or not.





## Chapter 4

### MRDSS in ordered contingency table

In this Chapter we will extend the MRDSS procedure to the testing of local odds ratios in ordered contingency table. Consider an  $R \times C$  contingency table with ordered categories in both rows and columns. Let  $X_{ij}$  be the frequency in the  $ij$ th cell,  $i = 1, \dots, R$ ,  $j = 1, \dots, C$ . Assume either the full multinomial model or the product multinomial model with cell probabilities  $p_{ij}$ . In either case, if we condition on both the column totals  $t_j$ ,  $j = 1, \dots, C$  and the row totals  $R_i$ ,  $i = 1, \dots, R$ , the conditional distribution of  $X_{ij}$ ,  $i = 1, \dots, R - 1$ ,  $j = 1, \dots, C - 1$  given  $R_i$ ,  $t_j$  is multivariate hypergeometric. Let  $n = \sum_{i=1}^R R_i = \sum_{j=1}^C t_j$ .

The conditional distribution expressed in exponential family form is

$$f_{\mathbf{X}}(\mathbf{x}|\boldsymbol{\nu}) \propto \exp \left( \sum_{i=1}^{R-1} \sum_{j=1}^{C-1} x_{ij} \nu_{ij} \right) \quad (4.0.1)$$

where  $\nu_{ij}$  are log odds ratios, i.e.,

$$\nu_{ij} = \log \frac{p_{ij} p_{RC}}{p_{iC} p_{Rj}}$$

with  $\mathbf{x} = (\mathbf{x}_1, \dots, \mathbf{x}_R)'$ ,  $\mathbf{x}_i = (x_{i1}, \dots, x_{iC})'$ ,  $\boldsymbol{\nu} = (\boldsymbol{\nu}_1, \dots, \boldsymbol{\nu}_R)'$ . See CS (2000). If we let

$$S_{ij} = \sum_{k=1}^i \sum_{l=1}^j X_{kl}$$

and let

$$\mu_{ij} = \log \frac{p_{ij} p^{(i+1)(j+1)}}{p_{i(j+1)} p^{(i+1)j}}$$

then with  $\mathbf{S} = (S_{11}, \dots, S_{RC})'$

$$f_{\mathbf{s}}(\mathbf{s}|\boldsymbol{\mu}) \propto \exp \left( \sum_{i=1}^{R-1} \sum_{j=1}^{C-1} \mu_{ij} S_{ij} \right). \quad (4.0.2)$$

Note (4.0.2) would also ensue for the model in which  $X_{ij}$  are independent Poisson variables with parameter  $\lambda_{ij}$ . Then upon conditioning on  $R_i$ ,  $\mathbf{X}_i$  is multinomial with parameter  $p_{ij} = \lambda_{ij} / \sum_{j=1}^C \lambda_{ij}$ . Conditioning next on  $t_j$  yields the multivariate hypergeometric of (4.0.1).

#### 4.1 Testing of local odds ratios in contingency table

We are interested in testing of local odds ratios for the  $R \times C$  table, i.e., hypotheses of

$$H_{ij} : \mu_{ij} = 0 \quad \text{vs} \quad K_{ij} : \mu_{ij} \neq 0 \quad (4.1.1)$$

or,

$$H_{ij} : \mu_{ij} = 0 \quad \text{vs} \quad K_{ij}^* : \mu_{ij} > 0 \quad (4.1.2)$$

A local  $2 \times 2$  table of frequencies is

$x_{ij}$	$x_{i(j+1)}$
$x_{(i+1)j}$	$x_{(i+1)(j+1)}$

(4.1.3)

and let  $T_{ij}$  be a statistic to test  $H_{ij}$ . Typical step-down and step-up procedures are based on statistics  $T_{ij}$  that depend only on the cell frequencies in (4.1.3). Such statistics are often Fisher's exact test statistics or Pearson's chi-square statistics.

Step-down or step-up procedures for the above contingency table are straight forward. However, as mentioned before, step-down or step-up methods are oftentimes inadmissible for vector risk function. For examples in  $2 \times C$ , see Chen, Cohen, and Sackrowitz (2009b).

## 4.2 $2 \times C$ tables

Our starting point is to assume the model where upon conditioning on row and column totals we have the multivariate hypergeometric distribution given in (4.0.2). We start with a result for  $R \times C$  tables.

**Lemma 4.2.1.** *A necessary and sufficient condition for a test  $\psi_{ij}(\mathbf{x})$  to be admissible is that for all  $S_{i'j'} (i' \neq i, j' \neq j)$ , except  $S_{ij}$ , fixed, the acceptance sections of the test are convex in  $S_{ij}$ .*

*Proof.* See Matthes and Truax (1967) □

Note that convex in the discrete case is defined for sample points whose coordinates take on integer values. A discrete set  $B$  is convex if whenever  $\mathbf{s}_1 \in B$ ,  $\mathbf{s}_2 \in B$ , all sample points between  $\mathbf{s}_1$  and  $\mathbf{s}_2$  are in  $B$ . Note that when  $R = 2$ ,  $\mathbf{S}$  depends only on  $S_{11}, \dots, S_{1(C-1)}$  and these depend only on  $X_{11}, \dots, X_{1(C-1)}$ .

Furthermore when  $R = 2$  an increase in  $S_{1j}$  by one unit while  $S_{1j'}$  remain fixed  $j' \neq j$  is accomplished with  $(X_{11}, \dots, X_{1j}, X_{1(j+1)}, \dots, X_{1(C-1)})' + \mathbf{g}$  where  $\mathbf{g} = (0, \dots, 1, -1, \dots, 0)'$  where 1 is in position  $j$ .

Whereas one cannot demonstrate that step-down and step-up procedures based on Fisher exact tests or Pearson chi-square tests are always inadmissible, we give examples (which are more typical than not) to indicate that those procedures often are inadmissible. It suffices to work with  $2 \times 3$  tables since extensions to  $R \times C$  tables would easily follow.

Example 4.2.1 : Consider a  $2 \times 3$  table as follows

			109
			100

90      60      59

Test  $H_{1j} : \mu_{1j} = 0$  vs  $K_{1j} : \mu_{1j} \neq 0$ ,  $j = 1, 2$ . For step-down using Fisher's P-value ( with FWER controlled at  $\alpha = 0.1$  ). The critical values are  $\alpha_1 = 0.05$ ,  $\alpha_2 = 0.1$ . Now suppose the frequencies are :

59   31   19  
31   29   40

Then the P-values are 0.093, 0.041 which leads to rejecting both  $H_{11}$  and  $H_{12}$ . However for frequencies

60   30   19  
30   30   40

the P-values are 0.061, 0.063 which means both hypotheses are accepted. For a first row of 55 35 19 ,  $H_{11}$  would be accepted which demonstrates that the acceptance section for  $H_{11}$  would not be an interval in  $S_{11}$  :

$S_{11}$	55	59	60
Decision	A	R	A

For the two-sided case using the same critical values of  $\alpha$ , using Pearson's chi-squared statistic the following tables of frequencies also provide an example where the acceptance section is not an interval.

65   51   38

39   49   66

P-values are 0.0973, 0.0373

66   50   38

38   50   66

P-values are 0.0523, 0.0523

Similarly, using the same critical value, for one-sided Fisher,  $\alpha = .1$

65	52	26	
40	48	44	P-values are 0.0983, 0.0392
66	51	26	
39	49	44	P-values are 0.0577, 0.0513

#### 4.2.1 New methodology

We start with the case  $R = 2$  and we observe  $\mathbf{S}$  with distribution given in (4.0.2).

The methods offered are related to the MRDSS method of CCS(2009a) which extends the MRD method of CSX(2009). The method, referred to as MRDSS, involves using Fisher's test statistics ( or Pearson's Chi-square statistics) for various sometimes collapsed tables that wind up as  $2 \times 2$  tables. We give the method using Fisher's statistics  $P_{1j}$  although Pearson's Chi-square statistics could also be used.

Recall there are  $(C - 1)$  local log odds ratios to be tested; namely  $H_{1j} : \mu_{1j} = 0$  vs  $K_{1j} : \mu_{1j} \neq 0$ ,  $j = 1, \dots, C - 1$ . The main method involves 3 stages. Stage 1 involves a step-down testing method; stage 2 involves screening and stage 3 involves a possible change due to sign differences. The method is as follows : Let  $0 < \alpha_1 < \dots < \alpha_{C-1}$ .

At stage 1,

(i) consider the  $(C - 1)$   $2 \times 2$  tables

$S_{1j}$	$R_1 - S_{1j}$
$\sum_{k=1}^j t_k - S_{1j}$	$R_2 - \sum_{k=1}^j t_k + S_{1j}$

(4.2.1)

Compute  $P_{1j}^{(1)}$  for Table  $j$ ,  $j = 1, \dots, C - 1$  and find  $P_{(1)}^{(1)}$ , the smallest among  $P_{1j}^{(1)}$ . If  $P_{(1)}^{(1)} = P_{1j_1}^{(1)} < \alpha_1$ , reject  $H_{(1)}$  and continue. Otherwise stop and accept  $H_{1j}$ ,  $j = 1, \dots, C - 1$ .

(ii) If  $j_1 = 1$  consider the  $2 \times (C - 2)$  table with column 1 left out. Proceed as in

step (i) . That is, form (C-2)  $2 \times 2$  tables

$$\begin{array}{|c|c|}
 \hline
 S_{1j} - S_{11} & R_1 - S_{1j} \\
 \hline
 \sum_{k=2}^j t_k - S_{1j} + S_{11} & R_2 - \sum_{k=1}^j t_k + S_{1j} \\
 \hline
 \end{array} \tag{4.2.2}$$

Compute  $P_{1j}^{(2)}$ ,  $j = 2, \dots, C - 1$  and find  $P_{1j_2}^{(2)} = \min_{2 \leq j \leq C-1} P_{1j}^{(2)}$ . If  $P_{1j_2}^{(2)} < \alpha_2$ , reject  $H_{1j_2}$  and continue. Otherwise stop and accept  $H_{(2)}, \dots, H_{(C-1)}$ . If  $1 < j_1 < C - 1$ , segment the  $2 \times C$  table into 2 tables. The first table is the  $2 \times j_1$  table consisting of the first  $j_1$  columns of the original table and the second table is  $2 \times (C - j_1)$  consisting the last  $(C - j_1)$  columns of the table. Now treat each table as in the  $2 \times C$  table case and form  $2 \times 2$  tables as in the step (i). That is, form  $(j_1 - 1)$  P-values for the  $2 \times j_1$  table and  $C - j_1 - 1$  P-values for the  $2 \times (C - j_1)$  table and then get  $P_{1j_2}^{(2)}$  as the minimum P-value and reject  $H_{1j_2}$  if  $P_{1j_2}^{(2)} < \alpha_2$  and continue. Otherwise stop and accept  $H_{(2)}, \dots, H_{(C-1)}$ .

If  $j_1 = C - 1$  then do essentially what was done when  $j_1 = 1$ .

(iii) If the process continues beyond step (ii), then continue for each table at step (ii) by further segmentation if necessary at all future steps. Compute P-values as in previous stages and get the min P-value and compare it with the appropriate critical value, i.e., at step  $m$ , if  $P_{1j_m}^{(m)} < \alpha_m$ , reject  $H_{1j_m}$  and continue. Otherwise stop and accept  $H_{(m)}, \dots, H_{(C-1)}$ .

At stage 2, screen the results of stage 1, as follows : Let  $\alpha_L < \alpha_U$  be two critical values between 0 and 1. Typically  $\alpha_L < \alpha_{C-1} \leq \alpha_U$ . Find Fisher's statistic for each local  $2 \times 2$  table. If the Fisher statistic is less than  $\alpha_L$  and at stage 1 the test accepted, switch to rejection. If the statistic exceeds  $\alpha_U$  and at stage 1 the test rejected, switch to accept. Otherwise maintain the results of stage 1.

At stage 3, switch a reject at stage 1 to a final accept at stage 3, if when screening, the statistic lies between  $\alpha_L$  and  $\alpha_U$  and if the Fisher statistic used in stages 1 and 2 were compiled using opposite sides of their respective 2 sided rejection regions. For example, suppose we are testing  $H_{11} : \mu_{11} = 0$  vs  $K_{11} : \mu_{11} \neq 0$ . Suppose that at stage

1, step 1 the table

$S_{11}$	$S_{iC} - S_{11}$
$t_1 - S_{11}$	$t_2 - S_{1C} + S_{11}$

yielded the minimum P-value  $< \alpha_1$  and thus  $H_{11}$  was rejected at stage 1. Note that (1 - P-value) based on Fisher's statistic for this table as a function of  $S_{11}$  is decreasing and then increasing. See Cohen (1987). Suppose further that the observed value of  $S_{11}$  was on the increasing part of the function. Now for the table

$x_{11}$	$x_{12}$
$x_{21}$	$x_{22}$

assume the Fisher test statistic P-value was between  $\alpha_L$  and  $\alpha_U$ . Further suppose for the observed value of  $x_{11}$  that (1 - P-value) as a function of  $x_{11}$  was on the decreasing part of the function. This would call for a switch of reject  $H_{11}$  to accept  $H_{11}$ .

#### 4.2.2 Example

We now illustrate the method with examples. The data to be used in the examples in this section and in section 5 refers to a sample of British males cross-classified by father's occupational status and son's occupational status. The data are drawn from Glass (1954). The occupations are ordered, in a sense, from highest (1), representing professional, administrative, executive to lowest (6), representing unskilled manual worker. These data have been analyzed by Goodman, Andersen, Benzecri, Baccini, Caussinus, De Falguerolles, Clogg, Rao, Cox, and Haberman (1991), Dardanoni and Forcina (1998) and Silvapulle and Sen (2005). Table 4.2.1 provides the data. Note  $A_i, i = 1, \dots, 6$  stands for father's occupational status while  $o_j$  stands for son's occupational status.



Table 4.2.1: Father and Son Occupation Status in British Males

	$o_1$	$o_2$	$o_3$	$o_4$	$o_5$	$o_6$
$A_1$	125	60	26	49	14	5
$A_2$	47	65	66	123	23	21
$A_3$	31	58	110	223	64	32
$A_4$	50	114	185	715	258	189
$A_5$	6	19	40	179	143	71
$A_6$	3	14	32	141	91	106

We first extract row one and two to form a  $2 \times 6$  table to illustrate our method as follows:

Stage 1 - step (i): Form  $2 \times 2$  tables where the entries in the first row, first column of each table is  $S_{11}, S_{12}, S_{13}, S_{14}, S_{15}$  respectively. These five tables and their corresponding P-values based on Fisher statistic are:

	125	154	185	94	211	68	260	19	274	5
	47	298	112	233	178	167	301	44	324	21
P-values	$4.91 \times 10^{-18}$		$2.80 \times 10^{-17}$		$6.29 \times 10^{-10}$		0.0159		0.0081	

The minimum P-value among the 5 tables occurs for the first table. Using critical values (0.01, 0.0125, 0.0167, 0.025, 0.05) we reject  $H_{11} : \mu_{11} = 0$  and continue.

Step (ii) : Consider the  $2 \times 5$  table formed by leaving out the first column of the  $2 \times 6$  table. Form four new  $2 \times 2$  tables whose first row-first column entries are  $S_{12} - S_{11}, S_{13} - S_{11}, S_{14} - S_{11}, S_{15} - S_{11}$  respectively. These four tables and their corresponding P-values are :

	60	94	86	68	135	19	149	5
	65	233	131	167	254	44	277	21
P-values	.0002		.0174		.5670		.1349	

The minimum P-value  $.002 < .0125$  so  $H_{12} : \mu_{12} = 0$  is rejected and continue.

Step (iii): Form the  $2 \times 4$  table with the first two columns of the original table left out. The entries are  $S_{13} - S_{12}, S_{14} - S_{12}, S_{15} - S_{12}$  respectively. These tables and their corresponding P-values are :

	24	68	75	19	84	5
	66	167	189	44	212	21
P-values	1		.7594		.3668	

The minimum P-value  $.3668 > .0167$  so that  $H_{13} : \mu_{13} = 0$ ,  $H_{14} : \mu_{14} = 0$  and  $H_{15} : \mu_{15} = 0$  are all accepted.

Stage 2 (screening) and stage 3 (sign): Choose  $\alpha_L = 0.01$  and  $\alpha_U = 0.05$  and screen the P-values of each of the 5 local  $2 \times 2$  tables. That is, the five tables are:

125	60	60	26	26	49	49	14	14	5
47	65	65	66	66	123	123	23	23	21

The corresponding P-values by Fisher's exact test are .0001, .0048, 1, .3232 and .1643. The screening stage then does not change any decision made in stage 1. Furthermore it is easy to check that the sign stage also makes no change.

### 4.3 $R \times C$ tables

In a  $2 \times C$  table, at MRD stage, after we reject  $H_i$ , we split the table into 2 small tables and do testing. This essential is to do testing conditional on  $S_{1i}$  as fixed. Now in a  $R \times C$  table, we can do essentially the same thing. We will first give the method and then illustrate it with an example.

#### 4.3.1 New methodology

Recall that in an  $R \times C$  table we wish to test  $(R - 1)(C - 1)$  individual hypotheses  $H_{ij} : \mu_{ij} = 0$  vs  $K_{ij} : \mu_{ij} \neq 0$ ,  $i = 1, \dots, R - 1$ ;  $j = 1, \dots, C - 1$ . Let  $\Omega_1 > \Omega_2 > \dots > \Omega_{(R-1)(C-1)} > 0$  be a set of critical values. We will do as follows at stage 1, MRD stage :

Step 1 : Form  $(R - 1)(C - 1)$   $2 \times 2$  tables :

$S_{ij}$	$S_{iC} - S_{ij}$
$S_{Rj} - S_{ij}$	$S_{RC} - S_{iC} - S_{Rj} + S_{ij}$

Find the statistics :

$$U_{ij}^{(1)} = (S_{ij} - \hat{E}_{ij}^{(1)}) / \sqrt{\hat{V}_{ij}^{(1)}} \quad (4.3.1)$$

where  $\hat{E}_{ij}^{(1)}$  and  $\hat{V}_{ij}^{(1)}$ , along with  $\hat{E}_{ij}^{(m)}$  and  $\hat{V}_{ij}^{(m)}$  for step  $m$ ,  $m = 1, 2, \dots$ ,  $(R-1)(C-1)$  will be determined below.  $U_{ij}^{(1)}$  will be used to test hypothesis  $H_{ij}$ . If  $|U_{i_1j_1}^{(1)}| = \max_{(i,j)} |U_{ij}^{(1)}| > \Omega_1$ , reject  $H_{i_1j_1}$ , record the sign of  $U_{i_1j_1}^{(1)}$  and continue. Note that  $(U_{ij}^{(1)})^2$  is equivalent to Pearson's chi-square statistic for the above  $2 \times 2$  table.

At step 2, find the statistics

$$U_{ij}^{(2)} = (S_{ij} - \hat{E}_{ij}^{(2)}) / \sqrt{\hat{V}_{ij}^{(2)}} \quad (4.3.2)$$

If  $|U_{i_2j_2}^{(2)}| = \max_{(i,j)} |U_{ij}^{(2)}| > \Omega_2$ , reject  $H_{i_2j_2}$ , record the sign of  $U_{i_2j_2}^{(2)}$  and continue.

The quantities  $\hat{E}_{ij}^{(1)}$ ,  $\hat{V}_{ij}^{(1)}$  will be estimated under two conditions:

- (I) all null hypotheses are assumed true
- (II) Row sums, column sums are fixed

The quantities  $\hat{E}_{ij}^{(2)}$ ,  $\hat{V}_{ij}^{(2)}$  will be estimated under two conditions:

- (I) all null hypotheses except  $H_{i_1j_1}$  are assumed true
- (II) Row sums, column sums, and  $S_{i_1j_1}$  are fixed

In general, at step  $m$ , suppose  $H_{i_1j_1}, \dots, H_{i_{m-1}j_{m-1}}$  have been rejected. Then  $\hat{E}_{ij}^{(m)}$  and  $\hat{V}_{ij}^{(m)}$  will be estimated under two conditions:

- (I) all null hypotheses except  $H_{i_1j_1}, \dots, H_{i_{m-1}j_{m-1}}$  are assumed true
- (II) Row sums, column sums, and  $S_{i_1j_1}, \dots, S_{i_{m-1}j_{m-1}}$  are fixed

Now we indicate exactly how  $\hat{E}_{ij}^{(m)}$  and  $\hat{V}_{ij}^{(m)}$  are estimated.

At step 1 let  $\lambda_{ij}$  denote the mean of cell  $(i, j)$ . Then estimate  $\lambda_{ij}$  by  $\hat{\lambda}_{ij}$ , where  $\hat{\lambda}_{ij}$  is the solution to the following set of equations

$$\sum_{k,l} \lambda_{kl} = n \quad (4.3.3)$$

$$\sum_{k=1}^R \lambda_{kj} = t_j \quad \text{for } j = 1, \dots, C-1 \quad (4.3.4)$$

$$\sum_{l=1}^C \lambda_{il} = R_i \quad \text{for } i = 1, \dots, R-1 \quad (4.3.5)$$

$$\lambda_{ij} \lambda_{(i+1)(j+1)} = \lambda_{(i+1)j} \lambda_{i(j+1)} \quad \text{for } 1 \leq i \leq R-1, 1 \leq j \leq C-1 \quad (4.3.6)$$

There are a total of  $1 + (C-1) + (R-1) + (R-1)(C-1) = RC$  equations in  $RC$  variables. The unique non-negative solution is  $\lambda_{ij} = R_i t_j / n$ .

At step 2, suppose  $H_{i_1 j_1}$  is rejected by the end of step 1. Estimate the means of cells again by using the same  $R \times C$  equations, except now replace the equation

$$\lambda_{i_1 j_1} \lambda_{(i_1+1)(j_1+1)} = \lambda_{(i_1+1)j_1} \lambda_{i_1(j_1+1)} \quad (4.3.7)$$

with equation

$$\sum_{k \leq i_1, l \leq j_1} \lambda_{kl} = S_{i_1 j_1} \quad (4.3.8)$$

In general at step  $m$ , we remove  $(m-1)$  equations of the type (4.3.6) and add  $(m-1)$  equations of the type (4.3.8).

To get the estimate  $\hat{V}_{ij}^{(m)}$  we think of the cell frequencies  $x_{ij}$  as independent normal variables with mean  $\lambda_{ij}$  and variance  $\lambda_{ij}$ . Recall  $S_{ij} = \sum_{l=1}^i \sum_{l=1}^j x_{il}$ , so  $\mathbf{S} = \mathbf{A}\mathbf{X}$  for the appropriate  $\mathbf{A}$ . It would follow that  $\mathbf{S} \sim N(\mathbf{A}\boldsymbol{\lambda}, \mathbf{A}\boldsymbol{\Sigma}\mathbf{A}')$  with  $\boldsymbol{\Sigma}$  being a diagonal matrix with diagonal elements equal  $(\lambda_{11}, \dots, \lambda_{RC})$ . Note that  $\boldsymbol{\Sigma}$  is covariance matrix of  $\mathbf{X}$ . Having estimated  $\lambda_{ij}$  by  $\hat{\lambda}_{ij}$  we thus have an estimator of  $\boldsymbol{\Sigma}_{\mathbf{S}} = \mathbf{A}\boldsymbol{\Sigma}\mathbf{A}'$ . However

to find  $\hat{V}_{ij}^{(m)}$ , we compute the conditional covariance matrix of  $\mathbf{S}$  under conditions :

- (i)  $S_{iC}$ ,  $i = 1, \dots, R - 1$  are known
- (ii)  $S_{Rj}$ ,  $j = 1, \dots, C$  are known
- (iii)  $S_{i_1 j_1}, \dots, S_{i_{m-1} j_{m-1}}$  are known.

The quantity  $V_{ij}^{(m)}$  represent the conditional variance of  $S_{ij}$ .  $V_{ij}^{(m)}$  is a function of  $\lambda_{ij}$  and is estimated accordingly.

We conclude this section with :

**Theorem 4.3.1.** *For an  $R \times C$  contingency table, assuming either the product multinomial model, full multinomial model or independent Poisson model, the MRDSS method using Pearson's Chi-square statistic or Fisher's statistic in the  $2 \times C$  case is admissible.*

*Proof.* CCS(2009a) prove that if a procedure  $\boldsymbol{\psi} = (\psi_{11}, \dots, \psi_{(R-1)(C-1)})'$ , consisting of  $(R - 1)(C - 1)$  individual test functions is admissible, then  $\boldsymbol{\psi}$  followed by a screening stage and a sign stage is also admissible. Thus for MRDSS to be admissible it suffices to prove that MRD is admissible. In CSX(2009) MRD was shown to be admissible in a multivariate normal model where residuals were defined as functions of the coefficients of the parameters to be tested. For the  $R \times C$  contingency table model the  $S_{ij}$ ,  $i = 1, \dots, R - 1$ ;  $j = 1, \dots, C - 1$  are the coefficients of the parameters to be tested and suitably centered and normalized they have the identical properties as the residuals  $U_{mj}$  in CSX(2009). That is, suppose we are examining the admissibility of the individual test of  $H_{ij} : \mu_{ij} = 0$  vs  $K_{ij} : \mu_{ij} \neq 0$ . Then  $|U_{ij}^{(m)}|$  given in (4.3.1) and (4.3.2) and given implicitly for  $m > 2$  decrease and then increase as a function of  $S_{ij}$  while all other  $S_{ij}$  are fixed. Also all other  $|U_{ij}^{(m)}|$  do not change. These are the properties needed to prove MRD is admissible.  $\square$

### 4.3.2 Example

In this section we illustrate the method with an  $R \times C$  table example. The data to be used is the same as the data in table 4.2.1 . For the purpose of illustration, we only

extract the first 3 rows of the original data for our example.

The data is :

	$o_1$	$o_2$	$o_3$	$o_4$	$o_5$	$o_6$
$A_1$	125	60	26	49	14	5
$A_2$	47	65	66	123	23	21
$A_3$	31	58	110	223	64	32

There are a total of  $2 \times 5 = 10$  local log odds ratios, i.e., a total of 10 hypotheses to be tested.

For MRD stage, we use critical values obtained from the significance level  $1 - (1 - \alpha)^{1/k}$ ,  $k = 1, \dots, 10$  for our test statistics at step 10,9, ..., 1, respectively, where  $\alpha = 0.05$ . Hence the critical values are:

$$(\Omega_1, \dots, \Omega_{10}) = (2.80, 2.77, 2.73, 2.68, 2.63, 2.57, 2.49, 2.39, 2.24, 1.96)$$

At stage 1 step 1, we first solve the equations (4.3.3) - (4.3.6) to get the estimated mean of each cell given the row and column totals, under the assumption all local log odds ratios equal to 0. The mean value of each cell is shown below in 4.3.1.

Table 4.3.1: Step 1 – Expected cell frequencies

	1	2	3	4	5	6
1	49.59	44.71	49.35	96.50	24.68	14.17
2	61.33	55.28	61.02	119.33	30.51	17.52
3	92.08	83.01	91.63	179.17	45.81	26.31

After this, we can compute the conditional variance of  $S_{ij}$ . The conditional variance is shown below in 4.3.2.

Note the zeros in 4.3.2 reflect the fact that the corresponding  $S_{ij}$  variables are fixed.

Now, we can compute the test statistics  $U_{ij}^{(1)}$ , shown in 4.3.3.

Table 4.3.2: Step 1 – Conditional variances of  $S_{ij}$ 

	1	2	3	4	5	6
1	30.82	47.18	52.66	25.27	10.16	0.00
2	41.37	63.33	70.70	33.92	13.64	0.00
3	0.00	0.00	0.00	0.00	0.00	0.00

Table 4.3.3: Step 1 – Test statistics  $U_{ij}^{(1)}$ 

	1	2	3	4	5
1	13.58	13.20	9.28	3.95	2.88
2	9.50	10.82	8.05	4.10	1.54

The maximum of these is 13.58, which is greater than the critical value 2.80, hence we reject the hypothesis  $H_{11}$  and continue to next step. We also record the sign of the test: +.

At step 2, we estimate the mean of each cell conditioned on the row and column summation being fixed, and conditioned on all local log odds ratios except  $\mu_{11}$  are 0, and also conditioned on  $S_{11}$  fixed. Solve the subset of equations (4.3.3) - (4.3.8) as explained earlier to get the estimated mean of each cell : shown in 4.3.4.

Table 4.3.4: Step 2 – Expected cell frequencies

	1	2	3	4	5	6
1	125.00	30.01	33.13	64.78	16.56	9.51
2	31.18	61.16	67.51	132.01	33.75	19.38
3	46.82	91.83	101.36	198.21	50.68	29.10

As in step 1, we can compute the conditional variance of  $S_{ij}$  : conditioned on  $S_{iC}, S_{Rj}, S_{11}$  are known and fixed. The conditional variance of  $S_{ij}$  are shown below in 4.3.5:

Now we can compute the test statistics  $U_{ij}^{(2)}$  :

The maximum of these is 7.18, which is greater than 2.77, so we reject  $H_{22}$  and continue to the next step. Also we record the sign of the test : +.

Table 4.3.5: Step 2 – Conditional variances of  $S_{ij}$ 

	1	2	3	4	5	6
1	0.00	20.20	31.14	18.11	7.46	0.00
2	17.02	47.87	62.71	33.51	13.67	0.00
3	0.00	0.00	0.00	0.00	0.00	0.00

Table 4.3.6: Step 2 – Test statistics  $U_{ij}^{(2)}$ 

	1	2	3	4	5
1		6.67	4.10	1.66	1.65
2	3.83	7.18	5.18	2.80	0.78

Step 3 : We estimate the mean of each cell conditioned on the row and column sum fixed, conditioned on all local log odds ratios ( except  $\mu_{11}$  and  $\mu_{22}$  ) are 0 , and also conditioned on  $S_{11}$  and  $S_{22}$  are fixed. As in step 2, solve the subset set of equations (4.3.3) - (4.3.8) to get the estimated mean of each cell.

Table 4.3.7: Step 3 – Expected cell frequencies

	1	2	3	4	5	6
1	125.00	42.79	29.72	58.11	14.86	8.53
2	46.19	83.02	57.66	112.75	28.83	16.56
3	31.81	57.19	114.63	224.15	57.31	32.91

Now, we can compute the conditional variance of  $S_{ij}$  : conditioned on  $S_{iC}$ ,  $i = 1, \dots, R - 1, S_{Rj}$ ,  $j = 1, \dots, C$ ,  $S_{11}$  and  $S_{22}$  are all fixed. The conditional variances of  $S_{ij}$  are in 4.3.8.

The test statistics  $U_{ij}^{(3)}$  are in 4.3.9.

The maximum of these is 3.74, which is greater than the critical value 2.73. So we reject  $H_{12}$ , record the sign of the rejection : +, and continue to step 4.



Table 4.3.8: Step 3 – Conditional variances of  $S_{ij}$ 

	1	2	3	4	5	6
1	0.00	21.15	29.93	16.69	6.84	0.00
2	12.55	0.00	36.33	30.82	13.14	0.00
3	0.00	0.00	0.00	0.00	0.00	0.00

Table 4.3.9: Step 3 – Test statistics  $U_{ij}^{(3)}$ 

	1	2	3	4	5
1		3.74	2.47	1.07	1.35
2	0.23		0.77	1.04	-0.25

Step 4: Estimate the mean of each cell conditioned on the row and column summation being fixed, and conditioned on all local log odds ratios ( except  $\mu_{11}$ ,  $\mu_{22}$ , and  $\mu_{12}$  ) are 0 . Also condition on  $S_{11}, S_{22}, S_{12}$ . Solve a set of equations to get the estimated mean of each cell :

Table 4.3.10: Step 4 – Expected cell frequencies

	1	2	3	4	5	6
1	125.00	60.00	25.12	49.11	12.56	7.21
2	43.46	68.54	62.26	121.74	31.13	17.88
3	34.54	54.46	114.63	224.15	57.31	32.91

Now, we can compute the conditional variance of  $S_{ij}$  : conditioned on  $S_{iC}$ ,  $i = 1, \dots, R-1, S_{Rj}$ ,  $j = 1, \dots, C$ ,  $S_{11}$  and  $S_{22}, S_{12}$  are all fixed. The conditional variance of  $S_{ij}$  are in 4.3.11.

Table 4.3.11: Step 4 – Conditional variances of  $S_{ij}$ 

	1	2	3	4	5	6
1	0.00	0.00	16.12	13.67	5.83	0.00
2	11.78	0.00	36.33	30.82	13.14	0.00
3	0.00	0.00	0.00	0.00	0.00	0.00

The test Statistics  $U_{ij}^{(4)}$  are in 4.3.12.

Table 4.3.12: Step 4 – Test statistics  $U_{ij}^{(4)}$ 

	1	2	3	4	5
1	NA	NA	0.22	0.21	0.92
2	1.03	NA	0.77	1.04	-0.25

The maximum of these is 1.04, which is smaller than the critical value 2.68. So MRD stops here, and all remaining hypotheses are accepted.

Now the screening stage. The Pearson's Chi-square test statistic for the 10 local  $2 \times 2$  tables are shown below:

Table 4.3.13: Screen – local Pearson's Chi-square P-values

	1	2	3	4	5
1	$2.5 \times 10^{-5}$	0.0052	0.9171	0.3540	0.1917
2	0.3761	0.0120	0.7323	0.1388	0.1492

If we choose  $\alpha_L = 0.005$ ,  $\alpha_U = 0.05$ , then it is clear that screening stage does not have any effect. So MRD+screening gives the same decisions as MRD.

It is clear that sign stage does not have any action either. So the decision of MRDSS is : reject  $H_{11}, H_{22}, H_{12}$  and accept all others.

#### 4.4 Sign stage does not have effect in $2 \times C$ tables

In the two examples, one for  $2 \times C$ , one for  $R \times C$ , the sign stage of MRDSS does not have effect. This is not by chance. We actually can show that the sign stage does not have effect in testing equality of adjacent proportion in a  $2 \times C$  table.

For a  $2 \times c$  table, want to test  $H_j : p_j = p_{j+1}$  for  $j = 1, \dots, (c - 1)$ .

For the hypothesis  $H_j$ , we combine the whole table to get a  $2 \times 2$  table  $A$ , with cell  $a_{ij}$ ,  $i, j = 1, 2$ , and row and column sum of this  $2 \times 2$  table are named as  $r_1, r_2, c_1, c_2$ , respectively. Note that  $a_{11} = \sum_1^j x_{1l}$ ,  $a_{12} = \sum_{j+1}^c x_{1l}$ ,  $a_{21} = \sum_1^j x_{2l}$ , and  $a_{22} = \sum_{j+1}^c x_{2l}$ .

Let  $\hat{p}_l = a_{11}/c_1$ ,  $\hat{p}_r = a_{12}/c_2$ ,  $\hat{p} = r_1/n$  and  $\hat{p}_j = x_{1j}/(x_{1j} + x_{2j})$

First, we have lemma 4.4.1 that will be used to prove lemma 4.4.2.

**Lemma 4.4.1.** *If  $0 < p_1 < x < p_2$ , and  $0 < w_1, w_2 < 1$ , then*

$$w_1 p_1 + (1 - w_1)x + p_2 > p_1 + (1 - w_2)x + w_2 p_2$$

The proof is easy. We omit it here.

**Lemma 4.4.2.** *For  $2 \times c$  table, at stage 1, if the residual  $U_j$  has largest absolute value and  $U_j < 0$ , then :*

- (1)  $\hat{p}_l < \hat{p} < \hat{p}_r$  ;
- (2)  $\hat{p}_j < \hat{p}_r$  ;
- (3)  $\hat{p}_j < (\hat{p}_l + \hat{p}_r)/2$ .

*Proof.* (1) is obvious. If  $j = 1$ , (2) and (3) are obvious, only need to consider  $j \geq 2$ .

Let

$$t_j = x_{1j} + x_{2j} \quad , \quad z = x_{1j}/q$$

First, we know that the residual square for  $j$  is:

$$U^2 = \frac{(a_{11} - r_1 c_1 / n)^2}{r_1 r_2 c_1 c_2 / n^3}$$

The residual square for  $j - 1$  is:

$$U^{*2} = \frac{(a_{11}^* - r_1 c_1^*/n)^2}{r_1 r_2 c_1^* c_2^*/n^3}$$

where  $a_{11}^* = a_{11} - t_j z$ ,  $c_1^* = c_1 - t_j$ .

Since  $r_1 r_2/n^3$  is the same factor for both residual squares, for now we can ignore them.

Let

$$F(q, z) = \frac{(a_{11} - qz - r_1(c_1 - q)/n)^2}{(c_1 - q)(c_2 + q)}$$

$$\frac{\partial F}{\partial q} \Big|_{q=0} = \frac{1}{c_2} (\hat{p}_l - \hat{p})(\hat{p}_l + \hat{p}_r - 2z)$$

.

If (2) is not true, then

$$(*) \quad \frac{\partial F}{\partial q} \Big|_{q=0} > 0$$

Hence  $F(q, z) > F(0, z)$  for small  $q > 0$ , and then we have a new  $2 \times 2$  table, with new  $a_{11}^{new} = a_{11} - qz$ , and the new  $\hat{p}_l, \hat{p}_r$ . It is easy to see that for this new  $2 \times 2$  table, (\*) still holds, so  $F(2q, z) > F(q, z)$ , continue the process until  $q = t_j$ , we get  $F(t_j, z) > F(0, z)$ . But this contradicts to the condition that  $U^2 > U^{*2}$ . So (2) is proved.

If (3) is not true, then  $z > (\hat{p}_l + \hat{p}_r)/2$  and  $\hat{p}_l < z < \hat{p}_r$ , since (\*) is true, we also have  $F(q, z) > F(0, z)$  for small  $q > 0$ . Now the new  $2 \times 2$  table, we have  $a_{11}^{new} = a_{11} - qz$ , and the new  $\hat{p}_l + \hat{p}_r$  beomes

$$\begin{aligned} & \frac{a_{11}^{new}}{c_1^{new}} + \frac{a_{12} + qz}{c_2 + q} \\ &= \hat{p}_l^{new} + (1 - w_2)z + (1 - w_2)\hat{p}_r \end{aligned}$$

where  $w_2 = c_2/(c_2 + q)$

the original  $\hat{p}_l + \hat{p}_r$  can be written as

$$\begin{aligned} & \frac{a_{11}^{new} + qz}{c_1^{new} + q} + \hat{p}_r \\ &= w_1 \hat{p}_l^{new} + (1 - w_1)z + \hat{p}_r \end{aligned}$$

Remember that  $\hat{p}_l < z < \hat{p}_r$ , so we have  $\hat{p}_l^{new} < \hat{p}_l$ , hence we have  $\hat{p}_l^{new} < z < \hat{p}_r$ , apply lemma 4.4.1, we see that the new  $\hat{p}_l + \hat{p}_r$  is smaller than the original  $\hat{p}_l + \hat{p}_r$ , which means (\*) is hold for the new  $2 \times 2$  table. So again we have  $F(2q, z) > F(q, z)$ , proceed until  $q = t_j$  we get  $F(t_j, z) > F(0, z)$ . But this contradicts to the condition that  $U^2 > U^{*2}$ . So (3) is proved. □

By symmetry, we have following Lemma.

**Lemma 4.4.3.** *For  $2 \times c$  table, at stage 1, if the residual  $U_j$  has largest absolute value and  $U_j > 0$ , then :*

- (1)  $\hat{p}_l > \hat{p} > \hat{p}_r$  ;
- (2)  $\hat{p}_j > \hat{p}_r$  ;
- (3)  $\hat{p}_j > (\hat{p}_l + \hat{p}_r)/2$ .

**Theorem 4.4.4.** *For  $2 \times c$  table, at stage 1, if the residual  $U_{j_1}$  has largest absolute value then  $U_{j_1}$  has same sign as that of  $\hat{p}_{j_1} - \hat{p}_{j_1+1}$ .*

*Proof.* Without loss of generality, assume  $U_{j_1} < 0$ , then from lemma 4.4.2 we know that  $\hat{p}_{j_1} < (\hat{p}_l + \hat{p}_r)/2$ . If we do a mirror reflection of the  $2 \times c$  table, i.e, if the original table is:

$x_{11}$	$x_{12}$	...	$x_{1j}$	...	$x_{1c}$
$x_{21}$	$x_{22}$	...	$x_{2j}$	...	$x_{2c}$

the mirror reflect table is:

$x_{1c}$	$x_{1(c-1)}$	...	$x_{1j}$	...	$x_{11}$
$x_{21}$	$x_{2(c-1)}$	...	$x_{2j}$	...	$x_{21}$

If we label the column of this mirror reflect table from right to left, then column 1 in both the original table and mirror reflect table denote the same column :  $(x_{11}, x_{12})'$ .

Now from lemma 4.4.3 we know that  $\hat{p}_{j_1+1} > (\hat{p}_l + \hat{p}_r)/2$ . Hence  $\hat{p}_{j_1} < \hat{p}_{j_1+1}$ .  $\square$

It is easy to see that theorem 4.4.4 is also true at any stage  $m$ . Hence MRD+screening is same as MRD+screening+sign, which is admissible.

## Chapter 5

### Computational issues and choosing of critical values

Step-down or step-up procedures oftentimes use P-values based on the marginal distribution of individual test statistics under individual null hypotheses. These procedures in general require little computational effort. There are standard ways to choose the critical values such that FWER or FDR is controlled at predefined levels. However, those procedures are oftentimes inadmissible. MRDSS has the advantage of being admissible and consistent. The screen stage in general is easy to perform without much effort. However, in the MRD stage, the computation of test statistics  $U_{mj}$  at step  $m$  needs some computation effort, and the choice of critical values in general need to be done by simulations.

#### 5.1 Computation of MRDSS in multivariate normal model

For the multivariate normal model, at the MRD stage, the inverse of  $\Sigma$  is needed. In some cases, the inversion can be derived theoretically. In the context of regression model, since MRD is equivalent to a forward method, the computation of MRD can be done for very large problems, i.e., very large number of hypotheses.

#### 5.2 Computation of MRDSS in ordered contingency table

For MRDSS in ordered  $R \times C$  tables, at the MRD stage, computation of test statistics  $U_{mj}$  at step  $m$  needs an estimation of the mean cell frequencies under following conditions :

- (1) row and column sum are fixed
- (2) odds ratio  $\theta_{ij} = 1$  for all  $(i, j)$  where  $H_{ij}$  has not been rejected.

(3)  $S_{i_1 j_1}, \dots, S_{i_{(m-1)} j_{(m-1)}}$  are fixed, where  $H_{i_1 j_1}, \dots, H_{i_{(m-1)} j_{(m-1)}}$  are rejected at step 1,  $\dots$ ,  $(m-1)$ , respectively.

As we mentioned before, the estimation of mean cell frequencies can be achieved by solving a set of equations. We now explicitly describe a numerical method to solve the equations.

At step 1, the unique non-negative solution of the equations (4.3.3) - (4.3.8) is:  $\hat{\lambda}_{ij} = R_i t_j / n$ , where  $R_i$  is the sum of row  $i$ , and  $t_j$  is the sum of column  $j$ .

At step  $m$ , to solve the equations for estimating  $\lambda_{ij}$ , we transform the equation-solving problem into a minimization problem. Let,

$$f_m(\boldsymbol{\lambda}) = \left( \sum_{k,l} \lambda_{kl} - n \right)^2 + \sum_{j=1}^{C-1} \left( \sum_{k=1}^R \lambda_{kj} - t_j \right)^2 + \sum_{i=1}^{R-1} \left( \sum_{l=1}^C \lambda_{il} - R_i \right)^2 + \sum_{i=1}^{R-1} \sum_{j=1}^{C-1} d_{ij}^2 \quad (5.2.1)$$

where

$$d_{ij} = \begin{cases} \lambda_{ij} \lambda_{(i+1)(j+1)} - \lambda_{(i+1)j} \lambda_{i(j+1)} & \text{if } H_{ij} \text{ is not rejected before step } m \\ \sum_{k \leq i_1, l \leq j_1} \lambda_{kl} - S_{ij} & \text{otherwise} \end{cases}$$

It is clear that  $f_m(\boldsymbol{\lambda}) \geq 0$  for all  $\boldsymbol{\lambda}$ .

Let  $\hat{\boldsymbol{\lambda}}$  be the unique non-negative solution of equations (4.3.3) - (4.3.8). This implies  $f_m(\hat{\boldsymbol{\lambda}}) = 0$ . Hence  $\hat{\boldsymbol{\lambda}}$  is the point that minimizes  $f_m$ . So by minimizing  $f_m$ , we can get the solution of equations (4.3.3) - (4.3.8).

It is obvious that  $f_m$  is a convex function for  $\boldsymbol{\lambda} \geq \mathbf{0}$ , hence the minimization of  $f_m$  can be done very easily and efficiently by existing software. In our study, we use the *nlm* function in the popular **R**(2008) software to minimize  $f_m$ .

After we solve the equations, i.e, we get  $\hat{\boldsymbol{\lambda}}$ , we compute the conditional variance of  $S_{ij}$ . This enables us to complete the computation of  $U_{ij}^{(m)}$ .



### 5.3 Choosing the critical values

Choosing of critical values needs to be done according to the situations. For MRDSS this, in principle, can be done by simulating a list of settings that cover or represent most of the interested parameter space. One can change the critical value to control FWER or FDR or to balance the type I and type II errors . Note here that the simulation needs to be done before we see the data. In the multivariate normal case that means, before simulation, we only know  $\Sigma$ , but not  $\mathbf{X}$ ; in the ordered  $R \times C$  contingency table, that means we know the row and column sums, but not the table itself.

For an  $R \times C$  ordered contingency table, the MRD statistics at step  $m$  is  $U_{mj}$ . For large sample size,  $U_{mj}$  has approximately a standard normal distribution under the global null hypothesis. For simplicity, we use critical values  $C_m = \Phi(1 - \alpha_m/2)$ , where  $\Phi$  is the CDF for standard normal distribution,  $\alpha_m = 1 - (1 - \alpha)^{1/(M-m+1)}$ , and  $M = (R - 1)(C - 1)$ ; for screen stage, we choose  $\alpha_U = \alpha$ ,  $\alpha_L = \alpha_1$ .

## Chapter 6

### Simulations of MRDSS in ordered contingency tables

We did some simulations to compare our method, MRDSS, to Holm's step down method. FWER is control at level  $\alpha = 0.05$  for Holm's step-down (SD) method for ordered contingency table. To control FWER or FDR, for MRD, usually we need to choose a set of critical values by simulation. In the case of  $R \times C$  table, we find that adding screen stage makes it relative easy to pick critical values.

For the MRD stage of MRDSS we use critical values obtained from the normal distribution based on significance levels  $\alpha_i = 1 - (1 - \alpha)^{\frac{1}{M+1-i}}$  in step  $i$ . Here  $\alpha = .05$ ,  $M$  is the total number of hypotheses to be tested. For the screen stage we use  $\alpha_L = 1 - (1 - \alpha)^{1/M}$ ,  $\alpha_U = \alpha = .05$ . For a  $3 \times 3$  table,  $M = 4$ ; for a  $3 \times 4$  table,  $M=6$ .

Note that if we only play MRD (instead of MRDSS) using the critical values mentioned above, FWER can not be controlled at many parameter points. Adding an intuitive reasonable screen stage, we found that FWER is controlled at all the parameter points we explored.

#### 6.1 Simulation for $3 \times 3$ tables

We first list 34 sets of local odds ratios. For the  $3 \times 3$  table, each set contains 4 local odds ratios.

For each set, we generate  $N = 10,000$   $3 \times 3$  tables from independent Poisson distributions with parameters in a  $3 \times 3$  matrix  $\lambda$ . The matrix  $\lambda$  is chosen such that the true local odds ratios are listed in the left 4 columns of Table 6.1.1, and the row and column sum of  $\lambda_{ij}$  are 60. Since local odds ratios and row/col sum of  $\lambda_{ij}$  uniquely define  $\lambda$ ,  $\lambda$

itself is not shown in the table.

We compare the expected number of type I errors, expected number of type II errors and FWER of MRDSS and SD. We also give the percentage power increase of MRDSS relative to SD.

For the  $3 \times 3$  table, note that both MRDSS and SD control FWER at  $\alpha = .05$ . Also note that in 29 out of 33 cases MRDSS had an increase in power over SD and in many cases the increase was substantial.

The type I and type II error columns reflect the average number of type I and type II errors respectively.

We define the power of a MTP as :

$$\text{power} = 1 - E \{ \# \text{ of type II errors} \} / \# \text{ of true non-null hypotheses.}$$

The percentage power increase of MRDSS relative to SD is defined as :

$$\text{power incr} = 100 \times (\text{power}_{MRDSS} - \text{power}_{SD}) / \text{power}_{SD}$$

## 6.2 Simulation for $3 \times 4$ tables

For  $3 \times 4$  tables, we did a simulate for total of 70 configurations of local odds ratios . For each row, the row sum of the Poisson parameter  $\lambda$  is 80, and for each column, the column sum is 60. For each configuration, the first 6 columns show the true local odds ratios. We then choose (compute) the Poisson parameters  $\lambda$  ( a  $3 \times 4$  matrix, one for each cell) based on the row/column sum and true local odds ratios.  $\lambda$  is not shown since it is uniquely determined from the configuration.

Using likewise critical values as before, i.e., for the MRD stage of MRDSS we use

critical values obtained from the standard normal distribution based on significance levels  $1 - (1 - \alpha)^{\frac{1}{M+1-i}}$  in step  $i$ ; for the screen stage we use  $\alpha_L = 1 - (1 - \alpha)^{1/M}$ ,  $\alpha_U = \alpha = .05$ . Here,  $M=6$ .

For each configuration, we simulate  $N = 10,000$   $3 \times 3$  tables from independent Poisson distributions with parameters ( a  $3 \times 4$  matrix computed as described above)  $\lambda$ .

We then summarize the simulation with mean number of type I error, mean number of type II errors, mean FWER, and mean increase in power.

See table 6.2.1 and table 6.2.2 for the simulation results for  $3 \times 4$  tables.

Note that MRDSS strongly controls FWER at level  $\alpha = .05$  in all 70 cases, except one ( where MRDSS has a mean FWER = 0.051 ). We also compare the percentage power increase of MRDSS relative to stepdown method. MRDSS had an increase in power with only one exception. The increase was substantial in most cases.

Table 6.1.1: Comparison of MRDSS to Holm's step down (SD) for  $3 \times 3$  tables

	$\theta_{11}$	$\theta_{21}$	$\theta_{12}$	$\theta_{22}$	Type I		Type II		FWER		% P. Inc
					MRDSS	SD	MRDSS	SD	MRDSS	SD	
1	1.0	1.0	1.0	1.0	0.038	0.036	0.000	0.000	0.036	0.031	
2	1.0	1.0	1.0	3.0	0.044	0.034	0.433	0.587	0.043	0.031	37.0
3	1.0	1.0	1.0	0.3	0.044	0.033	0.483	0.618	0.041	0.028	35.1
4	1.0	1.0	3.0	3.0	0.032	0.027	0.994	1.238	0.031	0.025	31.9
5	3.0	1.0	1.0	3.0	0.044	0.027	0.736	0.983	0.044	0.026	24.2
6	1.0	3.0	3.0	1.0	0.041	0.028	1.104	1.325	0.040	0.026	32.7
7	0.3	1.0	1.0	0.3	0.041	0.026	1.086	1.302	0.039	0.025	30.9
8	1.0	0.3	0.3	1.0	0.044	0.027	0.725	0.972	0.043	0.026	24.0
9	1.0	1.0	0.3	3.0	0.029	0.025	1.208	1.185	0.028	0.023	-2.9
10	1.0	1.0	0.3	0.3	0.030	0.024	0.992	1.227	0.029	0.022	30.4
11	1.0	3.0	3.0	3.0	0.022	0.013	1.651	1.979	0.022	0.013	32.1
12	1.0	0.3	0.3	0.3	0.020	0.015	1.338	1.677	0.020	0.015	25.6
13	0.3	3.0	3.0	3.0	0.000	0.000	2.379	2.304	0.000	0.000	-4.4
14	3.0	3.0	3.0	3.0	0.000	0.000	2.075	2.437	0.000	0.000	23.2
15	3.0	0.3	0.3	0.3	0.000	0.000	2.298	2.205	0.000	0.000	-5.2
16	0.3	0.3	0.3	0.3	0.000	0.000	2.073	2.412	0.000	0.000	21.4
17	1.0	1.0	1.0	0.5	0.037	0.028	0.812	0.869	0.035	0.024	43.1
18	0.5	1.0	1.0	0.5	0.035	0.026	1.630	1.757	0.034	0.024	52.5
19	1.0	0.5	0.5	1.0	0.034	0.022	1.510	1.682	0.034	0.021	53.9
20	1.0	1.0	0.5	3.0	0.025	0.022	1.414	1.450	0.024	0.021	6.6
21	1.0	1.0	0.5	0.5	0.026	0.018	1.549	1.741	0.025	0.017	74.3
22	1.0	0.5	0.5	0.5	0.019	0.011	2.264	2.554	0.019	0.011	65.1
23	0.5	3.0	3.0	3.0	0.000	0.000	2.695	2.711	0.000	0.000	1.3
24	3.0	0.5	0.5	0.5	0.000	0.000	3.120	3.154	0.000	0.000	4.0
25	0.5	0.5	0.5	0.5	0.000	0.000	3.059	3.453	0.000	0.000	72.0
26	1.0	1.0	1.0	2.0	0.043	0.032	0.787	0.860	0.042	0.028	51.5
27	1.0	1.0	2.0	2.0	0.029	0.023	1.554	1.740	0.028	0.021	71.6
28	2.0	1.0	1.0	2.0	0.035	0.024	1.511	1.675	0.035	0.023	50.7
29	1.0	2.0	2.0	1.0	0.036	0.024	1.632	1.757	0.035	0.023	51.6
30	1.0	2.0	2.0	2.0	0.018	0.012	2.387	2.626	0.018	0.012	63.9
31	2.0	2.0	2.0	2.0	0.000	0.000	3.061	3.463	0.000	0.000	74.9
32	1.0	1.0	0.5	2.0	0.024	0.024	1.726	1.718	0.024	0.021	-2.9
33	0.5	2.0	2.0	2.0	0.000	0.000	3.369	3.451	0.000	0.000	15.0
34	2.0	0.5	0.5	0.5	0.000	0.000	3.291	3.429	0.000	0.000	24.2

Table 6.2.1: Comparison of MRDSS (M) to Holm's step down (SD) for  $3 \times 4$  tables, where % Inc denotes % Power Increase.

	$\theta_{11}$	$\theta_{21}$	$\theta_{12}$	$\theta_{22}$	$\theta_{13}$	$\theta_{23}$	Type I		Type II		FWER		% Inc
							M	SD	M	SD	M	SD	
1	1.0	1.0	1.0	1.0	1.0	1.0	0.042	0.037	0.000	0.000	0.038	0.031	
2	1.0	1.0	1.0	1.0	1.0	2.0	0.040	0.030	0.799	0.894	0.038	0.027	90.1
3	1.0	1.0	2.0	1.0	1.0	1.0	0.049	0.033	0.788	0.887	0.047	0.029	86.7
4	2.0	1.0	1.0	1.0	1.0	1.0	0.046	0.032	0.798	0.890	0.044	0.028	84.6
5	1.0	1.0	1.0	1.0	2.0	2.0	0.036	0.024	1.571	1.793	0.034	0.021	107.5
6	1.0	1.0	2.0	2.0	1.0	1.0	0.044	0.024	1.557	1.788	0.042	0.022	108.7
7	2.0	1.0	1.0	1.0	1.0	2.0	0.051	0.027	1.544	1.761	0.049	0.024	90.4
8	1.0	2.0	1.0	1.0	1.0	2.0	0.045	0.025	1.600	1.793	0.043	0.023	93.3
9	1.0	1.0	2.0	1.0	1.0	2.0	0.049	0.025	1.535	1.748	0.048	0.023	84.9
10	1.0	1.0	1.0	2.0	1.0	2.0	0.037	0.028	1.545	1.789	0.036	0.026	115.7
11	2.0	1.0	1.0	1.0	2.0	2.0	0.039	0.021	2.320	2.660	0.038	0.019	99.7
12	1.0	2.0	1.0	1.0	2.0	2.0	0.040	0.022	2.428	2.706	0.039	0.019	94.9
13	1.0	1.0	2.0	1.0	2.0	2.0	0.032	0.019	2.315	2.675	0.031	0.017	110.7
14	1.0	1.0	1.0	2.0	2.0	2.0	0.035	0.018	2.419	2.716	0.034	0.018	104.3
15	2.0	1.0	2.0	2.0	1.0	1.0	0.039	0.022	2.316	2.655	0.038	0.020	98.4
16	2.0	2.0	2.0	2.0	1.0	1.0	0.024	0.013	3.113	3.593	0.023	0.013	117.8
17	1.0	1.0	2.0	2.0	2.0	1.0	0.038	0.019	2.431	2.728	0.037	0.018	108.9
18	1.0	1.0	2.0	2.0	1.0	2.0	0.038	0.022	2.305	2.645	0.037	0.021	95.8
19	1.0	1.0	2.0	2.0	2.0	2.0	0.025	0.014	3.114	3.593	0.024	0.013	117.7
20	2.0	2.0	1.0	1.0	2.0	2.0	0.027	0.013	3.140	3.589	0.027	0.012	109.1
21	1.0	2.0	1.0	2.0	2.0	2.0	0.024	0.013	3.242	3.640	0.024	0.012	110.2
22	1.0	2.0	2.0	1.0	2.0	2.0	0.033	0.016	3.166	3.599	0.033	0.016	107.7
23	1.0	2.0	2.0	2.0	1.0	2.0	0.031	0.015	3.218	3.583	0.031	0.015	87.7
24	1.0	2.0	2.0	2.0	2.0	1.0	0.032	0.013	3.280	3.667	0.031	0.013	116.6
25	2.0	2.0	2.0	2.0	2.0	2.0	0.000	0.000	4.694	5.392	0.000	0.000	114.7
26	1.0	1.0	1.0	1.0	1.0	3.0	0.042	0.030	0.422	0.621	0.040	0.026	52.7
27	1.0	1.0	3.0	1.0	1.0	1.0	0.046	0.029	0.430	0.647	0.045	0.026	61.5
28	3.0	1.0	1.0	1.0	1.0	1.0	0.045	0.033	0.424	0.626	0.042	0.029	54.1
29	1.0	1.0	1.0	1.0	3.0	3.0	0.036	0.029	1.044	1.368	0.034	0.025	51.3
30	1.0	1.0	3.0	3.0	1.0	1.0	0.047	0.025	0.965	1.350	0.046	0.024	59.2
31	3.0	1.0	1.0	1.0	1.0	3.0	0.053	0.032	0.763	1.149	0.051	0.029	45.4
32	1.0	3.0	1.0	1.0	1.0	3.0	0.047	0.030	1.011	1.342	0.045	0.027	50.2
33	1.0	1.0	3.0	1.0	1.0	3.0	0.048	0.025	0.768	1.134	0.046	0.022	42.2
34	1.0	1.0	1.0	3.0	1.0	3.0	0.040	0.029	0.954	1.321	0.038	0.026	54.1
35	3.0	1.0	1.0	1.0	3.0	3.0	0.038	0.021	1.446	1.919	0.036	0.020	43.7
36	1.0	3.0	1.0	1.0	3.0	3.0	0.039	0.021	1.715	2.143	0.038	0.019	50.0
37	1.0	1.0	3.0	1.0	3.0	3.0	0.035	0.024	1.471	1.951	0.033	0.022	45.7
38	1.0	1.0	1.0	3.0	3.0	3.0	0.038	0.020	1.686	2.149	0.037	0.019	54.4
39	3.0	1.0	3.0	3.0	1.0	1.0	0.042	0.024	1.348	1.850	0.041	0.023	43.7
40	3.0	3.0	3.0	3.0	1.0	1.0	0.025	0.014	2.211	2.755	0.024	0.013	43.8
41	1.0	1.0	3.0	3.0	3.0	1.0	0.045	0.022	1.723	2.188	0.044	0.021	57.2
42	1.0	1.0	3.0	3.0	1.0	3.0	0.039	0.022	1.351	1.844	0.039	0.022	42.6
43	1.0	1.0	3.0	3.0	3.0	3.0	0.026	0.016	2.216	2.738	0.026	0.016	41.3
44	3.0	3.0	1.0	1.0	3.0	3.0	0.032	0.016	2.213	2.724	0.031	0.016	40.1

Table 6.2.2: (Continue) Comparison of MRDSS (M) to Holm's step down (SD) for  $3 \times 4$  tables

	$\theta_{11}$	$\theta_{21}$	$\theta_{12}$	$\theta_{22}$	$\theta_{13}$	$\theta_{23}$	Type I		Type II		FWER		% Inc
							M	SD	M	SD	M	SD	
45	1.0	3.0	3.0	1.0	3.0	3.0	0.036	0.020	2.252	2.793	0.036	0.019	44.8
46	1.0	3.0	3.0	3.0	1.0	3.0	0.035	0.015	2.197	2.762	0.035	0.015	45.6
47	1.0	3.0	3.0	3.0	3.0	1.0	0.036	0.015	2.519	3.091	0.036	0.015	62.9
48	3.0	3.0	3.0	3.0	3.0	3.0	0.000	0.000	3.473	4.241	0.000	0.000	43.7
49	1.0	1.0	1.0	1.0	0.5	2.0	0.033	0.029	1.781	1.784	0.032	0.026	1.6
50	1.0	1.0	1.0	2.0	0.5	1.0	0.038	0.031	1.688	1.789	0.037	0.028	47.8
51	1.0	1.0	2.0	1.0	0.5	1.0	0.034	0.028	1.789	1.782	0.032	0.025	-3.4
52	1.0	2.0	1.0	1.0	0.5	1.0	0.040	0.029	1.659	1.778	0.038	0.026	53.6
53	2.0	1.0	1.0	1.0	0.5	1.0	0.031	0.024	1.717	1.784	0.029	0.022	31.1
54	1.0	1.0	2.0	0.5	1.0	1.0	0.038	0.025	1.743	1.773	0.036	0.023	13.5
55	1.0	2.0	1.0	0.5	1.0	1.0	0.031	0.025	1.766	1.768	0.029	0.022	0.6
56	2.0	1.0	1.0	0.5	1.0	1.0	0.034	0.024	1.677	1.783	0.033	0.022	48.9
57	0.5	1.0	1.0	1.0	2.0	2.0	0.026	0.021	2.437	2.675	0.025	0.019	72.9
58	1.0	0.5	1.0	1.0	2.0	2.0	0.027	0.020	2.452	2.688	0.026	0.019	75.6
59	1.0	1.0	0.5	1.0	2.0	2.0	0.029	0.021	2.526	2.676	0.028	0.019	46.1
60	1.0	1.0	1.0	0.5	2.0	2.0	0.027	0.022	2.571	2.691	0.026	0.020	39.1
61	2.0	1.0	1.0	1.0	0.5	2.0	0.029	0.020	2.602	2.661	0.028	0.018	17.4
62	1.0	2.0	1.0	1.0	0.5	2.0	0.033	0.021	2.573	2.683	0.031	0.020	34.8
63	1.0	1.0	2.0	1.0	0.5	2.0	0.036	0.019	2.601	2.654	0.035	0.017	15.4
64	1.0	1.0	1.0	2.0	0.5	2.0	0.028	0.020	2.505	2.695	0.026	0.018	62.3
65	2.0	2.0	2.0	2.0	0.5	0.5	0.000	0.000	4.914	5.360	0.000	0.000	69.6
66	2.0	2.0	0.5	0.5	2.0	2.0	0.000	0.000	5.135	5.322	0.000	0.000	27.5
67	0.5	0.5	2.0	2.0	2.0	2.0	0.000	0.000	4.897	5.357	0.000	0.000	71.7
68	2.0	0.5	2.0	0.5	2.0	2.0	0.000	0.000	5.056	5.361	0.000	0.000	47.6
69	0.5	2.0	2.0	2.0	2.0	0.5	0.000	0.000	5.166	5.355	0.000	0.000	29.3
70	2.0	0.5	2.0	2.0	0.5	2.0	0.000	0.000	5.026	5.296	0.000	0.000	38.3

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