MERIT: controlling Monte-Carlo error rate in large-scale Monte-Carlo hypothesis testing

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Abstract

Background: The use of Monte-Carlo (MC) p-values when testing the significance of a large number of hypotheses is now commonplace. It is known that a larger number of MC replicates is required to calculate a p-value near a threshold of significance than calculation of a p-value that is far from the threshold. However, it is not well appreciated that, in large-scale hypothesis testing, we will typically encounter at least *some* p-values near the threshold. As a result, the list of rejected null hypotheses (detections) from large-scale MC testing can vary when different MC replicates are used, resulting in lack of reproducibility. The method of Gandy and Hahn (GH) [1–3] is the only method that has directly addressed this problem, defining a Monte-Carlo error rate (MCER) to be the probability that any decisions on accepting or rejecting a hypothesis based on MC p-values are different from decisions based on *ideal* p-values, and then making decisions that control the MCER. Unfortunately, GH is frequently very conservative, often making no rejections at all, with a large number of hypotheses left "undecided".

Methods: In this article, we propose MERIT (Monte-Carlo Error Rate control In large-scale MC hypothesis Testing), a method for large-scale MC hypothesis testing that also controls the MCER but is more statistically efficient than the GH method. MERIT assumes a pre-determined number of MC replicates. Because GH is a sequential procedure, we also develop a version of GH that is optimized for a pre-determined number of MC replicates.

Results: Through extensive simulation studies, we demonstrated that MERIT controlled the MCER and substantially improved the sensitivity and specificity of detections compared to our pre-determined-replicate version of GH. We also illustrated our method by an analysis of gene expression data from a prostate cancer study.

1. Introduction

Modern scientific studies often require testing a large number of hypotheses; in particular, modern biological and biomedical studies of -omics (e.g., genomics, proteomics, metabolomics) typically test a large number ($\gg 100$) of hypotheses at a time. In these studies, p-values for testing individual hypotheses are first obtained and a procedure that corrects for multiplicity, such as the procedures of Benjamini and Hochberg (BH) [4], Bonferroni [5], or Holm [6], is then applied to make decisions on the hypotheses. When the p-values cannot be calculated analytically, they are frequently obtained by resampling methods such as permutation or bootstrap. For ease of exposition, hereafter we generically refer to any resampling-based method as a Monte-Carlo (MC) method, and refer to individual resamples as MC replicates.

The recommended form of an MC p-value is $\widehat{p}_i = (X_i + 1)/(n + 1)$ [7–9] for the ith hypothesis, where n is the number of MC replicates (i.e., MC sample size) and X_i is the number of "exceedances" (i.e., when the statistic based on an MC replicate "exceeds" the observed test statistic). When using a finite n, there will be a difference between the MC p-value and the *ideal* p-value that is based either on analytical methods or exhaustive resampling of replicates. It is also well known that the MC sample size required to test a hypothesis having a p-value near a threshold of significance is much larger than that required for a hypothesis having a p-value that is far from the threshold. What is less appreciated is that, when testing a large number of hypotheses, it is very likely that at least *some* hypotheses have ideal p-values near whatever threshold of significance is used. As a result, there can be noticeable variability in the list of hypotheses rejected by an MC test procedure in different runs that use different MC replicates. The list can also differ from that based on the ideal p-values. This is true whether the test procedure adopts a fixed stopping criterion (i.e., mandating a fixed MC sample size for all hypotheses), or a sequential stopping criterion [10] (i.e., allowing some tests to stop early after collecting sufficient information about its decision).

To date, only Gandy and Hahn (GH) [1–3] have *directly* addressed this problem. They

developed a method that can be coupled with any MC test method that has a sequential stopping criterion. Their method makes decisions on multiple hypotheses by controlling the family-wise Monte-Carlo error rate (MCER), which is the probability that any of their decisions on accepting or rejecting a hypothesis are different from what would have been obtained from the ideal p-values. It works in a sequential manner, giving a decision among "rejected", "accepted", and "undecided" to each test after each iteration and continuing sampling only for hypotheses that are "undecided".

To be more specific, denote the m null hypotheses by $H_{1,0}, H_{2,0}, \ldots, H_{m,0}$, the ideal p-values by $p_1^*, p_2^*, \ldots, p_m^*$, and the ideal decisions (between "rejected" and "accepted") made by the BH procedure that is applied to the ideal p-values by $D_1^*, D_2^*, \ldots, D_m^*$. Denote the decisions (among "rejected", "accepted", and "undecided") made by an MC test procedure by $\widehat{D}_1, \widehat{D}_2, \ldots, \widehat{D}_m$. Following GH, we define the total number of MC errors to be the sum of all disagreements between the D_i^*s and $\widehat{D}_i$s among hypotheses that are determined as "rejected" or "accepted" by the MC test procedure:

$$V = \sum_{i=1}^{m} \mathbb{I}\left(\widehat{D}_i = \text{rejected}, D_i^* = \text{accepted}\right) + \sum_{i=1}^{m} \mathbb{I}\left(\widehat{D}_i = \text{accepted}, D_i^* = \text{rejected}\right), \qquad (1)$$

where $\mathbb{I}(\cdot,\cdot)$ is an indicator function. Controlling the family-wise MCER at level α, i.e., $\Pr(V \geq 1) \leq \alpha$, assures that, among those tests that the MC test procedure actually decides, the probability that we reach a conclusion that is different from the decision we would make if we had the ideal p-values is less than α. Note that there is no error control on "undecided" hypotheses ($\widehat{D}_i = \text{undecided}$), which would require more MC replicates to reach a decision.

At each iteration of the MC test procedure, the GH method forms a two-sided Robbins-Lai confidence interval (CI) [11, 12] for each ideal p-value that maintains a joint coverage over all iterations (i.e., accounting for the possible differences in MC sample size for each test); the level of each CI is determined by using the Bonferroni correction. Then, the GH method applies the BH procedure to the collection of upper CI limits and, separately, to the collection of lower CI limits. Those tests for which both lower and upper limits are rejected are determined

as "rejected", those for which both limits are accepted are determined as "accepted"; the remaining tests are determined as "undecided". The GH method controls MCER at every iteration. However, it is extremely conservative due to the use of the Bonferroni correction, and thus tends to make no rejections at all when the MC sample size is not very large.

While the sequential stopping criterion has advantages (e.g., it can greatly reduce the MC sample size for tests that are either highly insignificant or highly significant), use of a fixed, pre-determined MC sample size is more common. Further, in many instances there may be little or no computational advantage to stopping some tests early, e.g., when the cost of evaluating the stopping criterion exceeds the cost of calculating the test statistics. Under these circumstances, the cost of satisfying an MCER at each iteration may not be justified. For these reasons, we now restrict our attention to MC procedures with fixed MC sample sizes.

In this article, we propose a method, called MERIT (Monte-Carlo Error Rate control In large-scale MC hypothesis Testing), that makes decisions on the hypotheses by controlling the same family-wise MCER as the GH method, but it works for MC test procedures with a fixed stopping criterion. We aim to maximize detection efficiency by minimizing the number of "undecided" hypotheses at a given MC sample size or by making conclusive decisions for all hypotheses with fewer MC replicates. We present our method in Section 2, examine its properties through simulation studies in Section 3, and apply it to a study of prostrate cancer with gene expression data in Section 4. Because one immediate advantage of using a fixed MC sample size is that the Robbins-Lai CI required for the sequential GH approach is much wider than any single-stage CI [13], in Section 2 we also develop a fixed-MC-sample-size version of GH that uses a single-stage CI, to allow for a more fair comparison in Sections 3 and 4. Finally, we conclude with a discussion in Section 5.

2. Methods

Suppose that a fixed number, n, of MC replicates have been collected for testing all m hypotheses. For testing the ith hypothesis $H_{i,0}$, let s_i be the observed test statistic and S_{ij}

be the test statistic calculated from the jth MC replicate. The input of our method is the matrix $I = \{I_{ij}\}_{m\times n}$, where $I_{ij} = \mathbb{I}(|S_{ij}| \geq |s_i|)$ is the exceedance indicator corresponding to a symmetric, two-sided statistic (note that I_{ij} can be redefined for one-sided tests or tests with asymmetric null distributions). We frequently use the total number of exceedances for each test, $X_i = \sum_{j=1}^{n} I_{ij}$. Because the replicates are sampled independently from the null distribution, we have $X_i \sim \mathrm{Bin}(n,\ p_i^*)$, which is a binomial variable with n trials and "success" rate being the ideal p-value p_i^*.

We first transform the problem of controlling the MCER into a problem of controlling the family-wise error rate (FWER) in testing a set of new but related hypotheses. Then, because step-wise procedures (where the criterion for rejecting hypotheses becomes less stringent in subsequent steps in case some hypotheses have been rejected in an earlier step) such as Holm's [6] are typically more powerful than single-step procedures such as the Bonferroni correction, we develop a step-wise procedure for testing the new hypotheses following the framework of Romano and Wolf [14, 15]. Because the Romano and Wolf framework for one-sided hypotheses [15] can have additional power gains by adopting Hansen's adjustment [16], we focus on one-sided hypotheses by converting two-sided hypotheses into pairs of one-sided hypotheses.

Corresponding to the pairs of one-side hypotheses, we partition the total MC errors in (1) into the type-I and type-II MC errors, which are defined by the first and second terms in (1) and denoted by V^{I} and V^{II}, respectively. We develop a procedure for testing a set of one-sided hypotheses, which makes decisions on the original hypotheses between "rejected" and "non-rejected" while controlling the family-wise type-I MCER $\Pr(V^{\mathrm{I}} \geq 1)$ at α_1; we develop another procedure for testing another set of one-sided hypotheses, which makes decisions on the original hypotheses between "accepted" and "non-accepted" while controlling the family-wise type-II MCER $\Pr(V^{\mathrm{II}} \geq 1)$ at α_2. After combining their results, we can determine each original hypothesis as "rejected", "accepted", or possibly "undecided", while controlling the family-wise MCER at $\alpha_1 + \alpha_2$, because $\Pr(V \geq 1) \leq \Pr(V^{\mathrm{I}} \geq 1) + \Pr(V^{\mathrm{II}} \geq 1)$. In what follows, we omit the term "family-wise" for simplicity. In Sections 2.1–2.3, we present our first

procedure. In Section 2.4, we obtain the second procedure by modifying the first procedure. In Section 2.5, we show how to combine results of the two procedures.

2.1 A procedure that rejects original hypotheses while controlling the type-I MCER

Suppose that the BH procedure with nominal false-discovery rate (FDR) ϕ is applied to the ideal p-values, which are sorted in an ascending order $p^*_{(1)} \leq p^*_{(2)} \leq \cdots \leq p^*_{(m)}$. If k is the largest integer such that $p^*_{(k)} \leq \phi \times k/m$, then the hypotheses corresponding to $p^*_{(1)}, \ldots, p^*_{(k)}$ are rejected and the remaining hypotheses are not. Thus, we call $\tau^* \equiv \phi \times k/m$ the *BH cutoff* for the ideal p-value, which separates the ideal p-values for rejected and non-rejected hypotheses.

If τ^* is known *a priori*, the result of the above BH procedure can be viewed as the truth of the following hypotheses:

$$H^*_{i,0} : p^*_i > \tau^* \qquad \text{vs.} \qquad H^*_{i,1} : p^*_i \leq \tau^*, \qquad i = 1, 2, \ldots, m. \tag{2}$$

Recall that a type-I MC error occurs when a hypothesis $H^*_{i,0}$ is true (i.e., not rejected using the ideal p-value) but rejected using the MC p-value; this would happen when the MC p-value is smaller than its corresponding ideal p-value. Then, a test procedure based on MC p-values that controls the FWER for testing $H^*_{i,0}$ at α_1 would control the type-I MCER at α_1.

In reality, τ^* is unknown since the ideal p-values are unknown. A reasonable strategy to control type-I MCER would be to choose some threshold τ satisfying $\tau < \tau^*$; this is intuitive, since, as we make τ smaller, we require smaller MC p-values to reject a hypothesis, and smaller MC p-values correspond to increased confidence in any rejections we make. Thus, we divide the problem of testing hypotheses in (2) into two sub-problems and develop a two-step procedure. In the first step, we find a lower limit τ_l for τ^* that satisfies $\tau_l < \tau^*$ with a probability of at least $(1 - \widetilde{\alpha}_1)$, where $\widetilde{\alpha}_1$ is chosen such that $0 < \widetilde{\alpha}_1 < \alpha_1$. In the second step, we consider the revised hypotheses, treating τ_ℓ as a constant:

$$\widetilde{H}_{i,0} : p^*_i > \tau_\ell \qquad \text{vs.} \qquad \widetilde{H}_{i,1} : p^*_i \leq \tau_\ell, \qquad i = 1, 2, \ldots, m. \tag{3}$$

We develop a test procedure that tests (3) while controlling the FWER at level $(\alpha_1 - \widetilde{\alpha}_1)$. Note that the same decision on $\widetilde{H}_{i,0}$ is transferred to $H^*_{i,0}$ and $H_{i,0}$. Then, by the relationship

$$\begin{aligned}\{V^{\mathrm{I}} \geq 1\} &= \{\tau_\ell > \tau^*, V^{\mathrm{I}} \geq 1\} \cup \{\tau_\ell \leq \tau^*, V^{\mathrm{I}} \geq 1\} \\ &\subset \{\tau_\ell > \tau^*\} \cup \{\tau_\ell \leq \tau^*, \text{ at least one } H^*_{i,0} \text{ is true but rejected}\} \\ &\subset \{\tau_\ell > \tau^*\} \cup \{\tau_\ell \leq \tau^*, \text{ at least one } \widetilde{H}_{i,0} \text{ is true but rejected}\},\end{aligned}$$

the type-I MCER $\Pr(V^{\mathrm{I}} \geq 1)$ is always bounded by the sum of $\Pr(\tau_\ell > \tau^*)$ and the FWER of the test procedure in testing (3), which is $\widetilde{\alpha}_1 + (\alpha_1 - \widetilde{\alpha}_1) = \alpha_1$. As the default, we choose $\widetilde{\alpha}_1 = \alpha_1/2$, i.e., partitioning the type-I MCER equally into the two sub-problems. We show in Supplemental Materials S1 that the equal partition scheme generally yields the highest power.

2.2 Step 1: construct a $(1 - \widetilde{\alpha}_1)$-level one-sided CI $[\tau_\ell, 1]$ for τ^*

We now turn our attention to constructing a one-sided CI $[\tau_\ell, 1]$ for τ^*. Note that, for any set of p-values, there is a corresponding BH cutoff; thus, we find the lower limit τ_ℓ for τ^* from a set of p-values that are "lower limits" for the ideal p-values p^*_i. To this aim, we consider the following sets of p-values, with each set indexed by a positive continuous value c:

$$p_{c,i} = \frac{X_i + 1 + c\sqrt{X_i + 1}}{n + 1 + c\sqrt{X_i + 1}}, \qquad i = 1, 2, \ldots, m. \tag{4}$$

Recall that the MC p-value $\widehat{p}_i = (X_i+1)/(n+1)$ provides a consistent estimate of p^*_i. The term $\sqrt{X_i + 1}$ in (4) is an approximation to $\sqrt{n\widehat{p}_i(1 - \widehat{p}_i)}$, which is the estimated standard error of $X_i + 1$; the term $(1 - \widehat{p}_i)$ is omitted because only the small p-values (in the neighborhood of τ^*) are of interest. As c goes to 0, $p_{c,i}$ converges to p^*_i. Because $p_{c,i} > \widehat{p}_i$ as long as $c > 0$ and $X_i < n$, when c is sufficiently large, $p_{c,i}$ is asymptotically larger than p^*_i, at least for small p^*_is.

Let $F^*(t)$ and $F_c(t)$ be the empirical distribution functions (EDF) of $(p^*_1, \ldots, p^*_m)$ and $(p_{c,1}, \ldots, p_{c,m})$, respectively, and τ^* and τ_c be their BH cutoffs. Storey et al. [17] gave a general result that, a BH cutoff τ can also be obtained from an EDF $F(t)$ of p-values by the formula $\tau = \max\{t : F(t) \geq t/\phi,\ t \in [0, 1]\}$, which means that τ is the intersection of $F(t)$

and the straight line t/ϕ, as illustrated in Figure 1. When t/ϕ is constrained to $[0,1]$ as $F(t)$, t must be constrained to $[0,\phi]$. Then we see from Figure 1 (right) that the intersection τ must lie in $[0,\phi]$ and is fully determined by the EDF of p-values in the range of $[0,\phi]$. If $F_c(t)$ is always no greater than $F^*(t)$ over $[0,\phi]$, as shown in Figure 1 (left), we must have $\tau_c \leq \tau^*$. It follows that

$$\Pr(\tau_c \leq \tau^*) \geq \Pr\left(F_c \prec F^*\right), \tag{5}$$

in which we use $\prec$ to denote that one function is always no greater than another function for $t \in [0,\phi]$. Note that τ_c and F_c in (5) are random because $p_{c,i}$ involves X_i that is based on MC replicates; τ^* and F^* are constant because we condition on the observed data. To construct a $(1-\widetilde{\alpha}_1)$-level one-sided CI $[\tau_\ell, 1]$ for τ^*, we are interested in c that satisfies

$$\Pr\left(F_c \prec F^*\right) \geq 1-\widetilde{\alpha}_1. \tag{6}$$

The probability on the left of (6) increases as c increases (because the increase of $p_{c,i}$ leads to the decrease of $F_c(t)$ at a given t). To make the CI for τ^* the tightest, we wish to find the smallest c that satisfies (6), denoted by c_ℓ. Finally, we set the lower limit τ_ℓ to τ_{c_ℓ}, which is the BH cutoff corresponding to the set of p-values in (4) indexed by c_ℓ.

It is difficult to find the smallest c that satisfies (6) analytically because F^* is unknown. Thus, we propose to obtain c_ℓ by bootstrap resampling. In the b-th bootstrap, we sample n columns from the input matrix I with replacement to form the bootstrap matrix $I^{(b)}$ and sum up the rows of $I^{(b)}$ to obtain the corresponding numbers of exceedances $(X_1^{(b)}, X_2^{(b)}, \ldots, X_m^{(b)})$. The number of bootstrap replicates B needs to be large, e.g., $B = 10^4$. Define the bootstrap p-values indexed by c as

$$p_{c,i}^{(b)} = \frac{X_i^{(b)} + 1 + c\sqrt{X_i^{(b)}+1}}{n+1+c\sqrt{X_i^{(b)}+1}}, \qquad i = 1, 2, \ldots, m.$$

Let $\widehat{F}$ and $F_c^{(b)}$ be the EDF for $(\widehat{p}_1, \ldots, \widehat{p}_m)$ and $\left(p_{c,1}^{(b)}, \ldots, p_{c,m}^{(b)}\right)$, respectively. Then we wish to find c_ℓ to be the smallest c that satisfies

$$B^{-1}\sum_{b=1}^{B} \mathbb{I}\left(F_c^{(b)} \prec \widehat{F}\right) \geq 1-\widetilde{\alpha}_1, \tag{7}$$

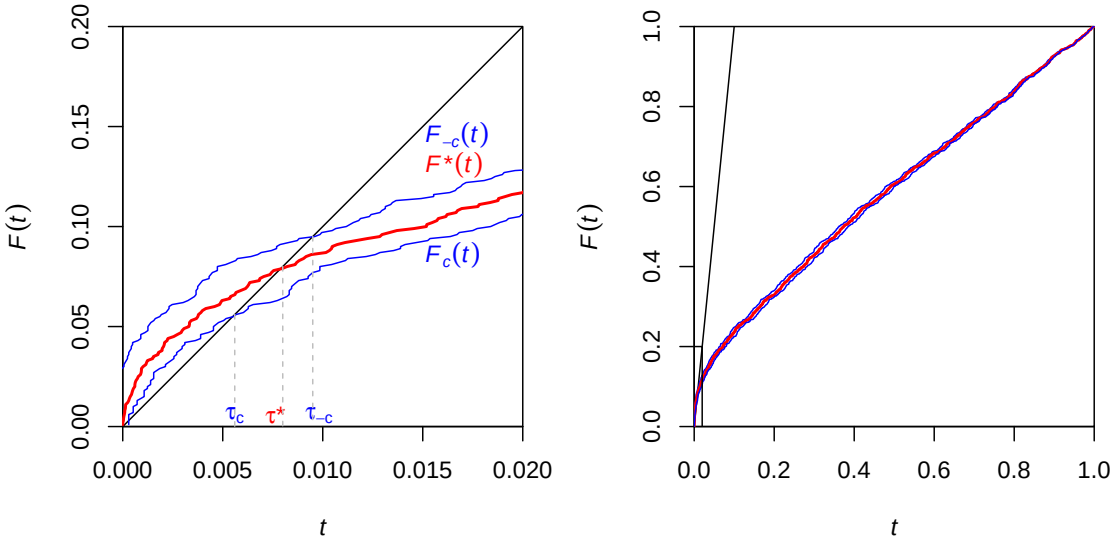

Figure 1: An example of $F^*(t)$, $F_c(t)$, and $F_{-c}(t)$ and their corresponding BH cutoffs τ^*, τ_c, and τ_{-c}. The black straight line is t/ϕ, where $\phi = 10\%$. The left plot is a zoom-in view of the bottom left corner of the right plot.

which is an empirical version of (6). In fact, it is still difficult to directly find the smallest c that satisfies (7). Alternatively, we find, for every b, the smallest c that guarantees $F_c^{(b)} \prec \widehat{F}$, denoted by $c_\ell^{(b)}$, and then set c_ℓ to be the $(1-\widetilde{\alpha}_1)$th quantile of $\left(c_\ell^{(1)}, c_\ell^{(2)}, \ldots, c_\ell^{(B)}\right)$. This strategy ensures that $(1-\widetilde{\alpha}_1)B$ indicator functions in (7) take the value of 1 when evaluated at $c = c_\ell$. The procedure here is summarized in Step 1 of Algorithm 1.

2.3 Step 2: test hypotheses in (3) given τ_ℓ while controlling the FWER at $(\alpha_1 - \widetilde{\alpha}_1)$

We use X_1, X_2, …, X_m defined earlier as the test statistics and let x_1, x_2, …, x_m denote their observed values. Let $x_{(1)} \leq x_{(2)} \leq \ldots \leq x_{(m)}$ be the ordered observed values, and $\widetilde{H}_{(1),0}$, $\widetilde{H}_{(2),0}$, …, $\widetilde{H}_{(m),0}$ be the corresponding hypotheses.

We start by testing the global null $\widetilde{H}_{(1),0} \cap \widetilde{H}_{(2),0} \cap \ldots \cap \widetilde{H}_{(m),0}$, which means that all p_i^*s are greater than τ_ℓ. We use $x_{(1)}$ as the test statistic for this test. Romano and Wolf [14, 15] proposed to calculate the p-value under the global null in this form:

$$\Pr\left(\min_{1\leq j\leq m} X_j \leq x_{(1)}\right), \tag{8}$$

where each X_j is a binomial random variable with n trials and some "success" rate θ_j that is under the null and determined below. It is likely that X_1, X_2, ..., X_m have some dependence structure in many applications; Romano and Wolf proposed to calculate (8) via bootstrap resampling that preserves the dependence structure. To avoid bootstrap resampling, we use the Bonferroni inequality to obtain an upper bound for (8), namely

$$\sum_{j=1}^{m} F_{\text{Bin}}(x_{(1)}; n, \theta_j), \tag{9}$$

where $F_{\text{Bin}}(x; n, \theta)$ denotes $\Pr(X \leq x)$ for $X \sim \text{Bin}(n, \theta)$. Expression (9) can be calculated analytically, although this simplification comes at the cost of losing some statistical power compared to using (8) directly. Note that the upper bound in (9) is valid under any dependence structure among the m tests.

Now we consider the problem of determining θ_js. In the worst case when all p_i^*s are close to the boundary τ_ℓ, we should choose $\theta_j = \tau_\ell$ for all js. Hansen [16] noted that it is possible to gain more power by making adjustments for null hypotheses that are "deep in the null", i.e., p_i^*s that are not near the boundary τ_ℓ but instead satisfy $p_i^* \gg \tau_\ell$. In the presence of a large number of tests, we expect many p_i^*s are "deep in the null". Intuitively, the hypotheses associated with very large p_i^*s can be removed and the "effective" number of tests that we need to adjust for can be considerably reduced, leading to improved power. Ideally, we should choose $\theta_j = \max\{\tau_\ell, p_j^*\}$. However, p_j^* is unknown. Hansen [16] proposed an estimator for p_j^* that leads to the choice

$$\theta_j = \begin{cases} \tau_\ell, & \text{if } \sqrt{n}\,(x_j/n - \tau_\ell)\,/\sqrt{\tau_\ell(1-\tau_\ell)} \leq \sqrt{2\log\log n}, \\ x_j/n, & \text{otherwise.} \end{cases}$$

Therefore, if the statistic x_j is sufficiently large, θ_j is set to the sample-based estimator x_j/n, and otherwise it is left unchanged at τ_ℓ.

Using this θ_j, if

$$\sum_{j=1}^{m} F_{\text{Bin}}(x_{(1)}; n, \theta_j) \leq \alpha_1 - \widetilde{\alpha}_1,$$

we reject $\widetilde{H}_{(1),0}$ and move to the next joint null $\widetilde{H}_{(2),0} \cap \ldots \cap \widetilde{H}_{(m),0}$ that excludes $\widetilde{H}_{(1),0}$; otherwise, we stop and declare that none of the hypotheses should be rejected. In general, for testing the joint null $\widetilde{H}_{(i),0} \cap \ldots \cap \widetilde{H}_{(m),0}$ for any i, we use $x_{(i)}$ as the test statistic. If

$$\sum_{j=i}^{m} F_{\mathrm{Bin}}(x_{(i)}; n, \theta_j) \leq \alpha_1 - \widetilde{\alpha}_1, \tag{10}$$

we reject $\widetilde{H}_{(i),0}$ and move to the next joint null that excludes $\widetilde{H}_{(i),0}$; otherwise, we stop and accept the remaining hypotheses. This step-wise procedure asymptotically controls the FWER in testing (3) at $(\alpha_1 - \widetilde{\alpha}_1)$ [15, 16]. Whenever $\widetilde{H}_{(i),0}$ is rejected, the corresponding original hypothesis $H_{(i),0}$ is rejected. This procedure is summarized in Step 2 of Algorithm 1.

The step-wise procedure here can be understood as a combination of Holm's test and Hansen's adjustment. We can see that, without Hansen's adjustment, this procedure reduces to Holm's test. Specifically, the left hand side of (10), with θ_j replaced by τ_ℓ, becomes $(m - i + 1)p_{(i)}$, where $p_{(i)} = F_{\mathrm{Bin}}(x_{(i)}; n, \tau_\ell)$ is the ith smallest p-value among all p-values for testing $\widetilde{H}_{(i),0}$s. Thus, (10) becomes $p_{(i)} \leq (\alpha_1 - \widetilde{\alpha}_1)/(m - i + 1)$, which is Holm's test. By adjusting for null hypotheses that are "deep in the null", we have $F_{\mathrm{Bin}}(x_{(i)}; n, \theta_j) \approx 0$ for very large θ_js and (10) becomes approximately $p_{(i)} \leq (\alpha_1 - \widetilde{\alpha}_1)/m_0$, where m_0 is a number that is smaller than $m - i + 1$. Therefore, our procedure gains more power than Holm's test.

2.4 A procedure that accepts original hypotheses while controlling the type-II MCER

We can readily modify the procedure in Sections 2.1–2.3 for testing a set of hypotheses that flip the null and alternative hypotheses $H^*_{i,0}$ and $H^*_{i,1}$ in (2). Thus, a rejection of the new null hypothesis, which is now $H^*_{i,1}$, leads to an acceptance of the original hypothesis $H_{i,0}$. As with the previous procedure, we divide the problem into two sub-problems, the first of which is to construct an at-least-$(1 - \widetilde{\alpha}_2)$-level one-sided CI $[0, \tau_u]$ for τ^*, where $0 < \widetilde{\alpha}_2 < \alpha_2$, and the second of which is to test the hypotheses that flip the null and alternative hypotheses $\widetilde{H}_{i,0}$ and $\widetilde{H}_{i,1}$ in (3) as well as replace τ_ℓ by τ_u. The details of this procedure are deferred to

Algorithm 1 The procedure that rejects original hypotheses while controlling type-I MCER

Input: matrix I, nominal FDR ϕ, nominal type-I MCER α_1

Step 1: construct a $(1-\widetilde{\alpha}_1)$-level one-sided CI $[\tau_\ell, 1]$ for τ^*.

Calculate $(X_1, X_2, \ldots, X_m)$, $(\widehat{p}_1, \widehat{p}_2, \ldots, \widehat{p}_m)$, and then $\widehat{F}$.

For each bootstrap replicate $b = 1, 2, \ldots, B$,

Sample n columns from I with replacement to form $I^{(b)}$.

Calculate $(X_1^{(b)}, X_2^{(b)}, \ldots, X_m^{(b)})$, $(p_{c,1}^{(b)}, p_{c,2}^{(b)}, \ldots, p_{c,m}^{(b)})$, and then $F_c^{(b)}$.

Find $c_l^{(b)}$ to be the smallest c that guarantees $F_c^{(b)} \prec \widehat{F}$.

Find c_ℓ, the smallest c that satisfies (6), to be the $(1-\widetilde{\alpha}_1)$ quantile of $(c_l^{(1)}, c_l^{(2)}, \ldots, c_l^{(B)})$.

Find the lower limit τ_ℓ to be the BH cutoff of p-values in (4) indexed by c_ℓ.

Step 2: test hypotheses in (3) given τ_ℓ while controlling the FWER at $(\alpha_1 - \widetilde{\alpha}_1)$.

Set $i = 1$.

while $i \leq m$,

If (10) does not hold, accept all remaining hypotheses $\widetilde{H}_{(i),0}$s and exit the loop.

Otherwise, reject $\widetilde{H}_{(i),0}$, update $i = i + 1$.

Whenever $\widetilde{H}_{(i),0}$ is rejected, $H_{(i),0}$ is rejected.

Output: a decision for every hypothesis $H_{i,0}$ between "rejected" and "non-rejected".

Supplemental Materials S2 and are summarized in Algorithm 2, which can also be found in that section. One important feature of this algorithm is that τ_u is found by using a negative value for c in (4), corresponding to the curve $F_{-c}(t)$ in Figure 1, guaranteeing that $\tau_\ell < \tau_u$, a result we require in the next subsection.

2.5 Combining results of the two procedures

If $H_{i,0}$ is rejected by the first procedure and non-accepted by the second procedure, it is determined as "rejected"; if $H_{i,0}$ is accepted by the second procedure and non-rejected by the first procedure, it is determined as "accepted"; if $H_{i,0}$ is non-rejected and non-accepted, it is determined as "undecided". Note that our method precludes the possibility that $H_{i,0}$ is both rejected and accepted, as this would correspond to simultaneously concluding that both $p_i^* < \tau_\ell$ and $\tau_u < p_i^*$ hold simultaneously, which is not possible since $\tau_\ell < \tau_u$. Finally, the overall MCER among the decisions that are either "rejected" or "accepted" (excluding those "undecided") is controlled at the level that is the sum of the type-I and type-II MCER. All components of MERIT and their relationships are depicted in Figure 2.

2.6 Modifying the GH method for a fixed MC sample size

Because the GH method is fully sequential while MERIT uses a pre-determined MC sample size, it is difficult to compare them directly. For this reason, we created a modified GH method with a fixed stopping rule. We also replaced each two-sided Robbins-Lai interval in GH by two one-sided Wilson intervals [18] because the Robbins-Lai interval cannot be one-sided and because the Wilson interval is more efficient [19]. In Supplemental Materials S3, we illustrate, using simulated data, that the two-sided Wilson interval (which is the intersection of the two one-sided Wilson intervals) is always narrower than the two-sided Robbins-Lai interval for $0 \leq p \leq 0.2$, the interesting range of p-values. To complete our modification of GH, we applied the BH procedure to the upper limits of the Wilson intervals to obtain rejected hypotheses and to the lower limits to obtain accepted hypotheses as in the original GH procedure. Similar

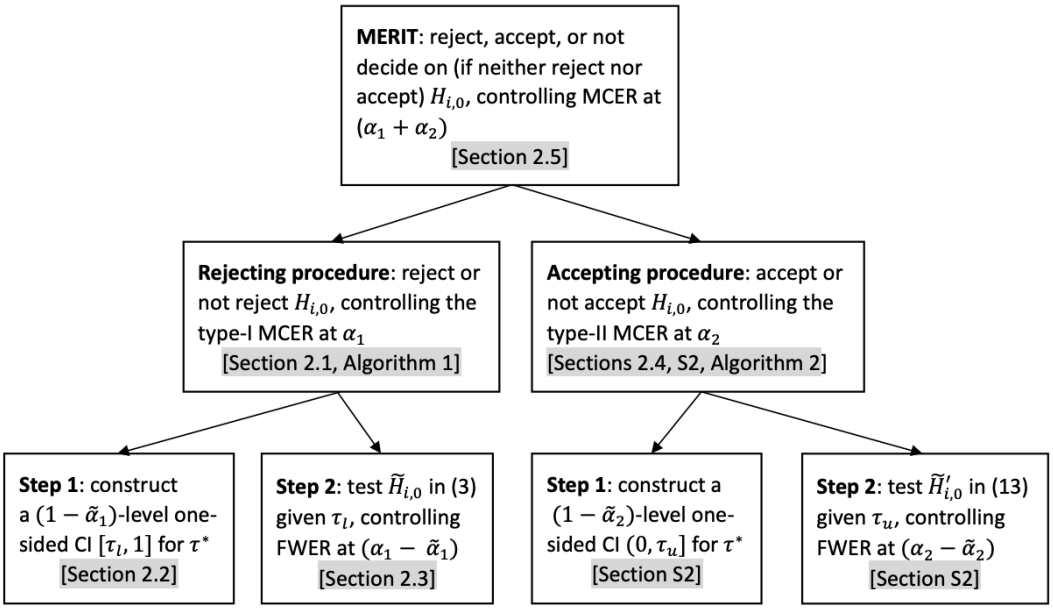

Figure 2: Components of MERIT.

arguments to those found in [1, 2] can be used to prove our modified GH procedure controls the type-I and type-II MCER.

3. Simulation studies

3.1 Setup

We conducted extensive simulation studies to evaluate the performance of our method. We evaluated the two procedures of our method (one rejecting hypotheses and one accepting hypotheses). We also compared MERIT to our modified GH method. In addition, we evaluated the naive approach that applies the BH procedure to the MC p-values, and we evaluated the type-I and type-II MCER separately. We refer to our method, the modified GH method, and the naive method as MERIT, GH, and NAIVE, respectively.

We considered $m = 100$, 1000, and 5000 tests. We assumed that 80% of m tests are under the null and the remaining tests are under the alternative; we sampled the p-values for tests

under the null independently from the uniform distribution $\mathrm{U}[0,1]$, and sampled the p-values for tests under the alternative independently from the Gaussian right-tailed probability model: $p_i^* = 1 - \Phi(Z_i)$, where $Z_i \sim \mathrm{N}(\beta, 1)$ and Φ is the standard normal cumulative distribution function. We set β to 1.5, 2 and 2.5; a larger value of β implies higher sensitivity to reject the alternative hypotheses. For each pair of values of m and β, we sampled 100 different sets of ideal p-values $(p_1^*, p_2^*, \ldots, p_m^*)$. Instead of generating actual data and calculating test statistics, we directly simulated the matrix I by independently drawing Bernoulli samples with the "success" rate p_i^*. The MC sample size n took a wide range of values, i.e., between 5,000 and 1,000,000. The nominal type-I and type-II MCER α_1 and α_2 were both set to 10%; the nominal FDR ϕ used to define the BH threshold was set to 10%.

For evaluating the rejecting procedure in each method, we use two metrics, the empirical type-I MCER and sensitivity, the latter of which is

$$\text{Sensitivity} = \frac{\sum_{i=1}^m \mathbb{I}(\widehat{D}_i = \text{rejected}, D_i^* = \text{rejected})}{1 \vee \sum_{i=1}^m \mathbb{I}(D_i^* = \text{rejected})}.$$

For evaluating the accepting procedure in each method, we also use two metrics, the empirical type-II MCER and specificity, the latter of which is

$$\text{Specificity} = \frac{\sum_{i=1}^m \mathbb{I}(\widehat{D}_i = \text{accepted}, D_i^* = \text{accepted})}{1 \vee \sum_{i=1}^m \mathbb{I}(D_i^* = \text{accepted})}.$$

Each result of these metrics was based on 1,000 replicates, which correspond to repeatedly sampled matrix I given a set of ideal p-values and the MC sample size n.

3.2 Simulation results

Figure 3 shows the type-I MCER and sensitivity for the three methods, MERIT, GH, and NAIVE, for testing $m = 1000$ hypotheses. Each box displays the variation of results of a method over the 100 sets of ideal p-values: the top and bottom lines represent the 75% and 25% quantiles and the middle bar indicates the median. Each point in each box represents results from 1,000 replicates. We can see that, for any combination of n and β, both MERIT

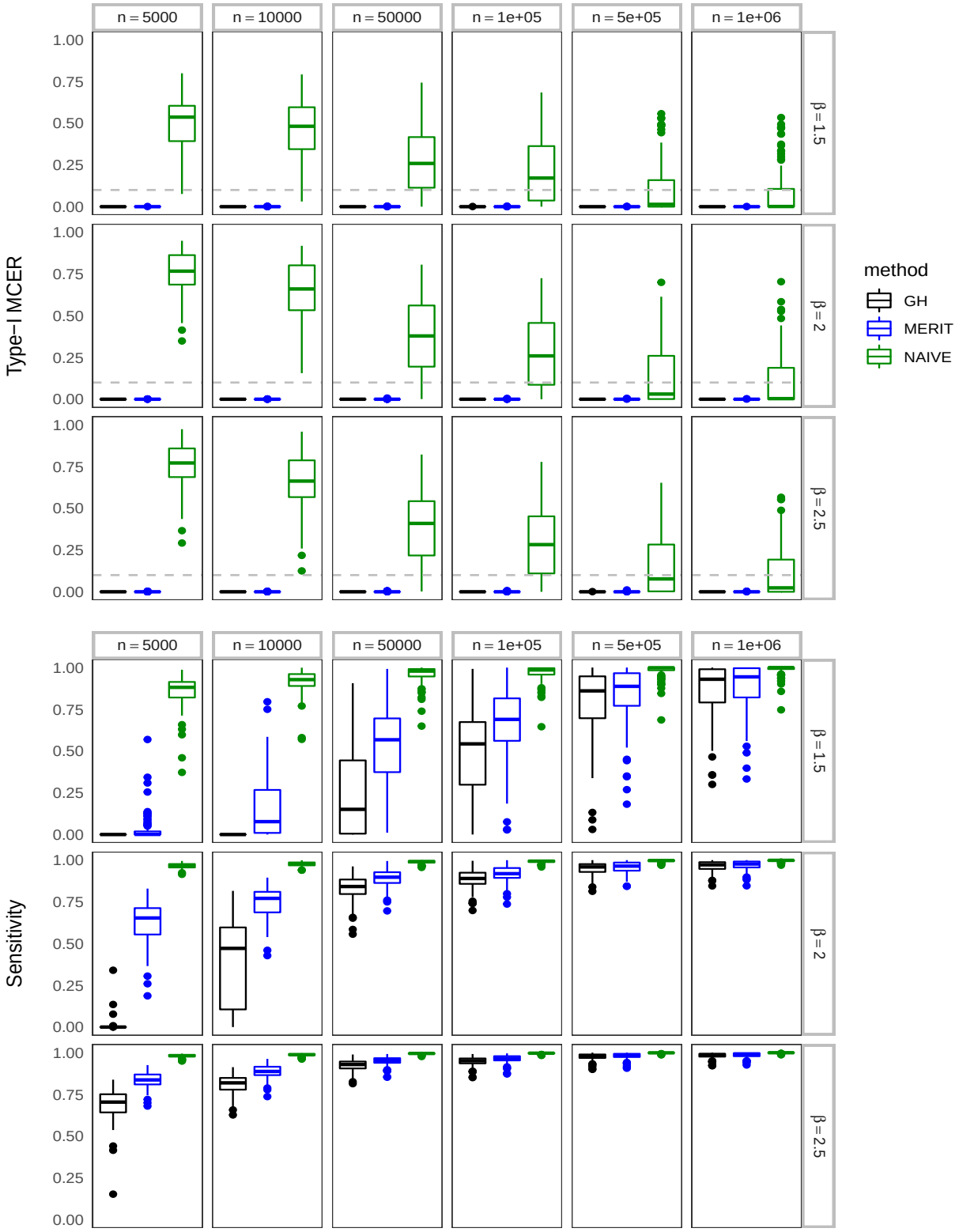

Figure 3: The empirical type-I MCER (upper panel) and sensitivity (lower panel) for $m = 1000$ tests. The gray dashed lines represent the nominal level 10%. Each point represents a different set of ideal p-values; results for each set of p-values are based on 1,000 MERIT runs.

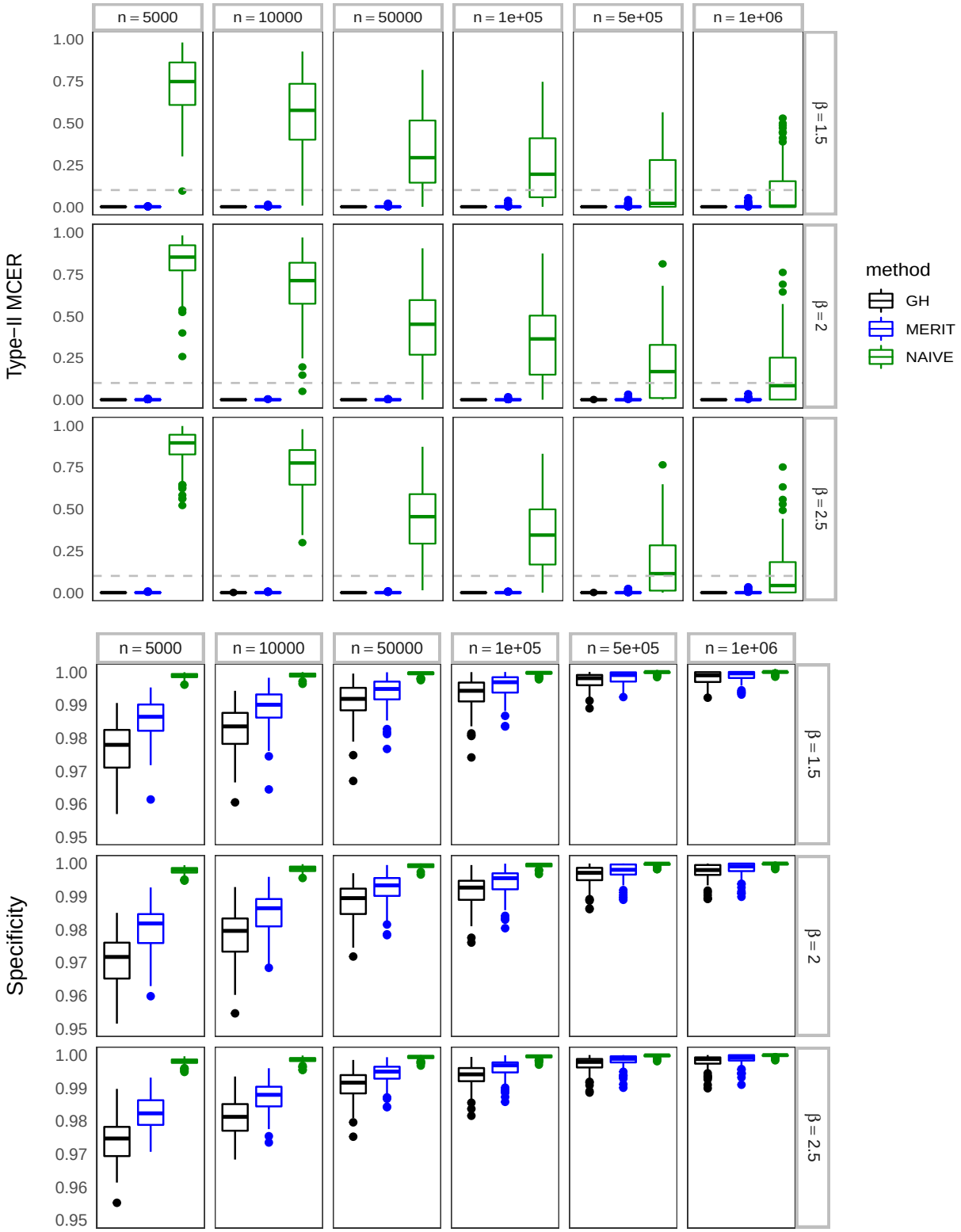

Figure 4: The empirical type-II MCER (upper panel) and specificity (lower panel) for $m = 1000$ tests.

and GH controlled the type-I MCER below the nominal level, while NAIVE did not. MERIT always had higher sensitivity than GH, which is more pronounced when n is not very large. In fact, MERIT rejected more hypotheses than GH for every set of ideal p-values (results not shown). As expected, the type-I MCER of NAIVE was highly inflated when n was low; although the error rate decreased as n was increased, it was still above the nominal level for many sets of ideal p-values even when n was as large as one million. One reason that the sensitivity of NAIVE was so high is because it did not allow "undecided" tests, so that every test was categorized either as "rejected" or "accepted". The results of type-II MCER and specificity are shown in Figure 4, which displays similar patterns as Figure 3. Note that the specificity remained relatively unchanged for different values of β because specificity pertains to null hypotheses only.

The results for $m = 100$ are shown in Figures S3–S4. With this small number of tests, NAIVE was more likely to control the type-I and type-II MCER because it was less likely to have ideal p-values near the threshold of significance. For the same reason, MERIT had higher sensitivity and specificity than in the $m = 1000$ case (for the same values of n and β). Again, MERIT and GH both controlled the type-I and type-II MCER and MERIT always had higher sensitivity and sensitivity than GH. Note that this behavior with changing m is because our ideal p-values were assumed to be fairly uniformly spread. If we had assumed a worst-case scenario in which most, or all, ideal p-values were at or near the threshold, we would not expect to see this improved behavior when m is decreased.

The results for $m = 5000$ are shown in Figures S5–S6. This scale of testing is more commonly seen in modern biological and biomedical studies of omics. Indeed, the prostate cancer data that we will apply our method to has 6033 tests corresponding to 6033 genes. In this case, NAIVE had highly inflated type-I and type-II MCER even with a million MC replicates, implying that the naive results had very poor reproducibility. Again, MERIT and GH both controlled the type-I and type-II MCER and MERIT always had higher sensitivity and sensitivity than GH. Interestingly, while the sensitivity of GH reduced from $m = 1000$

to $m = 5000$, the sensitivity of MERIT stayed quite robust, which suggests an increasing advantage of MERIT over GH for very large numbers of tests.

4. Application to the prostate cancer study

We applied MERIT, GH, and NAIVE to detect differentially expressed genes in a prostate cancer study [20]. The data contains microarray gene expressions for 6,033 genes and 102 subjects comprised of 52 prostate cancer patients and 50 healthy controls. We calculated the t-statistic (assuming equal variance) for each gene based on the observed data and n MC replicates (by permuting the case-control labels), from which we obtained the matrix I. As in the simulation studies, we considered a wide range of values for n and we set the nominal type-I and type-II MCER to 10% and the nominal FDR to 10%. For evaluation of reproducibility, we obtained the results for 10 different runs with different seeds for generating MC replicates.

The results are shown in Figure 5. In all cases, MERIT yielded more rejected tests (when there are non-zero rejections) and more accepted tests than GH; the advantage of MERIT is more clear when n is between 50,000 and 500,000. Interestingly, the relative numbers of rejections and acceptances of the three methods seem to match well with the sensitivity and specificity in the simulation study with $m = 5000$ and $\beta = 1.5$. To interpret the results in more detail, we focus on the first run of $n = 100,000$ MC replicates. MERIT detected 51 genes as differentially expressed and 5961 genes as non-differentially expressed, and left 21 gene "undecided"; in the same run, GH detected 0 gene as differentially expressed and 5954 as non-differentially expressed, and left 79 genes "undecided". Among the genes detected as differentially expressed by MERIT (or GH), the chance is less than 10% that there exists a gene that would be determined as non-differentially expressed if we obtained an infinite number of MC replicates; we have a similar guarantee for the genes determined as non-differentially expressed.

Because MERIT includes a bootstrap step, MERIT will require more run time than NAIVE. For the prostate cancer data, MERIT required ∼20 minutes (not including the gen-

eration of MC replicates and the calculation of t statistic) on a single core for one run of $n = 1,000,000$. Because the bootstrap procedure in Step 1 is the most computationally intensive part in our algorithm, the run time can be significantly reduced by paralleling the computation of bootstrap replicates to multiple cores. For example, one run of MERIT for the prostate cancer data with $n = 1,000,000$ required only ∼2 minutes on 10 cores.

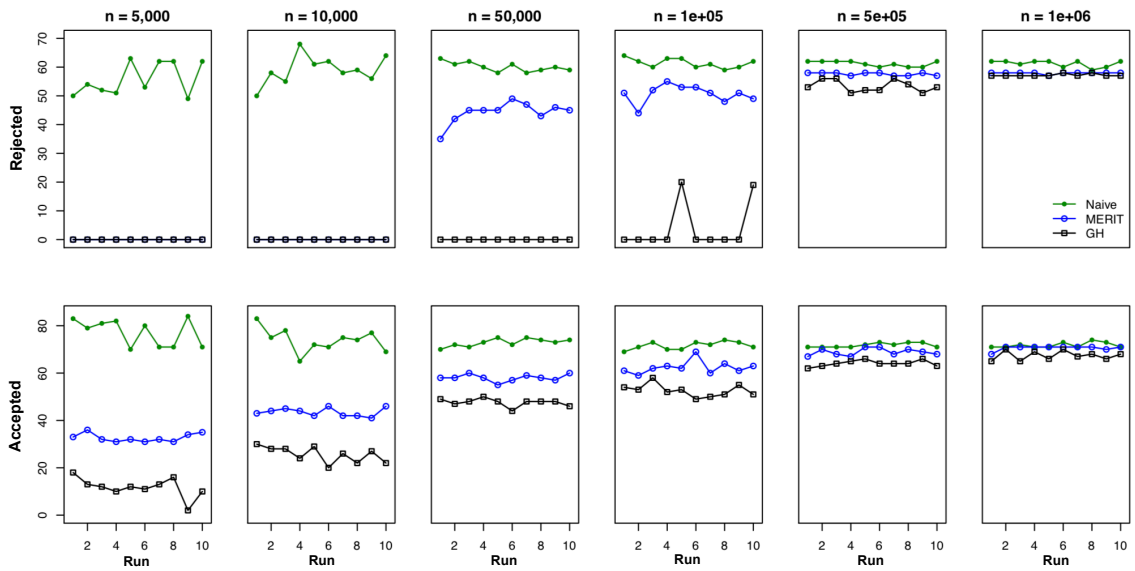

Figure 5: Results from analysis of the prostate cancer data. The upper panel shows the number of rejected hypotheses and the lower panel shows the last two digits (the first two digits are 59; for example, the last two digits 35 correspond to the complete number 5935) of the number of accepted hypotheses. For $n = 5,000$ and $10,000$, both MERIT and GH rejected no hypotheses.

5. Discussion

We have developed a method that can be coupled with any MC test method that has a fixed stopping criterion to make decisions on multiple hypotheses by controlling the family-wise MCER. We have implemented our method in the R package MERIT available on GitHub at `https://github.com/yli1992/MERIT`. Strictly speaking, our method is the only one that tackles this problem for MC hypothesis testing with a fixed stopping criterion. Although the

GH method can be modified for this problem, we have demonstrated that our method has higher sensitivity and specificity, especially when the MC sample size is only modestly large.

Following GH, we have defined MCER to only consider errors that correspond to incorrect decisions (i.e., rejections of the null hypothesis when ideal p-values would accept the null hypothesis, and *vice versa*) excluding hypotheses that are "undecided". One consequence of this choice is that the list of rejected hypotheses obtained using MERIT may vary from run to run even though MCER is controlled. Note however that, within the constraints of the MCER rates, this variability will be limited to switches between "rejected" and "undecided" hypotheses or between "accepted" and "undecided" hypotheses. Unlike MERIT, variability in the list of rejected hypotheses for NAIVE represents the more serious errors of switches between "rejected" and "accepted" hypotheses.

It would be interesting and useful to develop a way to quantify, for each hypothesis, how likely a switch between "rejected" and "undecided" is, in a single application of MERIT (switches between "accepted" and "undecided" are typically of lesser interest to investigators). We hope to consider this in future work. An alternative would be to define an MCER that includes switches between "rejected" and "undecided", although control of MCER under this definition may not be achievable if too many ideal p-values are close to the p-value threshold for rejection. In fact, the number of ideal p-values near this threshold also controls the number of "undecided" hypotheses in MERIT, and the distance between the MC p-value and this threshold presumably controls the likelihood of a switch between "rejected" and "undecided". In our experience, when there is a large number of "undecided" hypotheses, changing the target FDR to a value where there are relatively few empirical p-values can sometimes reduce the number of "undecided" hypotheses.

Here we have only considered only MC schemes that have a fixed stopping criterion. We feel this is reasonable, as our impression is that most MC hypothesis testing reported in the biological sciences used a fixed MC sample size. This also enables us to achieve higher efficiency, as it allows for application of a fairly sophisticated correction for testing multiplicity

to be applied only once, after all tests have been completed. For fairness, we have also modified the original, sequential, GH approach to allow for a more efficient approach when a fixed stopping criterion is used. Even with this boost, we showed that MERIT outperformed GH unless the MC sample size was 1,000,000 or greater.

References

1. Gandy A, Hahn G. MMCTest-a safe algorithm for implementing multiple Monte Carlo tests. Scandinavian Journal of Statistics. 2014;41(4):1083–1101.
2. Gandy A, Hahn G. A framework for Monte Carlo based multiple testing. Scandinavian Journal of Statistics. 2016;43(4):1046–1063.
3. Gandy A, Hahn G. QuickMMCTest: quick multiple Monte Carlo testing. Statistics and Computing. 2017;27(3):823–832.
4. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the royal statistical society Series B (Methodological). 1995;p. 289–300.
5. Bonferroni C. Teoria statistica delle classi e calcolo delle probabilita. Pubblicazioni del R Istituto Superiore di Scienze Economiche e Commericiali di Firenze. 1936;8:3–62.
6. Holm S. A simple sequentially rejective multiple test procedure. Scandinavian journal of statistics. 1979;p. 65–70.
7. Davison A, Hinkley D. Bootstrap Methods and Their Application, Cambridge Univ. Press, Cambridge. 1997;.
8. Manly BF. Randomization, bootstrap and Monte Carlo methods in biology. vol. 70. CRC press; 2006.
9. Phipson B, Smyth GK. Permutation P-values should never be zero: calculating exact P-values when permutations are randomly drawn. Statistical applications in genetics and molecular biology. 2010;9(1).

10. Sandve GK, Ferkingstad E, Nygård S. Sequential Monte Carlo multiple testing. Bioinformatics. 2011;27(23):3235–3241.

11. Darling D, Robbins H. Some further remarks on inequalities for sample sums. Proceedings of the National Academy of Sciences of the United States of America. 1968;60(4):1175.

12. Lai TL, et al. On confidence sequences. The Annals of Statistics. 1976;4(2):265–280.

13. Coe PR, Tamhane AC. Exact repeated confidence intervals for Bernoulli parameters in a group sequential clinical trial. Controlled clinical trials. 1993;14(1):19–29.

14. Romano JP, Wolf M. Exact and approximate stepdown methods for multiple hypothesis testing. Journal of the American Statistical Association. 2005;100(469):94–108.

15. Romano JP, Wolf M. Multiple testing of one-sided hypotheses: combining Bonferroni and the bootstrap. In: International Conference of the Thailand Econometrics Society. Springer; 2018. p. 78–94.

16. Hansen PR. A test for superior predictive ability. Journal of Business & Economic Statistics. 2005;23(4):365–380.

17. Storey JD, Taylor JE, Siegmund D. Strong control, conservative point estimation and simultaneous conservative consistency of false discovery rates: a unified approach. Journal of the Royal Statistical Society: Series B (Statistical Methodology). 2004;66(1):187–205.

18. Wilson EB. Probable inference, the law of succession, and statistical inference. Journal of the American Statistical Association. 1927;22(158):209–212.

19. Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. Statistical science. 2001;p. 101–117.

20. Singh D, Febbo PG, Ross K, Jackson DG, Manola J, Ladd C, et al. Gene expression correlates of clinical prostate cancer behavior. Cancer cell. 2002;1(2):203–209.

Supplementary Materials

S1. Comparing different schemes of splitting the nominal type-I MCER between the two sub-problems

We used simulations to compare different schemes for splitting the nominal type-I MCER in terms of the sensitivity of rejecting alternative hypotheses. Here, the nominal type-I MCER (α_1) was set to 10%. We considered 5 different schemes, 1:9, 3:7, 5:5, 7:3, and 9:1, where, for example, 1:9 means that the error rate ($\widetilde{\alpha}_1$) assigned to the first sub-problem was 1% and the error rate ($\alpha_1 - \widetilde{\alpha}_1$) assigned to the second sub-problem was 9%. We considered $m = 1000$ tests and drew 100 sets of ideal p-values. All results in Figure S1 suggest that the 5:5 scheme is a robust choice.

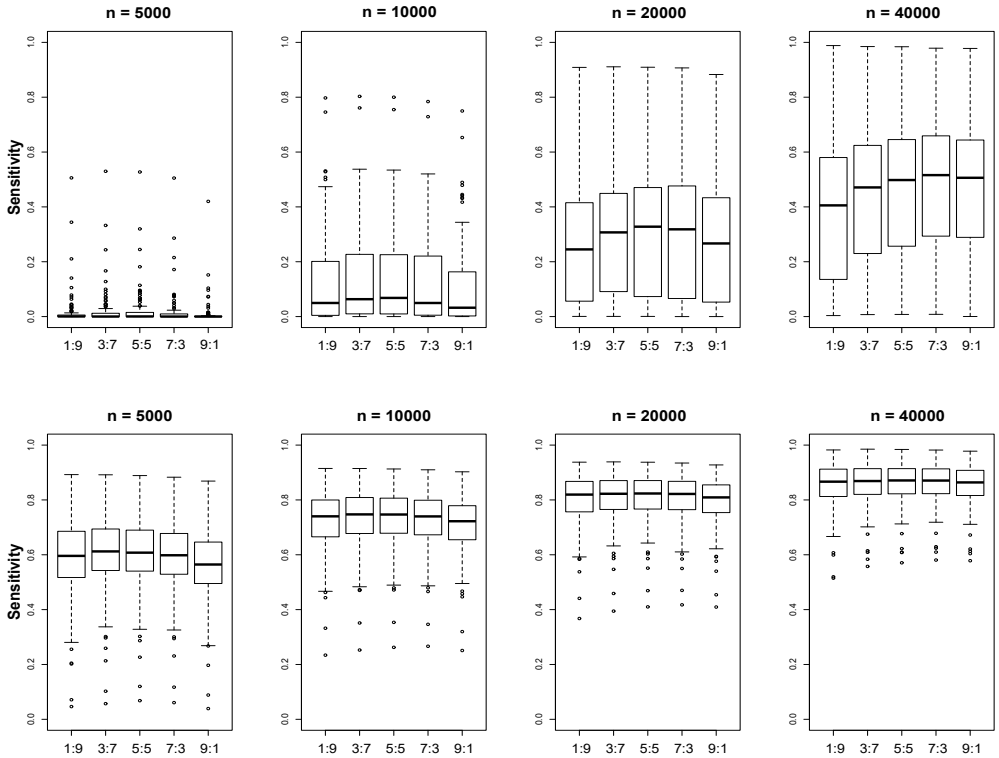

Figure S1: The empirical sensitivity of MERIT using different schemes for splitting the nominal type-I MCER. The upper and lower panels are based on $\beta = 1.5$ and 2.0, respectively.

S2. A procedure that accepts original hypotheses while controlling the type-II MCER

We consider the following hypotheses that "flip" the hypotheses in (2):

$$H_{i,0}^{*\prime} : p_i^* \leq \tau^* \qquad \text{vs.} \qquad H_{i,1}^{*\prime} : p_i^* > \tau^*, \qquad i = 1, 2, \ldots, m. \tag{11}$$

Note that a rejection of $H_{i,0}^{*\prime}$ corresponds to an acceptance of the original hypothesis $H_{i,0}$. Recall that a type-II MC error occurs when $H_{i,0}^{*\prime}$ is true (hence $D_i^* =$ rejected) but rejected using the MC p-value (hence $\widehat{D}_i =$ accepted). Then, a test procedure based on MC p-values that controls the FWER for testing $H_{i,0}^{*\prime}$ at α_2 would control the type-II MCER at α_2. Here, we develop a two-step procedure following the same idea as in Sections 2.1–2.3. In the first step, we construct an at least $(1 - \widetilde{\alpha}_2)$-level one-sided CI $(0, \tau_u]$ for τ^*, where $0 < \widetilde{\alpha}_2 < \alpha_2$. In the second step, we consider the revised hypotheses, treating τ_u as fixed:

$$\widetilde{H}_{i,0}' : p_i^* \leq \tau_u \qquad \text{vs.} \qquad \widetilde{H}_{i,1}' : p_i^* > \tau_u, \qquad i = 1, 2, \ldots, m. \tag{12}$$

We develop a test procedure that tests (12) while controlling the FWER at level $(\alpha_2 - \widetilde{\alpha}_2)$. Then, by the relationship that

$$\begin{aligned}
\{V^{\mathrm{II}} \geq 1\} &= \{\tau_u < \tau^*, V^{\mathrm{II}} \geq 1\} \cup \{\tau_u \geq \tau^*, V^{\mathrm{II}} \geq 1\} \\
&\subset \{\tau_u < \tau^*\} \cup \{\tau_u \geq \tau^*, \text{ at least one } H_{i,0}^{*\prime} \text{ is true but rejected}\} \\
&\subset \{\tau_u < \tau^*\} \cup \{\tau_u \geq \tau^*, \text{ at least one } \widetilde{H}_{i,0}' \text{ is true but rejected}\},
\end{aligned}$$

the type-II MCER $\Pr(V^{\mathrm{II}} \geq 1)$ is always bounded by the sum of $\Pr(\tau_u < \tau^*)$ and the FWER in testing (12), which is α_2. As the default choice, we choose $\widetilde{\alpha}_2 = \alpha_2/2$.

Step 1: construct a $(1 - \widetilde{\alpha}_2)$-level one-sided CI $(0, \tau_u]$ for τ^*

We find τ_u from a set of p-values that are "upper limits" for the ideal p-values. To this aim, we consider the following sets of p-values, with each set indexed by a positive continuous value c:

$$p_{-c,i} = \frac{X_i + 1 - c\sqrt{X_i + 1}}{n + 1 - c\sqrt{X_i + 1}}. \tag{13}$$

Note that we impose the restriction that $c < \sqrt{n+1}$; otherwise $n+1-c\sqrt{X_i+1}$ may become 0 or even negative and then $p_{-c,i}$ is not well-defined. However, negative values of the numerator *are* allowed, as illustrated in Figure 1 where the curve $F_{-c}(t)$ has non-zero value at $t = 0$. As c goes to 0, $p_{-c,i}$ converges to p_i^*. When c is sufficiently large, $p_{-c,i}$ is asymptotically smaller than p_i^*, as least for small p_i^*s.

Let $F_{-c}(t)$ be the EDF of $(p_{-c,1}, \ldots, p_{-c,m})$ and τ_{-c} be the BH cutoff. If $F_{-c}(t)$ is always no less than $F^*(t)$ over $(0, \phi]$, as shown in Figure 1 (left), we must have $\tau_{-c} \geq \tau^*$. It follows that

$$\Pr(\tau_{-c} \geq \tau^*) \geq \Pr\left(F^* \prec F_{-c}\right).$$

To construct a $(1-\widetilde{\alpha}_2)$-level one-sided CI $(0, \tau_u]$ for τ^*, we are interested in c that satisfies

$$\Pr\left(F^* \prec F_{-c}\right) \geq 1 - \widetilde{\alpha}_2. \tag{14}$$

The probability on the left of (14) increases as c increases (because the decrease of $p_{-c,i}$ leads to the increase of $F_{-c}(t)$ at a given t). Thus we wish to find the smallest c that satisfies (14), denoted by c_u. Finally, we set the upper limit τ_u to τ_{c_u}.

We obtain c_u using the same bootstrap replicates as in Section 2.2. Define the bootstrap p-values indexed by c as

$$p_{-c,i}^{(b)} = \frac{X_i^{(b)} + 1 - c\sqrt{X_i^{(b)}+1}}{n+1-c\sqrt{X_i^{(b)}+1}}, \qquad i = 1, 2, \ldots, m.$$

Let $F_{-c}^{(b)}$ be the EDF for $(p_{-c,1}^{(b)}, \ldots, p_{-c,m}^{(b)})$. We wish to find c_u to be the smallest c that satisfies

$$B^{-1} \sum_{b=1}^{B} \mathbb{I}\left(\widehat{F} \prec F_{-c}^{(b)}\right) \geq 1 - \widetilde{\alpha}_2, \tag{15}$$

which is the empirical version of (14). To this aim, we find, for every $b = 1, \ldots, B$, the smallest c that guarantees $\widehat{F} \prec F_{-c}^{(b)}$, denoted by $c_u^{(b)}$, and then set c_u to be the $(1-\widetilde{\alpha}_2)$th quantile of $(c_u^{(1)}, c_u^{(2)}, \ldots, c_u^{(B)})$. The procedure here is summarized in Step 1 of Algorithm 2.

Step 2: test hypotheses in (12) given τ_u while controlling the FWER at $(\alpha_2 - \widetilde{\alpha}_2)$

Let $\widetilde{H}'_{(1),0}$, $\widetilde{H}'_{(2),0}$, ..., $\widetilde{H}'_{(m),0}$ be the ordered hypotheses (12) that correspond to the ordered observed test statistics $x_{(1)}$, $x_{(2)}$, ..., $x_{(m)}$. We start by testing the global null $\widetilde{H}'_{(1),0} \cap \widetilde{H}'_{(2),0} \cap \ldots \cap \widetilde{H}'_{(m),0}$, which means that all p_i^* are less than τ_u. We use $x_{(m)}$ as the test statistic for this test. Following Romano and Wolf, we propose to calculate the p-value under the global null:

$$\Pr\left(\max_{1\le j\le m} X_j \ge x_{(m)}\right),$$

where each X_j is a binomial random variable with n trials and "success" rate θ'_j that is under the null. Using the Bonferroni inequality, we obtain an upper bound of the p-value to be

$$\sum_{j=1}^{m} F'_{\text{Bin}}(x_{(m)}; n, \theta'_j),$$

where $F'_{\text{Bin}}(x; n, \theta)$ denotes $\Pr(X \ge x)$ for $X \sim \text{Bin}(n, \theta)$. Using Hansen's adjustments for null hypotheses that are "deep in the null", we choose θ'_j to be

$$\theta'_j = \begin{cases} \tau_u, & \text{if } \sqrt{n}\,(x_j/n - \tau_u)\,/\sqrt{\tau_u(1-\tau_u)} \ge -\sqrt{2\log\log n}, \\ x_j/n, & \text{otherwise.} \end{cases}$$

Using this θ'_j, if

$$\sum_{j=1}^{m} F'_{\text{Bin}}(x_{(m)}; n, \theta'_j) \le \alpha_2 - \widetilde{\alpha}_2,$$

we reject $\widetilde{H}'_{(m),0}$ and move to the next joint null $\widetilde{H}'_{(1),0} \cap \ldots \cap \widetilde{H}'_{(m-1),0}$ that excludes $\widetilde{H}'_{(m),0}$; otherwise, we stop and declare that none of the hypotheses should be rejected. In general, for testing the joint null $\widetilde{H}'_{(1),0} \cap \ldots \cap \widetilde{H}'_{(i),0}$ for any i, we use $x_{(i)}$ as the test statistic. If

$$\sum_{j=1}^{i} F'_{\text{Bin}}(x_{(i)}; n, \theta'_j) \le \alpha_2 - \widetilde{\alpha}_2, \tag{16}$$

we reject $\widetilde{H}'_{(i),0}$ and move to the next joint null that excludes $\widetilde{H}'_{(i),0}$; otherwise, we stop and accept the remaining hypotheses. This step-wise procedure asymptotically controls the FWER in testing (12) at $(\alpha_2 - \widetilde{\alpha}_2)$. Whenever $\widetilde{H}'_{(i),0}$ is rejected, the corresponding original hypothesis $H_{(i),0}$ is accepted. This procedure is summarized in Step 2 of Algorithm 2.

Algorithm 2 The procedure that accepts original hypotheses while controlling type-II MCER

Input: matrix I, nominal FDR ϕ, nominal type-II MCER α_2

Step 1: construct a $(1-\widetilde{\alpha}_2)$-level one-sided CI $[0, \tau_u]$ for τ^*.

Calculate $(X_1, X_2, \ldots, X_m)$, $(\widehat{p}_1, \widehat{p}_2, \ldots, \widehat{p}_m)$, and then $\widehat{F}$.

For each bootstrap replicate $b = 1, 2, \ldots, B$,

Sample n columns from I with replacement to form $I^{(b)}$.

Calculate $(X_1^{(b)}, X_2^{(b)}, \ldots, X_m^{(b)})$, $(p_{-c,1}^{(b)}, p_{-c,2}^{(b)}, \ldots, p_{-c,m}^{(b)})$, and then $F_{-c}^{(b)}$.

Find $c_u^{(b)}$ to be the smallest c that guarantees $\widehat{F} \prec F_{-c}^{(b)}$.

Find c_u, the smallest c that satisfies (14), to be the $(1-\widetilde{\alpha}_2)$ quantile of $(c_u^{(1)}, c_u^{(2)}, \ldots, c_u^{(B)})$.

Find the upper limit τ_u to be the BH cutoff of p-values in (13) indexed by c_u.

Step 2: Test hypotheses in (12) given τ_u while controlling the FWER at $(\alpha_2 - \widetilde{\alpha}_2)$.

Set $i = m$.

While $i \geq 1$,

If (16) does not hold, accept all remaining hypotheses $\widetilde{H}'_{(i),0}$s and exit the loop.

Otherwise, reject $\widetilde{H}'_{(i),0}$, update $i = i - 1$.

Whenever $\widetilde{H}'_{(i),0}$ is rejected, $H_{(i),0}$ is accepted.

Output: a decision for every hypothesis $H_{i,0}$ between "accepted" and "non-accepted".

S3. Comparing the Robbins-Lai and Wilson intervals

We used simulations to compare the width of the two-sided Robbins-Lai interval and the two-sided Wilson interval. For each $p \sim [0, 0.2]$ (as large values of p are irrelevant because they will not lead to rejection of hypotheses for any reasonable error rate), we simulated the total number of exceedances $X \sim \text{Bin}(n, p)$, where $n = 100,000$. Then we calculated the width of the two intervals and obtained the average width over 1000 replicates. Finally, we formed the ratio of the average widths (Robbins-Lai:Wilson) and displayed it in Figure S2. We can see that the ratio is always above 1 (between 1.6 and 2).

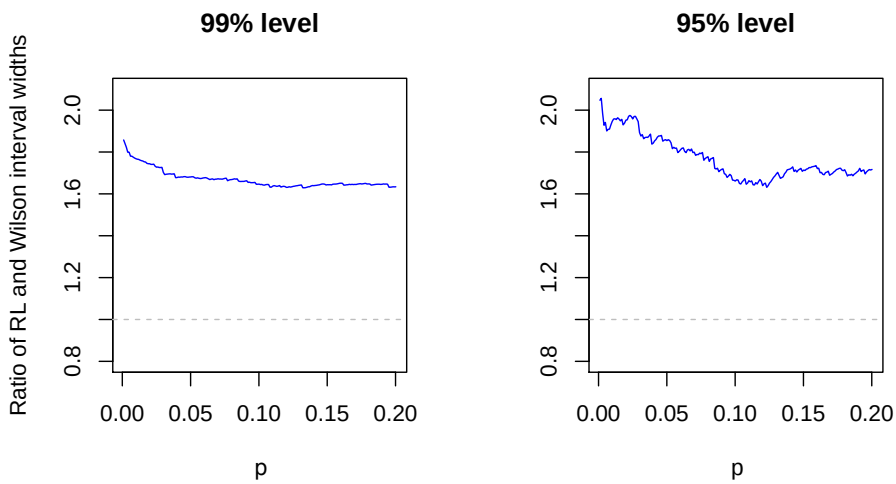

Figure S2: The ratio of the widths of the Robbins-Lai and Wilson intervals. The left and right panels pertain to 99%- and 95%-level intervals, respectively.

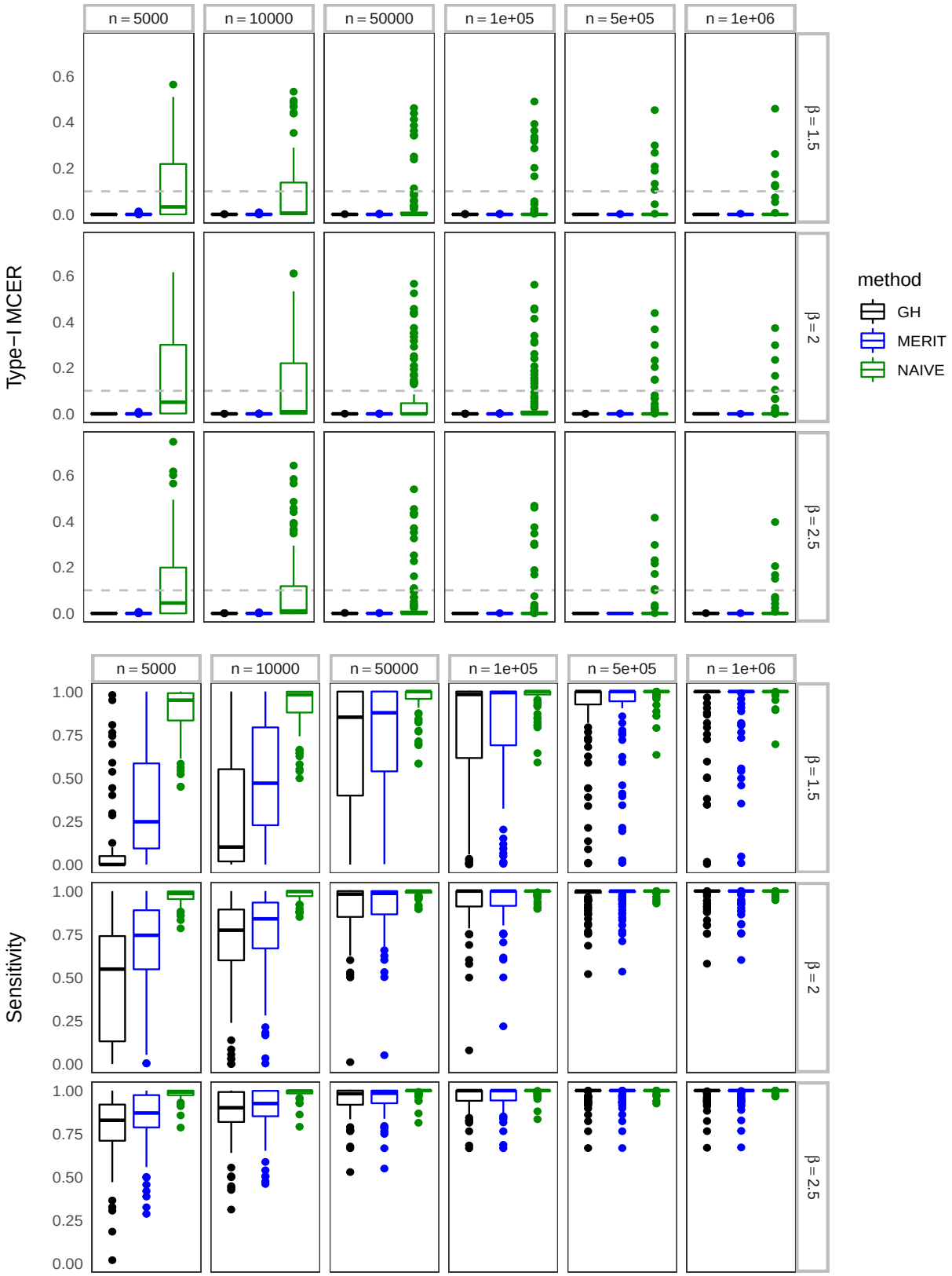

Figure S3: The empirical type-I MCER (upper panel) and sensitivity (lower panel) for $m = 100$ tests.

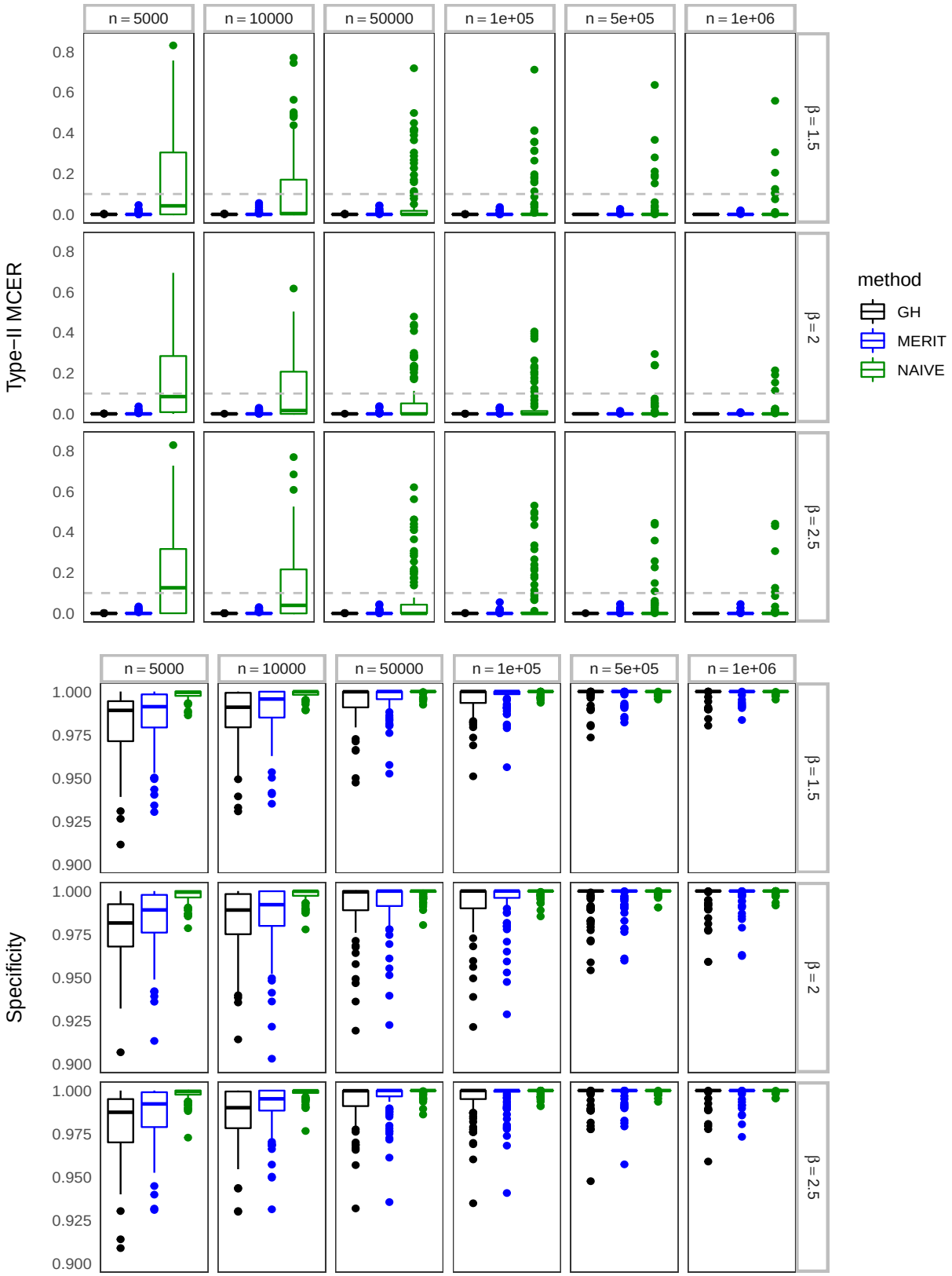

Figure S4: The empirical type-II MCER (upper panel) and specificity (lower panel) for $m = 100$ tests.

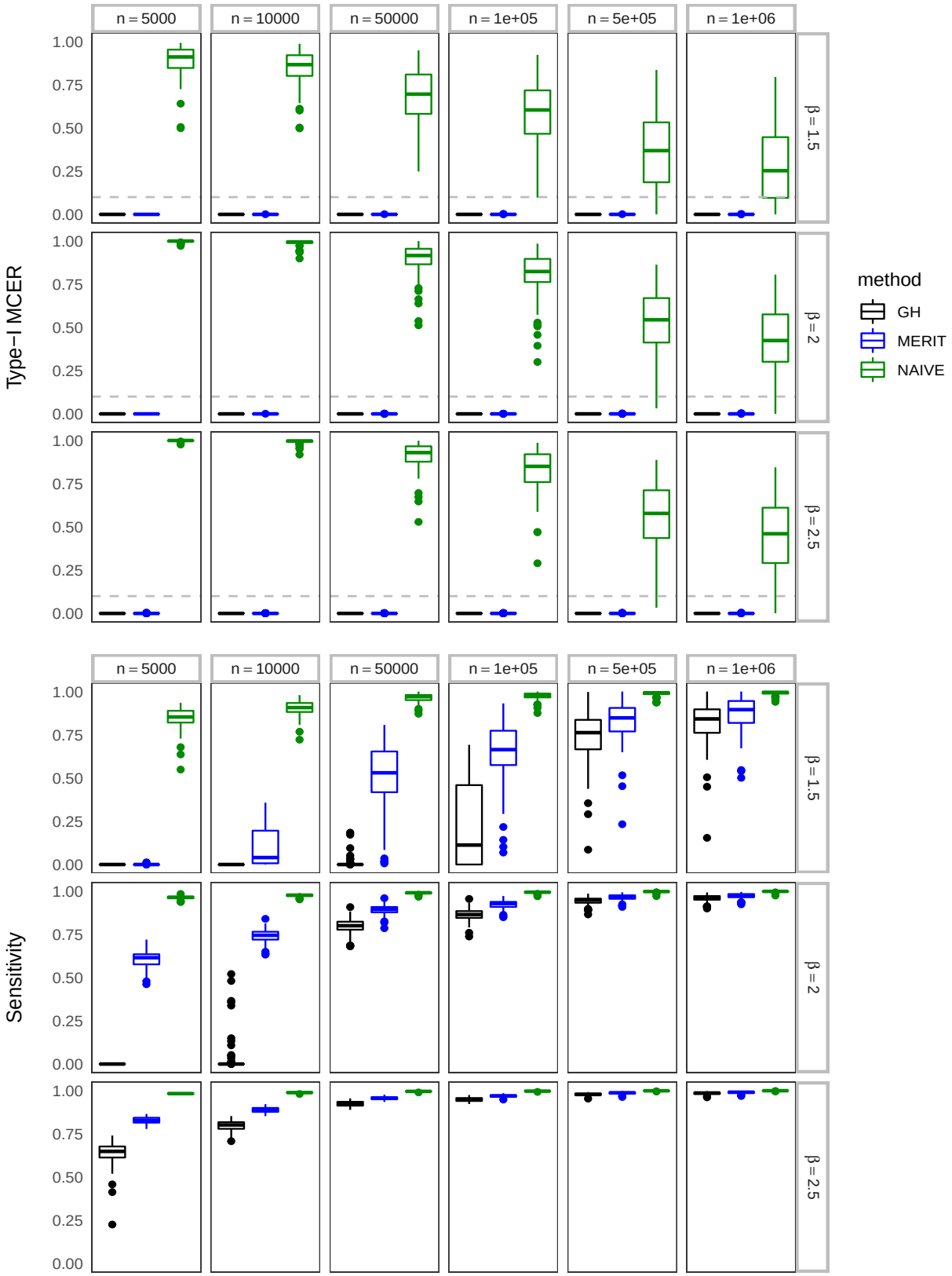

Figure S5: The empirical type-I MCER (upper panel) and sensitivity (lower panel) for $m = 5000$ tests.

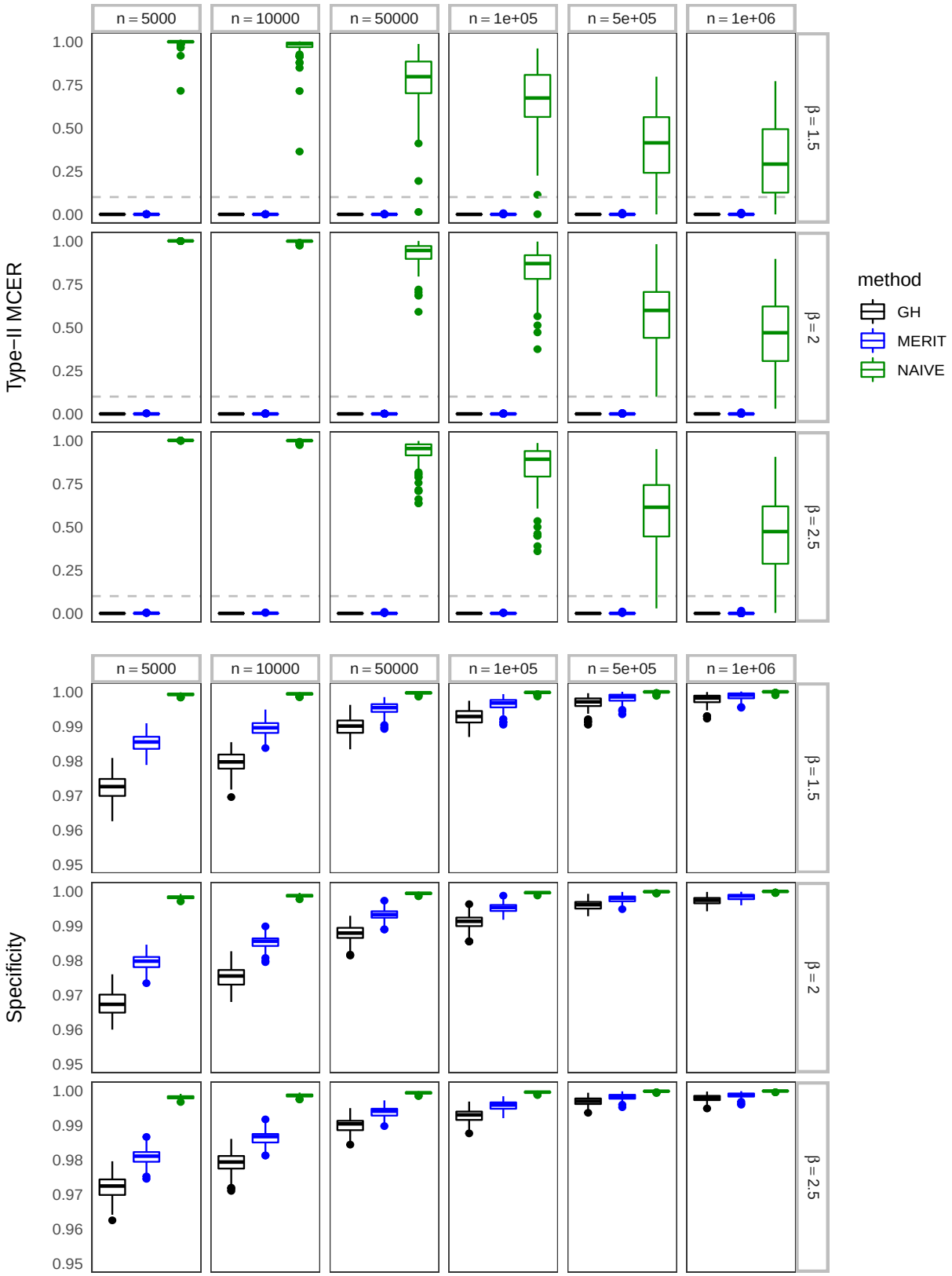

Figure S6: The empirical type-II MCER (upper panel) and specificity (lower panel) for $m = 5000$ tests.