Average Power and $\lambda$-power in Multiple Testing Scenarios when the Benjamini-Hochberg False Discovery Rate Procedure is Used*

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August 15, 2018

Abstract

We discuss several approaches to defining power in studies designed around the Benjamini-Hochberg (BH) false discovery rate (FDR) procedure. We focus primarily on the average power and the $\lambda$-power, which are the expected true positive fraction and the probability that the true positive fraction exceeds $\lambda$, respectively. We prove results concerning strong consistency and asymptotic normality for the positive call fraction (PCF), the true positive fraction (TPF) and false discovery fraction (FDF). Convergence of their corresponding expected values, including a convergence result for the average power, follow as corollaries. After reviewing what is known about convergence in distribution of the errors of the plugin procedure, Genovese and Wasserman (2004), we prove central limit theorems for fully empirical versions of the PCF, TPF, and FDF, using a result for stopped stochastic processes. The central limit theorem (CLT) for the TPF is used to obtain an approximate expression for the $\lambda$-power, while the CLT for the FDF is used to introduce an approximate procedure for determining a suitably small nominal FDR that results in a specified bound on the FDF with stipulated high probability. The paper also contains the results of a large simulation study covering a fairly substantial portion of the space of possible inputs encountered in application of the results in the design of a biomarker study, a micro-array experiment and a GWAS study.

Keywords: MSC-2008 Primary: 62L12; MSC-2008 Secondary: 62N02; Multiple testing; false discovery rate; average power; k power; LLN; CLT
arXiv: 1801.03989

*arXiv: 1801.03989
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1 Introduction

The explosion of available high-throughput technological pipelines in the biological and medical sciences over the past 20 years has opened up many new avenues of research that were previously unthinkable. The need to understand the role of power in the era of “omics” studies cannot be overstated. As a case in point, consider the promise and pitfalls of RNA expression micro-arrays. One of the take away themes is that new technologies such as this one enjoy initial exuberance and early victories (Alizadeh et al., 2000), followed by calls for caution from epidemiologists and statisticians (Baggerly and Coombes, 2009; Ioannidis, 2005). Some of the most constructive things gleaned from this journey, in hindsight, have been a thorough re-evaluation of what should constitute the “bar for science”. More and more researchers are starting to realize that some of the blame for lack of reproducibility is owed to lack of power (Ioannidis, 2005). Central to these renewed calls for scientific vetting has been the concept of multiple testing. Very early in the history of “omics” researchers realized that correction for multiple testing should be done and that the most commonly used method, Bonferroni correction, was by far too conservative for tens of thousands of simultaneous tests. Somewhat prophetically, half a decade before, Benjamini and Hochberg (1995) and colleagues introduced a new testing paradigm, that, in contrast to the Bonferroni procedure which controls the probability that one or more type I errors are committed, instead controls the proportion of false discoveries among the tests called significant. By now, use of the Benjamini-Hochberg (BH) false discovery rate (FDR) procedure for making statistical significance calls in multiple testing scenarios is widespread.

2 Definitions and Notation

Before describing the model of the data distribution, we need the following definition.

**Definition 2.1.** A family of pdf’s, \( \{f_\nu : \nu \geq 0\} \), has the monotone likelihood ratio property if and only if
\[
\nu' > \nu \implies \frac{f_{\nu'}}{f_\nu} \text{ is monotone increasing.}
\]

A family of CDF’s has the monotone likelihood ratio property if its members are absolutely continuous and the corresponding family of pdf’s has the property.
Now, consider $m$ simultaneous tests of hypotheses $i = 1, 2, \ldots, m$, each a test whether a location parameter is 0, $(H_{0,i})$ or non-zero $(H_{A,i})$. We start by supposing that an expected proportion, $0 < r < 1$, of the test statistics are distributed about non-zero location parameters. The test statistic distributions are modeled according to a mixture model, first introduced by Storey (2002) and others Baldi, Pierre and Long, A. D. (2001); Ibrahim et al. (2002). First, let $\{\xi_i\}_{i=1}^m$ be an i.i.d Bernoulli $\{0, 1\}$ sequence, with success probability, $r$. Denote the binomially distributed sum, $M_m = \sum_{i=1}^m \xi_i$, which is the number of test statistics belonging to the non-zero location parameter population. For a sample of size $n$ replicate outcomes resulting in $m$ simultaneous tests, let $X_{i,n}$ be the $i^{th}$ test statistic. We assume that conditional upon $\xi_i$, that its CDF is of the form:

$$F_{X_{i,n} | \xi_i} = (1 - \xi_i)F_{0,n} + \xi_iF_{A,n}. \quad (2)$$

In the above, $F_{0,n}$ is the common distribution of all null distributed tests, and $F_{A,n}$ is the common distribution of all non-null distributed tests. We assume that $F_{0,n}$ is the “minimal” element of a class of CDF’s, $F_n = \{F_{\nu,n} : \nu \geq 0\}$, satisfying the monotone likelihood ratio principle and that $F_{A,n} = \sum_{\ell=1}^h s_{\ell}F_{\nu_{\ell},n}$ is a finite mixture of elements $F_{\nu_{\ell},n} \in F_n$, including the possibility that the mixing proportions are degenerate at a single distribution. Note that since we will only consider only two-sided tests, our scope is solely focused on non-negative test statistics, $X_{i,n}$, since they represent the the absolute value of some intermediate quantity. We consider $X_{i,n}$ to be non-negative in the remainder of the paper. Let $\bar{F}$ denote the complementary CDF (cCDF), so that $\bar{F}_{0,n}(x) = \mathbb{P}\{X_{i,n} > x \mid \xi_i = 0\}$ and $\bar{F}_{A,n} = \mathbb{P}\{X_{i,n} > x \mid \xi_i = 1\}$. We will for nearly the entire paper make the assumption of independent hypothesis tests. While the Benjamini-Hochberg false discovery rate procedure is not immune to departures from the assumption of independent tests, the effect of departures from independence (i) do not affect the expected false discovery fraction or expected true positive fraction (defined precisely below) and (ii) discrepancies which do result from such departures are seen in the distribution of the FDF and TPF and are caused by a reduced effective number of simultaneous tests. For these reasons, results obtained under the assumption of independent hypothesis tests are still of great utility. We return to this discussion in the final section.
2.1 Mixed distribution of the P-values

For \( i = 1, 2, \ldots, m \), let \( P_i = \bar{F}_{0,n}(X_{i,n}) \) denote the two-sided nominal p-values corresponding to the test statistics, \( X_{i,n} \), and let \( P^m_{(i)} \) denote their order statistics. Notice that the nominal p-values, \( P_i, i = 1, 2, \ldots, m \) are i.i.d. having mixed CDF \( G(u) = \mathbb{P}\{P_i \leq u\} \),

\[
G(u) = (1 - r)u + r\bar{F}_{A,n}(\bar{F}_{0,n}^{-1}(u)). \tag{3}
\]

As we shall see in the proofs of Theorems 4.1, 4.3, and 4.6, below, the requirement that the family \( \{F_{\nu,n} : \nu \geq 0\} \) satisfies the monotone likelihood ratio principle guarantees that \( G \) is concave. Next in the original unsorted list of nominal p-values, \( \{P_i : i = 1, 2, \ldots, m\} \), let \( \{P_{1,i} : i = 1, 2, \ldots, M_m\} \) be the subset of nominal p-values corresponding to test statistics from the non-central population, in the order that they occur in the original unsorted list, e.g., if \( N_{m,i} = \min\{j : i = \sum_{\ell=1}^{j} \xi_{\ell}\} \) counts the number of non-centrally located statistics among the first \( i \) in the original unsorted list, then \( P_{1,i} = P_{N_{m,i}} \).

2.2 Numbers of significant calls, true postives and false positives

The Benjamini and Hochberg (B-H) false discovery rate (FDR) procedure (Benjamini and Hochberg, 1995) provides a simultaneous test of all \( m \) null hypotheses, that controls for multiplicity in a less conservative way than Bonferroni adjustment by changing the paradigm. Instead of controlling the probability that one or more null hypotheses is erroneously rejected, it controls the expected proportion of null hypotheses rejected that were true, or equivalently, the posterior probability that a test statistic has null location parameter given it was called significant. The algorithm is implemented by specifying a tolerable false discovery rate, \( f \), and then finding the largest row number, \( i \), for which the corresponding order statistic, \( P^m_{(i)} \), is less than \( if/m \). The total number of test statistics in the rejection region, \( J_m \), is given by the following expression:

**Definition 2.2.**

\[
J_m = \max \left\{ i : P^m_{(i)} \leq \frac{if}{m} \right\}.
\]

We will refer to \( J_m \) as the number of positive calls or discoveries which is consistent with the terminology of Benjamini and Hochberg, and we call the ratio \( J_m/m \) the positive call fraction.
Notice that expression 4 has the following alternate form:

\[ J_m = \sum_{i=1}^{m} I \{ P_i \leq m^{-1} J_m f \} \]  

(4)

The number of positive calls partitions into true positive calls and false positive calls

**Definition 2.3.** Let \( S_m \) denote the number of true positive calls:

\[ S_m = \sum_{i=1}^{m} \xi_i I (P_i \leq m^{-1} J_m f) \]  

(5)

**Definition 2.4.** Let \( T_m \) denote the number of false positive calls:

\[ T_m = \sum_{i=1}^{m} (1 - \xi_i) I (P_i \leq m^{-1} J_m f) \]  

(6)

There are several possible choices of normalizers for \( S_m \) and \( T_m \), depending upon the population value being estimated. Because power in the single hypothesis test scenario is the probability of rejection conditional upon the alternative distribution, it is natural to normalize by the number of non-null distributed statistics, \( M_m \):

**Definition 2.5.** We define the true positive fraction as the ratio \( S_m/M_m \).

Results concerning the false discovery rate will follow as corollaries to our other results. For this reason, we normalize the number of false positive calls, \( T_m \), by the number of positive calls, \( J_m \):

**Definition 2.6.** We define the false discovery fraction as the ratio \( T_m/J_m \).

In general we will use the term fraction for a ratio that is a random quantity and rate for its expectation.

Table 1 shows rows partitioning the test statistics into those that are non-null distributed, and those that are null distributed, numbering \( M_m \) and \( m - M_m \), respectively, and columns partitioning the results of hypothesis testing into the positives and negatives calls, numbering \( J_m \), and \( m - J_m \), respectively.
2.3 False discovery rate

Let $f_0 = (1 - r)f$. Benjamini and Hochberg (1995) showed in their original paper that their procedure controls the expected false discovery fraction, which they called the false discovery rate:

$$E \left[ \frac{T_m}{J_m} \right] = f_0 \leq f$$

In keeping with pervasive terminology, the phrase “false discovery rate” is applied to both the expected false discovery fraction, $f_0 = E [J_m^{-1} T_m]$, and in addition, the nominal value, $f$ which is used to set the threshold on the p-value scale. We will use the symbol BHFDR($f$) to denote the BH-FDR procedure at nominal false discovery rate, FDR = $f$. In this paper, whenever a random variable occurs in the denominator, we tacitly define the indeterminate $0/0$ to be $0$, which has the effect that all such ratios are defined jointly with the event that the denominator is non-zero.

3 The distribution of $S_m$ and notions of power in multiple testing scenarios

In the single hypothesis test situation, $m = 1$, we consider probabilities of rejection given $H_0$ is true or false. Under the setup introduced here, when $m = 1$, the BH-FDR, $f$ becomes the type I error probability, and the power as it is usually defined for a single hypothesis test, is the conditional expectation of $S_1$ given that $\xi_1 = 1$. In the case of multiple tests, $S_m$ is distributed

|                      | rej $H_{0,i}$ | acc $H_{0,i}$ | row Total |
|----------------------|--------------|---------------|-----------|
| $H_{0,i}$ is FALSE   | $S_m$        | $M_m - S_m$   | $M_m$     |
| $H_{0,i}$ is TRUE    | $T_m$        | $(m - M_m) - T_m$ | $m - M_m$ |
| col Total            | $J_m$        | $m - J_m$     | $m$       |

Table 1: Counts of true positives, false positives, false negatives and true negatives.
over values from zero to as high as $m$ so that naturally there are a multitude of avenues for conceptualizing the power. Consider first, that had we been using the Bonferroni procedure for multiple tests adjustment to threshold the test statistics arriving at $J_m$ positives and $S_m$ true positives, the distribution of $S_m$ would have been binomial with common success probability equal to the per-test power. The fact that the distribution of $S_m$ is not binomial when the BH-FDR criterion is used is what makes discussion of power more difficult. However, the common thread is that any discussion of power in the multiple testing scenario must be based upon some summary of the distribution of $S_m$, e.g. a right tail or a moment.

3.1 Various definitions of power in multiple testing scenarios

One of the first approaches was to use the probability that $S_m$ is non-zero: $\mathbb{P}\{S_m > 0\}$. Lee and Whitmore (2002) used a Poisson approximation to derive a closed-form expression for the probability to observe one or more true positives. This kind of power, the family-wise power, is arguably not a meaningful target of optimization for experiments built around a large number of simultaneous tests, especially when there are typically complex underlying hypotheses relying on positive calls for a sizable portion of those tests for which the alternative is true. For example, consider that in a micro-array experiment in which there will be downstream pathways analysis, we would start by assuming that there are around 3% or more of the $m$ tests for which the alternate hypothesis is true, and hope to make significant calls at an FDR of 15% for at least 80% of these non-null distributed statistics, so as to have a thresholded list of roughly 1600 genes to send to an analysis of pathways.

3.2 The Average Power and $\lambda$-power

Average Power

In the BH-FDR procedure for multiple testing, the role of the type I error played in the single testing scenario is assumed by the FDR which is an expected proportion. Therefore, it is natural
in the multiple testing scenario to consider a power that is also defined as an expected proportion. One interpretation of power in the setting of multiple testing that falls along this line of reasoning is the “average power”.

**Definition 3.1.** The average power is the expected true positive fraction, i.e. the expected proportion of all non-null distributed statistics that are declared significant by the BH FDR procedure.

\[
\pi_{av,m} = E \left[ \frac{S_m}{M_m} \right]
\]  

Notice that here the dependence upon \(m\) is made explicit, so that the average power depends upon the number of simultaneous tests in addition to quantities named above. Glueck et al. (2008) provided an explicit formula for the average power in a finite number, \(m\), of simultaneous test, but its complexity grows as the factorial of the number of simultaneous tests, and this is clearly intractable in the realm of micro-array studies and GWAS where there are tens of thousands or even a million simultaneous tests in question.

### 3.3 The plug-in estimate of the average power

Thinking heuristically for the moment, if \(m\) is very large as will be the case in many “omics” scenarios, then the positive call fraction \(J_m/m\) could be considered very close to a limiting value, \(\gamma\), if such a limiting value existed either in probability or almost surely. Continuing along heuristic lines then, we could replace the positive call fraction, \(J_m/m\), with the limiting constant, \(\gamma\), in the right hand side of expression 4, as well as in expressions 5 and 6, which define \(S_m\) and \(T_m\). If such a treatment were legitimate, the resulting analysis would be extremely easy as \(J_m, S_m\) and \(T_m\) would be sums of i.i.d’s and the usual L.L.N. holds, with limits given by the expected value of a single increment in the corresponding sum. This gives rise to the plug-in estimate of the average power,

\[
\pi_{pi} = P\{P_i < \gamma f | \xi_i = 1\} = \bar{F}_{A,n}(\bar{F}_{0,n}^{-1}(\gamma f))
\]  

Several authors have discussed this plug-in estimate of average power, for example Genovese and Wasserman (2004); Storey (2002). Independently, Jung (2005) and Liu and Hwang (2007) discuss sample size and power in the setting of multiple testing based upon the BH FDR procedure.
Without actually ever calling it the average power, they derive an expression very close to the above plugin estimate. Their derivation starts with the posterior probability that a statistic was drawn from the null-distributed population, given that it was called significant. Bayes theorem is used to express this in terms of the prior, $1 - r$ and $r$, and conditional, $\bar{F}_{0,n} \text{ and } \bar{F}_{A,n}$. They mistakenly equate this to the nominal false discovery rate, $f$, when in actuality it is the observed false discovery rate, $f_0 = (1 - r)f$. Not withstanding, their methodology is valid because the resulting power is, as we shall see below, the average power at the “oracle” threshold (Genovese and Wasserman (2004)) on the p-value scale, $\gamma f/(1 - r)$. This is the largest cut-off that is still valid at the nominal false discovery rate, $f$. Around the same time, Sun and Cai (2007), discussed a generalization of of the FDR procedure based upon the local FDR, and showed via decision theoretic techniques, that the false non-discovery rate, a quantity related to the average power, has better performance characteristics than the FDR under many circumstances. The paper also provided a very good survey of the then currently available results. While the ramifications of that work are great, the results provided here have merit in that the results and methodology supplied in the form of second order asymptotics for the TDF and the FDF are entirely new and have important ramifications in of themselves.

**The $\lambda$-Power**

Use of the average power in designing studies or deriving operating characteristics of them makes sense only when the width of the distribution of $S_m/M_m$ is very narrow. To have more definitive control over the true positive fraction, some authors have introduced the “K-power”. This was originally introduced in a model where the number of non-null distributed tests was fixed and was defined as the probability that the number of true positives exceeded a given integral threshold, $k$. Under the current setup in which the number of non-null distributed tests is a binomial random variable this no longer makes sense. We introduce instead the $\lambda$-power, which is the probability that the true positive fraction, $S_m/M_m$ exceeds a given threshold, $\lambda \in (0,1)$:

**Definition 3.2.** We define the $\lambda$-power:

$$\pi_{S/M}(\lambda) = P\left\{ \frac{S_m}{M_m} \geq \lambda \right\}. \tag{10}$$

We will also use the term “$\lambda_k$-power” to denote $\pi_{S/M}(k/100)$, the $\lambda$-power at threshold $k/100$. 

8
The associated quantile function is denoted:

\[ \lambda_{S/M}(\pi) = \pi^{-1}_{S/M}(\pi). \] (11)

As mentioned above, the \( \lambda \)-power becomes especially meaningful in experiments for which there are a small to intermediate number of simultaneous tests and for which the distribution of the TPF, \( S_m/M_m \), becomes non-negligibly dispersed. We prove a CLT for the true positive fraction which we use to approximate the \( \lambda \)-power. The accuracy of this approximation will be investigated in a simulation study.

**Remark 3.3.** Because the distribution of the TPF is nearly symmetric for even relatively small values of \( m > 50 \), the mean and median nearly coincide. Thus

\[ \pi_{S/M}(\lambda) \approx 1/2 \text{ when } \lambda = \pi_{pi} \] (12)

Because the \( \lambda \)-power takes the values 1 when \( \lambda = 0 \) and 0 when \( \lambda = 1 \) and is continuous by assumption, there exists a quantile, \( \lambda_{eq} = \pi^{-1}_{S/M}(\pi_{pi}) \), at which the \( \lambda \)-power equals the average power:

\[ \pi_{S/M}(\lambda_{eq}) = \pi_{pi}. \] (13)

Because the \( \lambda \)-power is a cCDF it is a non-increasing function of \( \lambda \),

\[ \pi_{S/M}(\lambda) < \pi_{pi} \text{ for } \lambda > \lambda_{eq} \text{ and } \pi_{S/M}(\lambda) > \pi_{pi} \text{ for } \lambda < \lambda_{eq} \] (14)

**Bounding the FDF**

We conclude the section on various notions of power with a brief diversion. The fact that the TPF may be non-negligibly dispersed at small to intermediate values of \( m \) leads to concern that the FDF distribution is similarly dispersed at these small to intermediate values of \( m \). This concern is addressed in one of the CLT results and in the simulation study. We introduce some notation for its cCDF and quantile function.

**Definition 3.4.** At BH-FDR \( f \), denote the FDF tail probability:

\[ \pi_{T/J}(\lambda) = \mathbb{P} \left\{ \frac{T_m}{J_m} \geq \lambda \right\}. \] (15)

Denote its quantile function:

\[ \lambda_{T/J}(p) = \pi^{-1}_{T/J}(p). \] (16)
At small and intermediate values of $m$, the value of $\lambda f_{T/J}$ required to bound the FDF by $f_0$ with probability bounded by $f_0$ can be as much as 100% larger than the FDR. As remarked above, this will be discussed further in the context of our CLT results and simulation studies below.

The remainder of the paper proceeds according to the following plan. Section 4 is a presentation of the main theoretical results, and this is done two subsections. In subsection 4.1, almost sure limits of the positive call fraction, true positive fraction and false discovery fraction, as the number of simultaneous tests tends to infinity, are shown to exist and are fully characterized. Convergence of the corresponding expectations, the true positive rate or average power, and false positive rate, follow as a corollaries. Subsection 4.2 contains central limit theorems (CLT’s) for the positive call fraction, true positive fraction and false discovery fraction. We also provide a lower bound for the average power at a finite number, $m$, of simultaneous tests. We show how these CLT results can be used to approximate the $\lambda$-power allowing tighter control over the TPF in power and sample size calculations, as well as how the approximate distribution of the FDF can be used to tighten down control over the FDF at both the design and analysis stage. Section 5 is devoted to a simulation study, in which we study the regions of the parameter space that are typical to small biomarker studies, micro-array studies and GWAS studies. We also focus on characteristics of the distribution of the FDF as the number of simultaneous tests grows. Weak consistency of $J_m/m, S_m/M_m$ and $T_m/J_m$ to $\gamma, \pi_{pi}$ and $(1 - \tau)f$ was proved in Storey (2002) and Genovese and Wasserman (2002). The paper Genovese and Wasserman (2004) is a study of consistency and convergence in distribution of the paths of the plug-in estimator, considered a stochastic process in the p-value plugin criterion, $t \in (0, 1)$. The strong consistency results and weak convergence results for the observed positive call fraction, true positive fraction and false discovery fraction presented here are new. Note that almost sure convergence of the positive call fraction is necessary for almost sure convergence of the true positive and false discovery fractions.
4 Theoretical Results

4.1 Law of Large Numbers

LLN for Positive Call Fraction, $J_m/m$

Theorem 4.1. If the family $\{F_{\nu,n} : \nu \geq 0\}$ is absolutely continuous and has the monotone likelihood ratio property, then

$$\lim_{m \to \infty} m^{-1} J_m = \sup\{u : u = G(uf)\} \equiv \gamma \text{ almost surely}, \quad (17)$$

Proofs of this and all other results are contained in the accompanying supplemental material.

Remark 4.2. When the family $\{F_{\nu,n} : \nu \geq 0\}$ has the monotone likelihood ratio property, $\gamma$ will be the unique non-zero solution of $G(uf) = u$.

Once the almost sure convergence of $J_m/m$ is established we can apply a result of Taylor and Patterson (1985) to establish convergence results for the true positive fraction.

LLN for the True Positive Fraction, $S_m/M_m$

Theorem 4.3. Under the conditions of theorem 4.1,

$$\lim_{m \to \infty} m^{-1} S_m = \mathbb{P}\{P_i \leq \gamma f, \xi_i = 1\} = r \bar{F}_{A,n}(\bar{F}_{0,n}^{-1}(gf)) \text{ a.s.}, \quad (18)$$

$$\lim_{m \to \infty} M_m^{-1} S_m = \mathbb{P}\{P_i \leq \gamma f \mid \xi_i = 1\} = \bar{F}_{A,n}(\bar{F}_{0,n}^{-1}(gf)) \equiv \pi_p \text{ a.s.} \quad (19)$$

and

$$\lim_{m \to \infty} \pi_{av,m} = \lim_{m \to \infty} \mathbb{E}\left[M_m^{-1} S_m\right] = \pi_p \quad (20)$$

Corresponding convergence results for the false discovery fraction and its expected value follow as a corollary.
LLN for the False Discovery Fraction, $T_m/J_m$

**Corollary 4.3.1.** Under the conditions of theorem 4.1,

\[
\lim_{m \to \infty} m^{-1} T_m = \mathbb{P}\{P_i \leq \gamma f, \xi_i = 0\} = (1 - r) \gamma f \text{ a.s.},
\]

\[
\lim_{m \to \infty} J_m^{-1} T_m = \mathbb{P}\{\xi_i = 0 \mid P_i \leq \gamma f\} = (1 - r)f \text{ a.s.}
\]

\[
\lim_{m \to \infty} \mathbb{E}[J_m^{-1} T_m] = (1 - r)f
\]

**Remark 4.4.** Because $T_m = J_m - S_m$ then by Theorem 4.3.1 and its corollary 4.3, we obtain the identity $(1 - r)f = 1 - r \pi_{m,i}/\gamma$, which can be rearranged to obtain an expression for the limiting positive call fraction:

\[
\gamma = \frac{r \pi_{m,i}}{1 - f_0}.
\]

**Remark 4.5.** If the nominal false discovery rate, $f$, is replaced by the inflated value, $f/(1 - r)$, resulting in the BHFRD$(f/(1 - r))$ procedure, note that the FDR is still controlled at the nominal value, $f$, since in this case, $\mathbb{E}[J - S / J] = f$ due to cancellation. This threshold, $\gamma f/(1 - r)$, on the $p$-value scale, has been called the oracle threshold by some authors, Genovese and Wasserman (2004), because it is the criterion resulting in the largest power which is still valid for a given FDR, $f$. Call this the oracle average power, $\pi_o$. The actual difference only begins to get appreciable as $r$ increases in size. In practice, as we will see in our simulation study, $r$ must be as large as 50% or more before this has a dramatic effect on the average power. Keep in mind that in practice when analyzing a given dataset, this increased power is only attainable at the stage of estimation if a reasonably good estimate of $r$ is possible. The fact that this is very problematic has also been a topic of much discussion.

Next, if we replace $\gamma$ in the definition of the IST average power 19 by the expression 24, we arrive at a new equation which gives an implicit definition for the IST average power.

**Corollary 4.5.1.** Under the conditions of theorem 4.1,

\[
\pi_{pi} = \tilde{F}_{A,n} \left( \tilde{F}_{0,n}^{-1} \left( (1 - f_0)^{-1} r \pi_{pi} f \right) \right).
\]
The almost sure convergence results given in Theorems 4.1, 4.3.1 and 4.3 above each have corresponding central limit results which we state now. The first, a CLT for the centered and \( \sqrt{m} \)-scaled positive call fraction, \( J_m/m \), is needed in the proof of the second and third results, CLT’s for centered and scaled versions of the false discovery fraction and the true positive fraction.

4.2 CLTs for the PCF, FDF, and TPF; Lower Bound for Average Power

**Theorem 4.6.** Under the conditions of theorem 4.1,

\[
\sqrt{m} \left( m^{-1} J_m - \gamma \right) \xrightarrow{D} N(0, \tau^2). 
\]

\[\text{(26)}\]

\[
\sqrt{m} \left( J_m^{-1} T_m - f_0 \right) \xrightarrow{D} N(0, \alpha^2). 
\]

\[\text{(27)}\]

\[
\sqrt{m} \left( M_m^{-1} S_m - \pi \right) \xrightarrow{D} N(0, \sigma^2). 
\]

\[\text{(28)}\]

The proof, which uses results on convergence of stopped stochastic processes, is constructive in nature producing fully characterized limiting distributions yielding asymptotic variance formulae. We reiterate the practical implications of these results.

**Approximating the \( \lambda \)-power via the CLT for the TPF**

Currently, multiple testing experiments are designed using the average power, \( \pi \), which is the mean of the distribution of \( S_m/M_m \). In cases in which the width of this distribution is non-negligible, e.g. \( m < 1000 \) simultaneous tests or so, we recommend using the \( \lambda \)-power instead of the average power. As we defined above, in equation 10, the \( \lambda \)-power is the probability that the TPF exceeds a given \( \lambda \). We will see in our simulation study that in the ranges of the parameter space investigated, this CLT approximation is quite good and can be used to approximate the \( \lambda \)-power:

\[
\pi_{S/M}(\lambda) = \mathbb{P}\{S_m/M_m \geq \lambda\} \approx \Phi(\sqrt{m}/\sigma(\pi - \lambda)), 
\]

\[\text{(29)}\]
where $\sigma$ above is the square-root of the asymptotic variance, $\sigma^2$, given in formula 56 in the proof of theorem 4.6.

**Enhanced control of the FDF via its CLT**

As defined above in expression 16 and the text leading up to it, $\lambda_{T/J}(p) = \pi_{T/J}^{-1}(p)$ is the quantile of the FDF distribution at upper tail probability, $p$. The CLT for the FDF can be used to approximate it:

$$\lambda_{T/J}(p) \approx f_0 + \frac{\alpha}{\sqrt{m}} \Phi^{-1}(1 - p).$$  \hspace{1cm} (30)

Here, $f_0 = (1-r)f$ as above, $\alpha$ is the square root of the asymptotic variance, $\alpha^2$ given in formula 58 in the proof of 4.6, and $\Phi^{-1}$ is the standard normal quantile function. This can be used in several different ways to bound the FDF with specified probability. Three possibilities are as follows. First, as a kind of loss function on lack of control inherent in the use of the BHFDR($f$) procedure, we could determine how large a threshold is required so that the FDF is bounded by $\lambda$ except for a tail probability of $f_0$

$$\lambda_{T/J}(f_0) = f_0 + \frac{\alpha}{\sqrt{m}} \Phi^{-1}(1 - f_0)$$  \hspace{1cm} (31)

A second way would to find the solution $f'$ to the following equation.

$$f_0 = (1-r)f' + \frac{\alpha}{\sqrt{m}} \Phi^{-1}(1 - (1-r)f_0).$$  \hspace{1cm} (32)

This would produce a reduced FDR, $f' < f$, at which the BHFDR($f'$) procedure would result in a FDF, $T_m/J_m$ of no more than $f_0$ with probability $1 - f_0$. The solution is

$$f' = f - \frac{\alpha}{(\sqrt{m}(1-r))\Phi^{-1}(1 - (1-r)f_0)}$$  \hspace{1cm} (33)

A third way to do this, and the most conservative of the three, would be to determine the value of a reduced FDR, $f'$, at which the BHFDR($f'$) procedure would result in a FDF no more than $f_0$ with probability $1 - (1-r)f'$, by solving the following equation numerically:

$$f_0 = (1-r)f' + \frac{\alpha}{\sqrt{m}} \Phi^{-1}(1 - (1-r)f').$$  \hspace{1cm} (34)

**Remark 4.7.** The farther apart $f'$ is from $f_0$ is an indication of the dispersion of the distribution of $T_m/J_m$.  

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Remark 4.8. The procedure summarized in equation 34, for finding a reduced FDR, $f'$, at which BHFDR($f'$) would produce an FDF of no more than $f_0$ with probability $1 - (1 - r)f'$, can also be used at the analysis phase. Note that expression 58 in the proof of 4.6 for the asymptotic variance, $\alpha^2$, of $T_m/J_m$ depends only upon $f_0 = (1 - r)f$ and $\gamma$. Thus we can replace $f_0$ with $f$ and estimate $\gamma$ from the data using the plug-in estimate, $J_m/m$. This has important ramifications for the setting of small to intermediate number of simultaneous tests, $m \leq 1000$.

Lower Bound for finite simultaneous tests average power

As we will see in the simulation study which follows, the IST average power is in fact extremely close to the finite simultaneous tests (FST) average power for the broad ranges of the parameters studied. Nevertheless, it is still useful to have bounds for the FST average power.

Theorem 4.9. The FST average power, $\pi_{av,m}$, is bounded below by the following quantity, $\pi_{av,m}^L$, given below.

$$\pi_{av,m} \geq \sum_{\ell=1}^{m} \left( \binom{m}{\ell} r^\ell (1 - r)^{m-\ell} \frac{1}{\ell} \sum_{s=1}^{\ell} \bar{B}_{\ell-s+1,s} \left( \tilde{F}_{\nu,n} \left( 1 - \tilde{F}_{0,n}^{-1} \left( \frac{sf}{m} \right) \right) \right) \right)$$

An upper bound that seems to work in practice is the expression obtained by replacing $J_m/m$ with $r/(1 - f_0)$ in equation 59 in the proof of Theorem 4.9.

5 Simulation Study

We conducted four simulation studies. The first three of these had fixed $m$ and ranges of the other parameters chosen based upon relevance to subject matter areas. The first, with $m = 200$, was meant to model biomarker studies. In a second simulation study, we varied $m$ in order to study characteristics of the FDF distribution as $m$ grows. In the third, in which $m = 54,675$, was meant to model micro-array studies for while the fourth, for which $m = 1,000,000$, was meant to model genome wide association (GWA) studies.

In all four cases, the test statistic distributions, $F_{0,n}$ and $F_{\nu,n}$, were chosen to be t-distributions of $2n - 2$ degrees of freedom. The common non-centrality parameter was fixed at $\nu = \sqrt{n/2\theta}$. 15
This corresponds to a two group comparison as is often done. For each of these simulation studies, we chose subject matter relevant ranges for the four parameters, the expected proportion of non-null tests, $r$, the location parameter, $\theta$, and the false discovery rate, $f$. Except when set explicitly as in the fourth case, a range sample sizes, $n$, in increments of 5, was chosen to result in powers between 60% and 95% at each setting of the other parameters. We conducted a total of four simulation studies. The first, with $m = 200$ simultaneous tests, was meant to model biomarker studies. The second, with varying sizes of $m$ ranging from 1,000 to 20,000 was done in order to assess the width of the FDF distribution and the adequacy of the CLT approximation to it. The third, with $m = 54,675$ was meant to model human oligo-nucleotide micro-array experiments, and the forth with $m = 1,000,000$ was meant to model GWA studies. We present the first two of these in the main text and the remainder in the supplementary material.

For each of these four parameters, the IST average power, $\pi_{\mu}$, from line 20 of Theorem 4.3, the oracle power, $\pi_o$, mentioned in remark 4.5 above, and the lower bound, $\pi_{L,m}$, from Theorem 4.9. We computed the approximate $\lambda_{75}$- and $\lambda_{90}$- powers using expression 29 based upon the CLT for the TPF (theorem 4.6) using the expression for the asymptotic variance, $\sigma^2$ (expression 56 given in the proof). Also, at each combination of parameters, we conducted 1,000 simulation replicates. At each simulation replicate, we began by generating $m$ i.i.d. Bernoulli $\{0, 1\}$ variables, with success probability, $r$, to assign each of the $m$ test statistics to the null (0) or non-null (1) populations, recording the number, $M_m$, of non-null distributed test statistics. This was followed next by drawing $m$ test statistics from $F_0,n$ or $F_\nu,n$, being the central and non-central (respectively) t-distribution of $2n - 2$ degrees of freedom, corresponding to the particular value of $\xi_i$. Next, the B-H FDR procedure was applied and the number of positive calls, $J_m$, and number of true positives, $S_m$ were recorded. At the conclusion of the 1,000 simulation replicates, we recorded the simulated average power as the mean over simulation replicate of the TPF, $S_m/M_m$. In addition, the simulated $\lambda_{75}$- and $\lambda_{90}$- powers were derived as the fraction of simulation replicates of the TPF that exceeded 0.75 and 0.90, respectively. Finally we computed the sample size required for $\lambda_{90}$ power.

In another simulation study, focused on the distribution of the FDF for increasing $m$. At each combination of the parameters considered, we computed the reduced FDR, $f'$, required to bound
the FDF with probability $(1 - r)f'$ as the unique numerical solution to expression \ref{eq:34}. We also computed the sample sizes $n_{0,0}$ and $n_{0,1}$ required for specified average power under BHFDR($f$) and under BHFDR($f'$), respectively. Sample sizes $n_{1,0}$ and $n_{1,1}$ at specified $\lambda$-power under the corresponding procedure were also derived. A simulation, conducted in a fashion identical to that described above, under BHFDR($f'$), was done at each combination of parameters, this time including the additional two parameters $m$ and specified power. From simulation replicates of the FDF, $T_m/J_m$, we computed the probability in excess of $f_0$.

All calculations were done in R, version 3.5.0 (R Core Team (2016)) using a R package, \texttt{pwrFDR}, written by the author Izmirlian (2018), available for download on \texttt{cran}. Simulation was conducted on the NIH Biowulf cluster (NIH High Performance Computing Staff (2017)), using the swarm facility, whereby each of 50 nodes was tasked with carrying out 20 simulation replicates resulting in 1,000 simulation replicates for each configuration of parameters.

5.1 Biomarker Studies

For the first simulation study we considered experiments typical of biomarker studies with $m = 200$ simultaneous tests. We attempted to cover a broad spectrum of parameters spanning the domain of typical biomarker study designs. The false discovery rate, $f$, was ranged over the values 1%, and from 5% to 30% in increments of 5%. The expected number of tests with non-zero means, $E[M_m] = mr$, was varied over the values 5, 10 and 20, and from 10 to 100 in increments of 10, representing values of $r$ ranging from 0.025 to 0.5. The effect size, $\theta$, was allowed to vary from 0.6 to 1.5 in increments of 0.1. At each configuration, a range of sample sizes were chosen to result in powers between 50% and 98% as mentioned above. This resulted in 2,648 configurations of the parameters, $f, E[M_m], \theta$, and $n$ (full set of parameter combinations). The job took roughly 7 minutes on the NIH Biowulf cluster.

Table 2 tabulates the IST average power, the oracle power and the simulated mean of the TPF at 28 different parameter settings excerpted from the full set of 2,648 parameter combinations. Over the full set of parameter settings, the both the IST $\pi_{\mu}$, and oracle $\pi_o$ powers are very close to the simulated average power. The difference between the IST power, $\pi_{\mu}$, and the simulated power was less than 0.15, 0.95 and 2.00 at 50%, 90% and 99% of the parameter settings, respectively. As remarked earlier, the oracle power is actually the average power at
the oracle threshold. Since it borders on feasible, we allowed \( r \) to take values as large as 0.5 for which the oracle threshold has a substantial gain in power. The oracle power differed from the IST power by 1.8%, 8.5% and 16% at 50%, 90% and 99% of the parameter settings, respectively, suggesting that the oracle threshold is worth considering. Recall that our IST power, \( \pi \), can be set to the oracle threshold by setting the FDR to \( f/(1-r) \). However, careful consideration must be taken if using the oracle threshold to design a study, since when its time to actually threshold the data one needs a plug-in estimate of \( r \) and as discussed extensively in the literature, this can be problematic. The lower bound comes within roughly 10% of the simulated power, with differences with the simulated power less than 36%, 45%, 50%, 56% and 71% at 20%, 40%, 50%, 60% and 80% of the parameter settings, respectively.

Table 3 displays, at threshold 0.75 and at threshold 0.90, the \( \lambda \) power as derived from the CLT and estimated from simulation replicates (hatted version), respectively, excerpted from the full set of 2,648 parameter combinations as before. In the last column is the ratio of the sample size required for \( \lambda_{90}\)-power to the original sample size. First, we note that when restricted to powers strictly between 50% and 100%, occurring at 1,488 parameter combinations, the CLT approximate- and simulated- \( \lambda_{75}\)-power were within the following relative error of one another (median over parameter conditions (lower quartile, upper quartile)): 2% (0.7%, 4.5%), with 23.1% over 5%. Corresponding results for the simulated and CLT approximate \( \lambda_{90}\)-power for powers strictly between 50% and 100% occurring at 1275 of the parameter values, were within the following relative error of one another 3.3% (1.3%, 9.2%), with 37.6% over 5%. The greater discrepancy between CLT approximate \( \lambda \)-powers and simulated values is due to the lack of accuracy of the CLT asymptotic approximation at such small sample sizes, \( n \). Note that for sample sizes in excess of \( n = 20 \) the degree of accuracy starts to improved dramatically, especially at higher powers. Also noteworthy is corroboration in ordering of the average power and \( \lambda_k \)-power based upon the size of \( k \) relative to 100\( \lambda_{eq} \). All values of \( \lambda_{eq} \) are less than 90%, but some are between 75% and 90%, and the ordering of average power and \( \lambda \) powers is in accordance with expression 14.

Furthermore the discrepancy between the average power and the \( \lambda \)-power is reflective difference between \( \lambda \) and \( \lambda_{eq} \). This trend is echoed in the magnitude of the sample size ratio, with magnitude increasing in the discrepancy between \( \lambda_{eq} \) and 0.90. Note that in this case, as the
number of simultaneous tests, \( m \), is relatively “small”, the distribution of the TPF, \( S_m/M_m \), is more dispersed and therefore, growth in the \( \lambda \)-powers is more gradual with increasing sample size.

5.2 The false discovery fraction, intermediate number of simultaneous tests

The second simulation study was focused on the use of the CLT for the FDF to find a bound for the FDF with large probability. We varied the number of simultaneous tests, \( m \), over 1000, 2500, 5000, 7500, 10000 and 20000. The effect size, \( \theta \), was varied over 2/3, 5/6 and 1. The proportion of statistics drawn from the non-null distributed population, \( r \), ranged over 0.025, 0.05 and 0.075 and the FDR, \( f \), ranged over the values 0.1, 0.15 and 0.2. At each set of values of these parameters, we used expression 34 based upon the CLT for the FDF to find a reduced FDR at which the BH-FDR procedure would result in an FDF of no more than \( f_0 \) with large probability. We calculated the sample sizes required for specified average power under the original and reduced FDR. Sample sizes required for specified \( \lambda_{90} \)-power under the original and reduced FDR were also calculated. Finally, the probability that the FDF exceeded \( f_0 \) under the reduced FDR was estimated from simulation replicates.

Table 4 tabulates the reduced FDR, \( f' \), required to bound the FDF by \( f_0 \) with probability \( 1 - (1 - r)f' \), and the sample sizes \( n_{0.0} \) and \( n_{0.1} \), required for specified average power under BHFDR(\( f \)) and under BHFDR(\( f' \)), respectively. Also shown are the sample sizes, \( n_{1.0} \) and \( n_{1.1} \), required for specified \( \lambda_{90} \)-power under BHFDR(\( f \)) and under BHFDR(\( f' \)), respectively, as well as the simulated tail probability, \( \hat{\pi}_{T/J}(f_0) \), in excess of \( f_0 \). The general trend for increasing \( m \) as the distribution of \( T_m/J_m \) collapses to a point mass at \( f_0 \) are a value of \( f' \) closer to \( f \), and sample sizes under BHFDR(\( f' \)) that are less inflated relative to corresponding sample sizes under BHFDR(\( f \)). The simulated right tail probability, \( \hat{\pi}_{T/J} \) should in theory have only simulation error about its theoretical value, \( (1 - r)f' \). However, as \( f' \) is derived from an approximation based upon a CLT, we expect the accuracy of the approximation to improve with larger \( m \). Not surprisingly, the results are consistent with these observations. Over the full set of 324 parameter settings we obtained the following results (median, (lower quartile, upper quartile)). The ratio of the reduced FDR, \( f' \), to the original FDR, \( f \): 0.79 (0.69, 0.86) when \( m \leq 10,000 \), and 0.91 (0.88,
when $m > 10,000$, showing that the reduced FDR gets closer in value to the original FDR with increasing $m$. The ratio of sample size required for average power at BH-FDR($f'$) to that at BH-FDR($f$): 1.06 (1.04, 1.1) when $m \leq 10,000$ and 1.03 (1.02, 1.04) when $m > 10,000$, showing that the inflation factor reduces with increasing $m$. This is also the case when the sample sizes are derived for given $\lambda_{90}$-power: 1.05 (1.03, 1.08) when $m \leq 10,000$ and 1.02 (1.0025, 1.03) when $m > 10,000$, respectively. Finally, the ratio of the simulated tail probability, $\hat{\pi}_{T/J}(f_0)$ to the CLT approximated value: 1.02 (0.95, 1.11) when $m \leq 10,000$ and 0.995 (0.94, 1.0675) when $m > 10,000$ respectively, highlighting that the CLT approximation gets better with increasing $m$.

In order to judge the relative impact changes in the parameters had, especially those unique to this setting of multiple testing, we computed numerical partial derivatives of the power function with respect to the proportion of test statistics distributed as the non-null distribution $r$, the effect size $\theta$, and the FDR $f$. The partials were then scaled to the range of the relevant parameter (max minus min) so that unit changes were comparable and corresponded to the ranges of the parameters considered. Numerical partial derivatives were computed at all 10,020 configurations of the parameters. These results were summarized separately for each of the three parameters by calculating quartiles of the respective numerical partial derivative at each given level of the respective parameter, over all configurations of all other parameters resulting in powers of 50%, 60%, 70%, 80% and 90%. The results corresponding to median values at 70% power are displayed in Figure 2.

6 Discussion

We proved LLNs for the PCF, FDF and TPF as well as CLTs for $\sqrt{m}$ scaled versions of them. Our LLN result for the TPF allowed characterization of the large $m$ limit and this in turn allowed a proper interpretation of the power discussed in Jung (2005) and in Liu and Hwang (2007), being nearly identical to the average power. Our CLT result for the TPF allowed us to introduce the $\lambda$-power, similar in nature to the $k$-power discussed by previous authors. The $\lambda$-power allows tighter control over the TPF in the design of multiple testing experiments by bounding the distribution of the TPF by an acceptable threshold, rather than just its mean, as is the case with the average
power. Our CLT result for the FDF provides a technique whereby an investigator can determine a reduced FDR at which the usual BH-FDR procedure will result in a FDF no greater than a stipulated value with arbitrary large probability. This latter technique is useful both at the design phase as well as the analysis phase because the asymptotic variance depends only upon the limiting PCF, $\gamma$, and proportion belonging to the null distributed population, $1 - r$ and one can use $J_m/m$ as an estimate of $\gamma$ and consider $1 - r \approx 1$ when faced with a data analysis. Key to the proofs of the LLN results was, first, the LLN for the PCF, $J_m/m$, which was proved directly via a simple argument. Prior results by Genovese and Wasserman (2004) obtained convergence only in probability. Once established we applied a result of Taylor and Patterson (1985) for a.s. convergence of triangular arrays of finite exchangeable sequences The proofs of the CLT results was made possible by building on the work of Genovese and Wasserman (2004) which considered $p$-values thresholded at a deterministic $t$, treating them as stochastic processes. We applied a result of Silvestrov (2004) for weak convergence of stopped stochastic processes.

In a very large and thorough simulation study, we investigated three major domains of the space of operating characteristics typically encountered in the design of multiple testing experiments: two larger $m$ domains, $m = 54,675$ typical to human RNA expression micro-array studies, and $m = 1,000,000$ typical to GWA studies and a smaller $m$ domain, $m = 200$ which is typical of biomarker studies. In each case, we compared the average power derived from the TPF LLN limit to simulated values and observed at all ranges of sample sizes that the agreement was quite good. We also used the CLT result for the TPF to compute approximate $\lambda$ powers and compared these with the simulation distribution. Agreement in this case was overall very good, but there was some breakdown in the level of accuracy in the asymptotic approximation at simultaneous tests $m < 100$. The last simulation study was focused upon the procedure for bounding the FDF with large probability and its behavior as the number of simultaneous tests, $m$, grows from hundreds to tens of thousands. We noted that overall, the method is feasible, even when the asymptotic approximation begins to fail, as it always offers tighter control of the FDF than the BH-FDR procedure alone.

We investigated departures from the assumption of independent hypothesis tests by conducting a simulation in which tests were correlated within blocks according to a compound symmetry structure under a multivariate normal, having marginal variances equal to 1. For the purposes
of this investigation, we fixed the block size to 100, effect size 1.25, FDR at 15%, proportion of
non-null distributed tests, \( r \), at 5% for 2000 simultaneous tests. We varied sample sizes from
14 to 16 and block correlation from 0 to 80% in increments of 10%. The average power, \( \lambda_{75} \)
power, empirical FDR and probability that the FDF exceeds 18% are tabulated in table 5 over
the ranges of sample sizes and block correlations considered. As we can see, comparing the
independent tests lines for each of the two sample sizes, 14 and 16, with corresponding values for
correlated test statistics, a very important point can be made. From the standpoint of the mean,
there is virtually no difference. This is to say that the empirical FDR and average power are
virtually unaffected when there are correlated blocks of tests. Notable differences do occur in the
distributions of the TPF and FDF as the \( \lambda_{75} \)-power for independent test statistics is 30% in a
sample of 14, and 87% in a sample of 16, respectively, while the values when there are correlated
blocks of tests are substantially greater for a sample of 14 and substantially less in a sample of
16, respectively. Discrepancies between the independent tests versus correlated blocks of tests in
the same direction are also observed in the probability that the FDF exceeds 18%. The reason
for this is that correlated blocks of test statistics result in a reduced effective number of tests.
Apparently, the observed effective number of test statistics is large enough that the empirical
means are still very good estimates of their almost sure limiting values, but not great enough for
stability in the distribution of empirical means at the ranges of parameters under consideration.
The conclusion to be drawn is not that the BH-FDR procedure is to be avoided because it is not
completely immune to departures from the independent test statistics assumption. By analogy, is
any limit theorem meaningless because it doesn’t apply to a sample size of 3? Quite not. The
first conclusion to be drawn is that the empirical means appear to be unaffected in the ranges
of parameters considered here. If one is truly comfortable controlling the false discovery rate
and powering studies using the average power, then one can ignore the appropriateness of the
independence assumption. Problems start to occur when one uses the tails of the distribution of
the FDF and TPF, as we are making the case for use here. However, rather than give up on the
use of the BH-FDR procedure altogether, the phenomenon should be viewed from the lens of
the effective number of simultaneous tests. So, ironically, the problem is solved if one can simply
increase the number of simultaneous tests.

Drawing away from the specific discussion of correlated tests and widening the focus to the
conclusions to be drawn from the paper as a whole, the point to be made is that the quantities arising in the BH-FDR procedure, the expected FDF which is controlled, and the expected TPF which forms the basis of a power calculation, should be seen for what they are, location parameters. Because first and second order asymptotics in the FDF and TPF occur as the number of simultaneous tests tends to infinity, then within the scope of reasonable ranges of parameters, e.g. effect size no more than 1 or so, and sample sizes within the ranges seen for equipment that is either very expensive per replicate or just starting to get a bit cheaper, say a few tens of replicates, then the following generalizations can be made. For more than 20,000 simultaneous tests, the means and the distributions effectively coincide so that controlling the FDR and using the average power to derive sample sizes is well supported. This is great news for GWAS and RNA-seq studies for example. However, for less than one or two thousand simultaneous tests, one must use second order asymptotics to control the type I-like error and calculate sample sizes using the CLT’s for the FDF and TPF in the manner outlined here. For on the order of a hundred or so simultaneous tests, asymptotic approximation using the CLT’s may not be appropriate. In this case, simulation is advised. This cautionary note is of particular importance in many biomarker studies.
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7 Appendix: Further simulation studies

7.1 RNA Expression Micro-array Studies

The third simulation study we considered experiments typical of human RNA expression micro-array studies using the Affymetrix Hgu133plus2 oligonucleotide mRNA gene chip. In this case, there are $m = 54,675$ simultaneous tests. We attempted to cover a broad spectrum of parameters spanning the domain typical of micro-array study designs. The false discovery rate, $f$, was ranged over the values 1%, and from 5% to 30% in increments of 5%. The expected number of tests with non-zero means, $E[M_m] = mr$, was varied from 100 to 2500 in increments of 100 representing...
values of $r$ ranging from 0.0018 to 0.046. The effect size, $\theta$, was allowed to vary from 0.6 to 1.5 in increments of 0.1. At each configuration, a range of sample sizes were chosen to result in powers between 60% and 95% as mentioned above. This resulted in 10,020 configurations of the parameters, $f, E[M_m], \theta$, and $n$ (full set of parameter combinations). The job took roughly 12 hours on the NIH Biowulf cluster.

Table 6 tabulates the IST average power, the oracle power and the simulated mean of the TPF at 28 different parameter settings excerpted from the full set of 10,020 parameter combinations. Over the full set of parameter settings, the both the IST, $\pi$, and oracle, $\pi_o$, powers are very close to the simulated average power. The difference between the IST power, $\pi$, and the simulated power was less than 0.022%, 0.077% and 0.19% at 50%, 90% and 99% of the parameter settings, respectively. The oracle power differed from the IST power by less than 0.15%, 0.5% and 0.92% at 50%, 90% and 99% of the parameter settings, respectively. As remarked earlier, the oracle power is actually the average power at the oracle threshold, but for such small values of $r \leq 0.046$ there is not much gain in power to be had. The lower bound comes within roughly 10% of the simulated power, with differences with the simulated power less than 2.1%, 4.5%, 6.2%, 8.5% and 15% at 20%, 40%, 50%, 60% and 80% of the parameter settings, respectively.

Table 7 displays, at threshold 0.75 and at threshold 0.90, the $\lambda$ power as derived from the CLT 4.6 and estimated from simulation replicates (hatted version), respectively, excerpted from the full set of 10,020 parameter combinations as before. In the last column is the ratio of the sample size required for $\lambda_{90}$-power to the original sample size. First, we note that when restricted to powers strictly between 50% and 100%, occurring at 1,066 parameter combinations, the CLT approximate- and simulated- $\lambda_{75}$-power were within the following relative error of one another (median over parameter conditions (lower quartile, upper quartile)): 0.4% (0.2%, 1.2%), with 2.4% over 5%. Corresponding results for the simulated and CLT approximate $\lambda_{90}$-power for powers strictly between 50% and 100% occurring at 1476 of the parameter values, were within the following relativer error of one another 0.5% (0.2%, 1.3%), with 1.8% over 5%. Also noteworthy is corroboration in ordering of the average power and $\lambda_k$-power based upon the size of $k$ relative to 100$\lambda_{eq}$. All values of $\lambda_{eq}$ are less than 90%, but some are between 75% and 90%, and the ordering of average power and $\lambda$ powers is in accordance with expression 14. Furthermore the discrepancy between the average power and the $\lambda$-power is reflective difference between $\lambda$ and
\( \lambda_{eq} \). This trend is echoed in the magnitude of the sample size ratio, with magnitude increasing in the discrepancy between \( \lambda_{eq} \) and 0.90. The relatively rapid rise in sample size, \( n \), of all \( \lambda \)-powers is an indication of the degree to which the distribution of the TPF, \( S_m/M_m \), is spiked.

### 7.2 GWA Studies

The last simulation study we considered experiments typical of GWA studies with \( m = 1,000,000 \) simultaneous tests. We attempted to cover a broad spectrum of parameters spanning the domain typical of GWA study designs. The false discovery rate, \( f \), was ranged over the values 0.5\%, 1\%, 5\% and 10\%. The expected number of tests with non-zero means, \( E[M_m] = mr \), was varied from 400 to 1000 in increments of 200 representing values of \( r \) ranging from 4e-04 to 0.001. The effect size, \( \theta \), was allowed to vary from 0.08 to 0.68 in increments of 0.2. At each configuration, a range of sample sizes were chosen to result in powers between 50\% and 98\% as mentioned above. This resulted in 512 configurations of the parameters, \( f, E[M_m], \theta, \) and \( n \) (full set of parameter combinations). The job took roughly 5 hours on the NIH Biowulf cluster.

Table 8 tabulates the IST average power, the oracle power and the simulated mean of the TPF at 32 different parameter settings excerpted from the full set of 512 parameter combinations. Over the full set of parameter settings, the both the IST, \( \pi_i \), and oracle, \( \pi_o \), powers are very close to the simulated average power. The difference between the IST power, \( \pi_i \), and the simulated power was less than 0.031, 0.087 and 0.147 at 50\%, 90\% and 99\% of the parameter settings, respectively. The oracle power differed from the IST power by 0.0038\%, 0.0081\% and 0.011\% at 50\%, 90\% and 99\% of the parameter settings, respectively. As remarked earlier, the oracle power is actually the average power at the oracle threshold, but for such small values of \( r \leq 0.001 \) the gain in power is now less than 1\%. The lower bound comes within roughly 10\% of the simulated power, with differences with the simulated power less than 0.83\%, 3.8\%, 6.9\%, 9.6\% and 15\% at 20\%, 40\%, 50\%, 60\% and 80\% of the parameter settings, respectively.

Table 9 displays, at threshold 0.75 and at threshold 0.90, the \( \lambda \) power as derived from the CLT 4.6 and estimated from simulation replicates (hatted version), respectively, excerpted from the full set of 512 parameter combinations as before. In the last column is the ratio of the sample size required for \( \lambda_{90} \)-power to the original sample size. First, we note that when restricted to powers strictly between 50\% and 100\%, occurring at 68 parameter combinations, the CLT
approximate- and simulated- \( \lambda_{75} \)-power were within the following relative error of one another (median over parameter conditions (lower quartile, upper quartile)): 0.5% (0.2%, 1.3%), with 1.5% over 5%. Corresponding results for the simulated and CLT approximate \( \lambda_{90} \)-power for powers strictly between 50% and 100% occurring at 87 of the parameter values, were within the following relative error of one another 0.6% (0.2%, 1.2%), with 1.1% over 5%. Also noteworthy is corroboration in ordering of the average power and \( \lambda_k \)-power based upon the size of \( k \) relative to \( 100 \lambda_{eq} \). All values of \( \lambda_{eq} \) are less than 90%, but some are between 75% and 90%, and the ordering of average power and \( \lambda \) powers is in accordance with expression 14. Furthermore the discrepancy between the average power and the \( \lambda \)-power is reflective difference between \( \lambda \) and \( \lambda_{eq} \). This trend is echoed in the magnitude of the sample size ratio, with magnitude increasing in the discrepancy between \( \lambda_{eq} \) and 0.90. Notice that over values considered the ranges of \( \sqrt{n\theta} \) are comparable among the the micro-array, GWAS and biomarker simulation studies. Therefore, the “all” or “nothing” rapid rise in the \( \lambda \)-powers with increasing sample size here must be solely due to the distribution of the TPF, \( S_m/M_m \), being even more dramatically spiked, since the number of simultaneous tests, \( m \), is in this case, considerably larger.

8 Appendix: Proofs

Proof of Theorem 4.1. The author wishes to thank Professor Thomas G. Kurtz (Kurtz, 2016) for assistance with this proof. Recall the nominal p-values, \( P_i = \tilde{F}_{0,n}^{-1}(X_{i,n}) \), their common CDF, \( G \), listed in expression 3 in the text and their order statistics \( P_{m(i)} \). Let \( G_m \) be the empirical C.D.F. of \( \{P_1, P_2, \ldots, P_m\} \).

\[
G_m(u) = m^{-1} \sum_{i=1}^{m} I(P_i \leq u)
\]  

(35)

By Kolmogorov’s theorem, \( G_m(u) \xrightarrow{a.s.} G(u) \) at all continuity points, \( u \), of \( G \). By assumption the family \( \{F_{\nu,n}^{-1} : \nu \geq 0\} \) is absolutely continuous and has the monotone likelihood ratio property. It follows that each of the ratios \( f_{\nu,n}/f_{0,n} \) is monotone and hence the mixture of likelihood ratios, \( f_{A,n}/f_{0,n} = \sum_s s_i f_{\nu_i,n}/f_{0,n} \) is monotone. It follows that \( G \) is concave and therefore \( G(uf) = u \) has one non-zero solution which we will call \( \gamma \). Let \( \mathcal{N} \subset \Omega \) be the set of measure zero such that \( G_m(\gamma f) \to G(\gamma f) \) for all \( \omega \in \Omega \setminus \mathcal{N} \), and consider \( \omega \) fixed in this set of measure 1 for the
remainder of this proof. Substituting $m^{-1}J_m f$ for $u$ in expression 35 shows that

$$m^{-1}J_m = G_m(m^{-1}J_m f)$$

(36)

Let $H_m(u) = G_m(uf) - u$ and $H(u) = G(uf) - u$. While $H^{-1}(0) = \{0, \gamma\}$ contains only 0 and a unique non-zero solution, $G_m$ is a step function and therefore, $H_m^{-1}(0) = \{0, u_1, u_2, \ldots, u_k\}$ can contain multiple non-zero solutions. None-the-less, for each $m$, $H_m^{-1}(0)$ is a finite set. By definition, $J_m/m$ is an element of the set $H_m^{-1}(0)$. It follows that

$$m^{-1}J_m \leq \sup H_m^{-1}(0) = \max H_m^{-1}(0).$$

where the second line follows because the set is finite. Thus, taking limsup with respect to $m$ on both sides above gives:

$$\limsup_m m^{-1}J_m \leq \limsup_m \max H_m^{-1}(0) = H^{-1}(0) = \gamma.$$

where the last equality follows because we can interchange the order of the limsup and maximum and because the limit exists. In the other direction, next note that because $m^{-1}J_m$ is a solution to $u = G_m(uf)$, it also follows that $m^{-1}J_m \geq u$ for every $u$ such that $u < G_m(uf)$. Thus,

$$m^{-1}J_m \geq \sup\{u : u < G_m(uf)\} = \sup H_m^{-1}((0, \infty)).$$

(37)

Because of the convexity of the limiting function, $G$, it follows, for $m$ large enough, that $\sup H_m^{-1}((0, \infty)) = \max H_m^{-1}(0)$. Therefore, upon taking liminf with respect to $m$ on both sides we have:

$$\liminf_m m^{-1}J_m \geq \liminf_m \sup H_m^{-1}((0, \infty)) = \liminf_m \max H_m^{-1}(0) = H^{-1}(0) = \gamma$$

where the last equality follows because we can interchange the order of liminf and the maximum and because the limit exists. This completes the proof. \qed
Proof of Theorem 4.3. First, we note that

$$m^{-1} S_m = m^{-1} \sum_{i=1}^{m} \xi_i I \left( P_i \leq m^{-1} J_m f \right),$$

(38)

is the average of row $m$ in a triangular array of finite exchangeable sequences. We will apply Theorem 1 of Taylor and Patterson (1985). Let $W_{m,i} = \xi_i I \left( P_i \leq m^{-1} J_m f \right), \mu_m = E[W_{m,1}]$ and $Z_{m,i} = W_{m,i} - \mu_m$. We must show that (i) the increments on the $m$th row, $W_{m,i}$, each converge almost surely to respective elements of a sequence $W_{\infty,i}$; (ii) the increments $W_{m,i}$ have variances tending to a limit and (iii) for each $m,i$ and $j$, the covariance of increments $W_{m,i}$ and $W_{m,j}$ tend to zero.

Remark 8.1. Our condition (i), element-wise almost sure convergence, which on surface appears weaker than the corresponding first condition in the cited reference, almost sure monotone decreasing distances to the limit, is sufficient in the context of the other assumptions. See the remark following the proof of Theorem 3 in that reference.

Verification of condition (i) is trivial, as it follows by Theorem 4.1 that $W_{m,i} \rightarrow W_{\infty,i} = \xi_i I \left( P_i \leq \gamma f \right)$ almost surely as $m \rightarrow \infty$ for each $i$. Let $\mu = E[W_{\infty,1}]$. Condition (ii) follows easily since $Z_{m,i}$ is bounded, so that by the LDCT, for each $i$, $E[Z_{m,i}^2] \rightarrow E[Z_{\infty,i}^2]$ as $m \rightarrow \infty$. Note that the same argument verifies that $\mu_m \rightarrow \mu$. Next, to verify that condition (iii) is satisfied, note first, for $1 \leq i_1 < i_2 \leq m$, that $(W_{m,i_1} - \mu_m)(W_{m,i_2} - \mu_m)$ is bounded above by 4, and converges almost surely to $(W_{\infty,i_1} - \mu)(W_{\infty,i_2} - \mu)$, by Theorem 4.1. Thus, condition (iii) follows by the LDCT. We may now apply Theorem 1 of Taylor and Patterson (1985) to conclude that $m^{-1} \sum_{i=1}^{m} Z_{m,i} \rightarrow 0$ almost surely as $m \rightarrow \infty$. Therefore,

$$\lim_{m \rightarrow \infty} m^{-1} S_m = \lim_{m \rightarrow \infty} \mu_m + m^{-1} \sum_{i=1}^{m} Z_{m,i}$$

$$= \mu,$$

with probability one,

and the last written expectation is equal to $r \mathbb{P} \{ P_i \leq \gamma f \mid \xi_i = 1 \}$. Because $m^{-1} M_m \rightarrow r$ almost surely as $m \rightarrow \infty$, it follows that $M_m^{-1} S_m \rightarrow \mathbb{P} \{ P_i \leq \gamma f \mid \xi_i = 1 \} = \pi_{\mu}$ almost surely as $m \rightarrow \infty$. Because $m^{-1} S_m$ is bounded by 1, the average power, its expectation, also converges to $\pi_{\mu}$ as $m \rightarrow \infty$ by the LDCT. \qed
**Proof of Corollary 4.3.1.** The first and second statements follow immediately from Theorems 4.1 and 4.3:

\[ m^{-1}T_m = m^{-1}(J_m - S_m) \xrightarrow{a.s.} \gamma - r \pi_{\mu_i} = (1 - r) f, \]

and

\[ J_m^{-1}T_m = 1 - J_m^{-1}S_m \xrightarrow{a.s.} 1 - r \pi_{\mu_i}/\gamma = (1 - r) f. \]

where the last equality in each of the expressions above follow since \( \gamma = G(\gamma f). \) The third statement follows by the LDCT.

**Proof of Corollary 4.5.1.** In the definition of the IST power function, \( \pi_{\mu_i}, \) appearing in the statement of Theorem 4.3, \( \pi_{\mu_i} = \bar{F}_{\nu,n}(\bar{F}_{0,n}^{-1}(\gamma f)) \) we substitute \( \gamma = (1 - f_0)^{-1} r \pi_{\mu_i} \) from expression 24 obtaining the result.

**Proof of Theorem 4.6.** The proof of both statements is made possible by considering each as a stopped stochastic process. We first revisit the empirical CDF’s defined in the proofs of Theorems 4.1 and 4.3. In the case of \( J_m/m, \) we have,

\[ G_m(t) = m^{-1} \sum_{i=1}^{m} I(P_i \leq t), \]

\[ G(t) = (1 - r) t + r \bar{F}_{\nu,n}(\bar{F}_{0,n}^{-1}(t)). \]

First, by the standard theory of empirical distributions, see for example Shorack, Galen R. and Wellner, Jon A. (1984)

\[ W_m(t) = \sqrt{m} (G_m(t) - G(t)) \xrightarrow{D} W(t), \]

a Gaussian process with covariance function

\[ \rho(s, t) = G(s \wedge t) - G(s) G(t). \]

Having shown that the paths of the centered and scaled stochastic process \( W_m \) converge in distribution, we can obtain the CLT for the centered and scaled version of the positive fraction, \( J_m/m, \) claimed in expression 26, by appealing to a result concerning weak limits of stopped stochastic processes. Towards this end, define the family of filtrations,

\[ \mathcal{F}_t = \sigma (\{ \xi_i I(P_i \leq t), (1 - \xi_i) I(P_i \leq t), i \geq 1 \}). \]
Note that $W$ and $W_m$ are adapted to $\mathcal{F}_t$ for all $m \geq 1$, and that $\tau_m = m^{-1} J_m f$ is a stopping-time with respect to this filtration since, clearly, $\{\tau_m \leq t\} \in \mathcal{F}_t$. We will apply Theorem 4.2.1 of Silvestrov (2004) to conclude that $W_m(\tau_m)$ converges in distribution to $W(\gamma f)$. To do so, we must verify the following three conditions.

i. $(W_m, \tau_m) \overset{D}{\to} (W, \gamma f)$

ii. $P\{\lim_{t \to 0} W(\gamma f + t) = W(\gamma f)\} = 1$

iii. For all $\delta > 0, \lim_{\epsilon \to 0} \limsup_{m \to \infty} P\{\Delta(W_m, c, 1) > \delta\} = 0$

where $\Delta(x, c, 1)$ is the Skorohod modulus of compactness,

$$\Delta(x, c, 1) = \sup_{t, t', t'' \in [0, 1]} \sup_{t - \epsilon < t' < t < t' + \epsilon} |x(t) - x(t')| + |x(t'') - x(t)|$$

Having already established that the paths of $W_m$ converge in distribution to those of $W$ above 43, as well as the almost sure convergence of $\tau_m = J_m f/m$ to the constant $\tau = \gamma f$ in theorem 4.1, then part (i) is satisfied by Slutsky’s theorem. Item (ii) is true because the limiting process, $W$, a Gaussian process, is almost surely continuous at every $t \in [0, 1]$. The almost sure continuity of the limiting process, $W$, also guarantees that the third condition, (iii), holds as well. Thus

$$W_m(m^{-1} J_m f) \overset{D}{\to} W(\gamma f),$$

where the limiting random variable is normally distributed, of mean zero, and variance

$$\rho(\gamma f, \gamma f) = G(\gamma f) - G^2(\gamma f) = \gamma (1 - \gamma)$$

The statement 46 is nearly statement 26, except that in 26, centering is with respect to the deterministic limit, $\gamma = G(\gamma f)$. Thus, starting with $\sqrt{m} (J_m/m - \gamma)$ we add and subtract, obtaining a “delta-method” term. We can now write

$$X_m = \sqrt{m} (m^{-1} J_m - \gamma)$$

$$= \sqrt{m} (G_m(m^{-1} J_m f) - G(\gamma f))$$

$$= \sqrt{m} (G_m(m^{-1} J_m f) - G(m^{-1} J_m f)) + \sqrt{m} (G(m^{-1} J_m f) - G(\gamma f))$$

$$= W_m(m^{-1} J_m f) + f \hat{G}(\gamma f) X_m + \epsilon_m$$
where $\epsilon_m = o_p(1)$. The conclusion of this portion of the proof requires that $f \hat{G}(\gamma f) < 1$. By the monotone likelihood ratio property, it follows that $G$ is concave as is the function $fG$. Because $fG(u) = u$ when $u = 0$ and when $u = \gamma f$, then there is exactly one $u_1 \in (0, \gamma f)$ for which $f \hat{G}(u_1) = 1$. By the concavity of $fG$, $f \hat{G}(u) > 1$ for $0 < u < u_1$ and $f \hat{G}(u) < 1$ for $u_1 < u < \gamma f$. Thus $f \hat{G}(\gamma f) < 1$. With this bound in hand, the steps above leading to 48 can be iterated ad-infinitum, yielding

$$X_m = \left(W_m(m^{-1} J_m f) + \epsilon_m\right) \sum_{k=0}^{\infty} f^k \hat{G}(\gamma f)^k$$

$$= \frac{W_m(m^{-1} J_m f) + o_p(1)}{1 - f \hat{G}(\gamma f)} \xrightarrow{D} X = \frac{W(\gamma f)}{1 - f \hat{G}(\gamma f)},$$

which establishes claim 26 above and identifies the form of the limiting mean zero normal random variable. Its variance, $\tau^2$, is given by

$$\tau^2 = \frac{\gamma(1-\gamma)}{(1 - \hat{G}(\gamma f)^f)^2}. \quad (49)$$

Next, we turn our attention towards verification of the CLT for the centered and scaled TPF, $S_m/M_m$, which is claim 28 above. We first revisit the empirical sub CDF’s corresponding to the joint outcome of the indicator $\xi_i$ and the indicator $I(P_i \leq t)$ and their almost sure deterministic limits.

$$G_{m,0}(t) = m^{-1} \sum_{i=1}^{m} (1 - \xi_i) I(P_i \leq t), \quad (50)$$

$$G_{m,1}(t) = m^{-1} \sum_{i=1}^{m} \xi_i I(P_i \leq t), \quad (51)$$

$$G_0(t) = (1 - r) t, \quad (52)$$

$$G_1(t) = r \bar{F}_{\nu,n}(\bar{F}_0^{-1}(t)). \quad (53)$$

This time we look at the bivariate process with components scaled and centered versions of $G_{m,0}(t)$ and $G_{m,1}(t)$. Again, from the standard results concerning empirical CDF’s, (Genovese...
and Wasserman, 2004; Shorack, Galen R. and Wellner, Jon A., 1984) the following bivariate process converges in distribution.

\[
\begin{bmatrix}
W_{m,0}(t) \\
W_{m,1}(t)
\end{bmatrix} = \sqrt{m} \begin{bmatrix}
G_{m,0}(t) - G_0(t) \\
G_{m,1}(t) - G_1(t)
\end{bmatrix} \overset{d}{\to} \begin{bmatrix}
W_0(t) \\
W_1(t)
\end{bmatrix},
\]

where the limit is a bivariate Gaussian process with covariance kernel

\[
R(s,t) = \begin{bmatrix}
G_0(s \land t) - G_0(s) G_0(t) & -G_0(s) G_1(t) \\
-G_0(t) G_1(s) & G_1(s \land t) - G_1(s) G_1(t)
\end{bmatrix}.
\]

We remark in passing, something which should be already clear, that \(W_m(t) = W_{m,0}(t) + W_{m,1}(t)\) and \(W(t) = W_0(t) + W_1(t)\). If follows from some algebra and the fact that \(\gamma = G(\gamma f)\) that this “new characterization” of \(W\) is consistent with the characterization of the process given above. This allows us to compute covariances between \(W(t)\) and either \(W_0(t)\) or \(W_1(t)\) according to the covariance kernel, \(R(s,t)\), as needed below. Note that \(W_0, W_1\) and for all \(m, W_{m,0}, W_{m,1}\) are all adapted to the filtration, \(\mathcal{F}_t\) and that \(\tau_m = m^{-1} J_m f\) is a stopping time with respect to the it, so that once again we apply the result of Silvestrov (2004) to obtain convergence of the stopped bivariate process. As remarked above, the conditions are satisfied since convergence is already established and the limit is almost surely continuous.

\[
\begin{bmatrix}
W_{m,0}(J_m f/m) \\
W_{m,1}(J_m f/m)
\end{bmatrix} = \sqrt{m} \begin{bmatrix}
G_{m,0}(J_m f/m) - G_0(J_m f/m) \\
G_{m,1}(J_m f/m) - G_1(J_m f/m)
\end{bmatrix} \overset{d}{\to} \begin{bmatrix}
W_0(\gamma f) \\
W_1(\gamma f)
\end{bmatrix}, \quad (54)
\]

Focusing for the moment on the second component above in (54) and adding and subtracting as before,

\[
X_{m,1} \equiv \sqrt{m} \left( m^{-1} S_m - r \pi_m \right)
= \sqrt{m} \left( G_{m,1}(J_m f/m) - G_1(\gamma f) \right)
= \sqrt{m} \left( G_{m,1}(J_m f/m) - G_1(J_m f/m) \right)
+ \sqrt{m} \left( G_1(J_m f/m) - G_1(\gamma f) \right)
\]

Thus,

\[
X_{m,1} \overset{d}{\to} X_1 = W_1(\gamma f) + f \dot{G}_1(\gamma f) X
= W_1(\gamma f) + \frac{\dot{G}_1(\gamma f) f}{1 - f G(\gamma f)} (W_0(\gamma f) + W_1(\gamma f))
\]

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which is a mean zero normal random variable having variance equal to

$$\text{var}[X_1] = v_1 + \dot{G}_1^2(\gamma f) f^2 r^2 + 2f \frac{\dot{G}_1(\gamma f) (v_1 + c_{0,1})}{1 - f \dot{G}(\gamma f)}$$

(55)

where $v_1 = r \pi_{\mu} - r^2 \pi_{\mu}^2$ and $c_{0,1} = -r (1 - r) \gamma f \pi_{\mu}$. To complete the proof of statement 28 we need only apply the delta method once more, for a ratio estimate. Before proceeding, we note that

$$\sqrt{m}(M_m/m - r) = \sqrt{m} (G_{m,1}(1) - G_1(1))$$

$$\overset{d}{\rightarrow} W_1(1)$$

Thus,

$$Z_{m,1} = \sqrt{m} \left( \frac{S_m}{M_m} - \pi_{\mu} \right)$$

$$= \sqrt{m} \left( \frac{S_m/m - r \pi_{\mu}}{M_m/m - \pi_{\mu}} \right)$$

$$= \frac{1}{r} \sqrt{m} \left( \frac{S_m}{m} - r \pi_{\mu} \right) - \frac{r \pi_{\mu}}{r^2} \sqrt{m} \left( \frac{M_m}{m} - r \right) + \epsilon_m$$

$$\overset{d}{\rightarrow} \frac{1}{r} \left\{ W_1(\gamma f) + \frac{f \dot{G}_1(\gamma f)}{1 - f \dot{G}(\gamma f)} (W_0(\gamma f) + W_1(\gamma f)) \right\} - \frac{r \pi_{\mu}}{r^2} W_1(1)$$

$$\equiv Z_1 = N(0, \sigma^2)$$

where $\epsilon_m$ above is a new term that is $o_p(1)$ and this completes the proof of statement 28 above and identifies the form of the limiting mean zero normal random variable, $Z_1$. Its variance is given by

$$\sigma^2 = r^{-2} \left( \text{var}[X_1] - 2 \pi_{\mu} \text{cov}[X_1, W_1(1)] + \pi_{\mu}^2 \text{var}[W_1(1)] \right)$$

(56)

where $\text{var}[X_1]$ was given above, $\text{var}[W_1(1)] = r (1 - r)$, and

$$\text{cov}[X_1, W_1(1)] = r (1 - r) \left\{ \pi_{\mu} + f \dot{G}_1(\gamma f) \frac{\gamma f + \pi_{\mu}}{1 - f \dot{G}(\gamma f)} \right\}$$

(57)

The proof of the CLT for the centered and scaled version of the false discovery fraction follows fairly easily from the parts proved above. First, re-writing the centered and scaled difference in terms of the TPF, gives the first line, for which we again invoke the delta method, which yields
Convergence of all quantities in the second line was established above. The remaining lines are algebraic, and make use of the fact that \( \dot{G}_1(t) = \dot{G}(t) - (1 - r) \) (line 5) and \( G(\gamma f) = \gamma \) (line 6). As before, \( \epsilon_m \) is a new term that is \( o_p(1) \). The limiting random variable is of mean zero and normally distributed, having variance equal to

\[
\alpha^2 = \frac{(1 - r) f \left( 1 - (1 - r) f \gamma \right)}{\gamma}
\]

Proof of Theorem 4.9. Before we begin, we present an alternate expression for the event that the number of true positives is \( s \) or greater.

\[
\{S_m \geq s\} = \left\{ P_{1,(s)} \leq \frac{J_m f}{m} \right\}
\]

This is clearly the case, since there can be \( s \) or more true positives if and only if the \( s^{th} \) order statistic in the non-null distributed population is less than the threshold \( J_m f / m \). Now, towards obtaining a lower bound, we begin with the fact that the expected value of discrete non-negative variable can be derived as the sum of its cCDF. This can be used to write an expression of the
FST average power by first conditioning on $M_m$:

\[
\pi_{av,m} = \mathbb{E}[S_m/M_m] = \sum_{\ell=1}^{m} \ell^{-1} \mathbb{E}[S_m \mid M_m = \ell] \mathbb{P}\{M_m = \ell\}
\]

\[
= \sum_{\ell=1}^{m} \ell^{-1} \sum_{s=1}^{m} \mathbb{P}\{S_m \geq s \mid M_m = \ell\} \mathbb{P}\{M_m = \ell\}
\]

\[
= \sum_{\ell=1}^{\infty} \ell^{-1} \sum_{s=1}^{m} \mathbb{P}\{P_{1,(s)} \leq f_{J_m/m}\} \mathbb{P}\{M_m = \ell\}
\]

\[
\geq \sum_{\ell=1}^{\infty} m^{-1} \sum_{s=1}^{m} \mathbb{P}\{P_{1,(s)} \leq fs/m\} \mathbb{P}\{M_m = \ell\},
\]

where the first equality is just the law of total probability, conditioning on values of $M_N$, the second equality is just the fact that an expectation of a non-negative random variable is the sum over values of $s$ of its cCDF, the third equality is an application of the alternate expression stated above, and the lower bound in the last line is deduced by observing that $P_{1,(s)} \leq f_{J_N/N}$ if and only if $J_N \geq s$. The last written line is equal to $\pi_{av,m}^L$ as presented in Theorem 4.9 because the CDF of the $s^{th}$ order statistic, $P_{1,(s)}$, takes the form shown involving the beta distribution. \(\square\)
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Figure 1: Density plot of true positive fraction, $S_m/M_m$, when $m=10,000$, showing average power (heavy dashed line) which nearly coincides with the mode and median. The $\lambda$-power is the tail probability to the right of a given threshold, $\lambda$. Also shown (light dotted line) are $\lambda_{S/M}(\pi_m)$, the threshold at which the $\lambda$-power is equal to the average power and the approximate normal asymptotic distribution, (dot-dash line).
Figure 2: Numerical partial derivatives of power function with respect to θ, f and r, with ranges considered scaled to unity.
Table 2: Excerpted results from a simulation study modelling biomarker studies, $m = 200$. IST average power, oracle power, lower bound and simulated average power for a selection of effect sizes, values of $\mathbb{E}[M_m]$, FDR, and $n$.

| Eff Sz | $\mathbb{E}[M_m]$ | n  | FDR  | $\pi_{av,m}$ | $\pi_{o}$ | $\tau_{av,m}$ |
|--------|------------------|----|------|---------------|----------|---------------|
| 0.60   | 5 70             | 0.15 | 0.224 | 0.704         | 0.707    | 0.692         |
| 0.60   | 5 80             | 0.15 | 0.235 | 0.700         | 0.798    | 0.790         |
| 0.60   | 5 90             | 0.15 | 0.241 | 0.860         | 0.863    | 0.850         |
| 0.60   | 5 100            | 0.15 | 0.246 | 0.906         | 0.908    | 0.896         |
| 0.60   | 20 50            | 0.15 | 0.052 | 0.664         | 0.685    | 0.668         |
| 0.60   | 20 60            | 0.15 | 0.052 | 0.781         | 0.796    | 0.774         |
| 0.60   | 20 70            | 0.15 | 0.053 | 0.859         | 0.870    | 0.857         |
| 0.60   | 20 80            | 0.15 | 0.053 | 0.911         | 0.919    | 0.905         |
| 0.60   | 60 40            | 0.15 | 0.388 | 0.706         | 0.777    | 0.708         |
| 0.60   | 60 50            | 0.15 | 0.388 | 0.823         | 0.872    | 0.823         |
| 0.60   | 60 60            | 0.15 | 0.388 | 0.927         | 0.927    | 0.927         |
| 0.60   | 100 30           | 0.15 | 0.546 | 0.632         | 0.796    | 0.634         |
| 0.60   | 100 40           | 0.15 | 0.563 | 0.788         | 0.895    | 0.788         |
| 0.60   | 100 50           | 0.15 | 0.563 | 0.879         | 0.946    | 0.875         |
| 0.80   | 5 40             | 0.15 | 0.222 | 0.697         | 0.701    | 0.678         |
| 0.80   | 5 50             | 0.15 | 0.239 | 0.844         | 0.847    | 0.842         |
| 0.80   | 5 60             | 0.15 | 0.247 | 0.924         | 0.925    | 0.909         |
| 0.80   | 20 30            | 0.15 | 0.052 | 0.652         | 0.712    | 0.685         |
| 0.80   | 20 40            | 0.15 | 0.052 | 0.859         | 0.870    | 0.857         |
| 0.80   | 60 20            | 0.15 | 0.385 | 0.616         | 0.703    | 0.617         |
| 0.80   | 60 30            | 0.15 | 0.388 | 0.845         | 0.889    | 0.843         |
| 0.80   | 100 20           | 0.15 | 0.561 | 0.717         | 0.855    | 0.715         |
| 0.80   | 100 30           | 0.15 | 0.563 | 0.896         | 0.955    | 0.897         |
| 1.00   | 5 30             | 0.15 | 0.233 | 0.790         | 0.794    | 0.774         |
| 1.00   | 20 20            | 0.15 | 0.052 | 0.699         | 0.720    | 0.704         |
| 1.00   | 20 30            | 0.15 | 0.053 | 0.913         | 0.921    | 0.908         |
| 1.00   | 60 20            | 0.15 | 0.388 | 0.853         | 0.697    | 0.853         |
| 1.00   | 100 20           | 0.15 | 0.563 | 0.904         | 0.960    | 0.903         |
Table 3: Excerpted results from a simulation study modelling biomarker studies, $m = 200$. Shown are the $\lambda$-power at $\lambda = 75\%$ and at $90\%$ from CLT and from simulations, $\lambda_{SM}(\pi_{pi})$, and samplesize ratio. The IST average power is also shown for comparison.
Table 4: Excerpted results from the simulation study on the use of the CLT for the FDF to bound the FDF with large probability with FDR and \( r \) fixed at 15\% and 2.5\%, respectively. Displayed are the parameter settings, \( m, \theta, \) and power, followed by the value of the reduced FDR, \( f' \) required to bound the FDF with probability \( 1 - f_0 \), the sample sizes \( n_{0,0}, n_{0,1}, n_{1,0}, \) and \( n_{1,1} \), required for specified average power at BHFDR(\( f \)) specified average power at BHFDR(\( f' \)), specified \( \lambda_{90} \)-power at BHFDR(\( f \)), and specified \( \lambda_{90} \)-power at BHFDR(\( f' \)). The last column is the simulated value, \( \hat{\pi}_{T/J}(f_0) \), of the tail probability of the FDF under BHFDR(\( f' \)).

| \( m \)  | \( \text{Eff Sz} \) | Power | \( f' \) | \( n_{0,0} \) | \( n_{0,1} \) | \( n_{1,0} \) | \( n_{1,1} \) | \( \hat{\pi}_{T/J}(f_0) \) |
|-----|-------|-------|-----|-------|-------|-------|-------|----------------|
| 1000 | 0.6667 | 0.6   | 0.069 | 51    | 65    | 75    | 89    | 0.0760        |
| 1000 | 0.6667 | 0.8   | 0.071 | 66    | 78    | 91    | 102   | 0.0900        |
| 1000 | 0.8333 | 0.6   | 0.069 | 33    | 43    | 50    | 59    | 0.0790        |
| 1000 | 0.8333 | 0.8   | 0.071 | 43    | 51    | 59    | 67    | 0.0880        |
| 1000 | 1.0000 | 0.6   | 0.069 | 24    | 31    | 36    | 42    | 0.0910        |
| 1000 | 1.0000 | 0.8   | 0.071 | 31    | 36    | 42    | 47    | 0.0770        |
| 2500 | 0.6667 | 0.6   | 0.097 | 51    | 57    | 75    | 83    | 0.1020        |
| 2500 | 0.6667 | 0.8   | 0.098 | 66    | 72    | 87    | 94    | 0.0980        |
| 2500 | 0.8333 | 0.6   | 0.097 | 33    | 38    | 50    | 54    | 0.0880        |
| 2500 | 0.8333 | 0.8   | 0.098 | 43    | 47    | 57    | 61    | 0.1100        |
| 2500 | 1.0000 | 0.6   | 0.097 | 24    | 27    | 36    | 39    | 0.1150        |
| 2500 | 1.0000 | 0.8   | 0.098 | 31    | 34    | 40    | 43    | 0.1040        |
| 5000 | 0.6667 | 0.6   | 0.112 | 51    | 55    | 75    | 80    | 0.1290        |
| 5000 | 0.6667 | 0.8   | 0.113 | 66    | 70    | 85    | 90    | 0.0970        |
| 5000 | 0.8333 | 0.6   | 0.113 | 33    | 36    | 50    | 53    | 0.1080        |
| 5000 | 0.8333 | 0.8   | 0.113 | 43    | 46    | 56    | 58    | 0.1260        |
| 5000 | 1.0000 | 0.6   | 0.113 | 24    | 26    | 36    | 38    | 0.1080        |
| 5000 | 1.0000 | 0.8   | 0.113 | 31    | 33    | 39    | 41    | 0.1050        |
| 7500 | 0.6667 | 0.6   | 0.120 | 51    | 54    | 75    | 80    | 0.1120        |
| 7500 | 0.6667 | 0.8   | 0.120 | 66    | 69    | 85    | 88    | 0.1100        |
| 7500 | 0.8333 | 0.6   | 0.120 | 33    | 36    | 50    | 53    | 0.1020        |
| 7500 | 0.8333 | 0.8   | 0.120 | 43    | 45    | 55    | 57    | 0.1210        |
| 7500 | 1.0000 | 0.6   | 0.120 | 24    | 26    | 36    | 38    | 0.1090        |
| 7500 | 1.0000 | 0.8   | 0.120 | 31    | 32    | 39    | 41    | 0.1160        |
| 10000| 0.6667 | 0.6   | 0.124 | 51    | 53    | 75    | 78    | 0.1310        |
| 10000| 0.6667 | 0.8   | 0.124 | 66    | 69    | 84    | 87    | 0.1060        |
| 10000| 0.8333 | 0.6   | 0.124 | 33    | 35    | 50    | 51    | 0.1420        |
| 10000| 0.8333 | 0.8   | 0.124 | 43    | 45    | 55    | 57    | 0.1150        |
| 10000| 1.0000 | 0.6   | 0.124 | 24    | 25    | 36    | 38    | 0.1250        |
| 10000| 1.0000 | 0.8   | 0.124 | 31    | 32    | 39    | 40    | 0.1040        |
| 20000| 0.6667 | 0.6   | 0.131 | 51    | 52    | 75    | 78    | 0.1240        |
| 20000| 0.6667 | 0.8   | 0.132 | 66    | 68    | 83    | 85    | 0.1300        |
| 20000| 0.8333 | 0.6   | 0.131 | 33    | 35    | 50    | 51    | 0.1360        |
| 20000| 0.8333 | 0.8   | 0.132 | 43    | 45    | 54    | 55    | 0.1160        |
| 20000| 1.0000 | 0.6   | 0.131 | 24    | 25    | 36    | 36    | 0.1240        |
| 20000| 1.0000 | 0.8   | 0.132 | 31    | 32    | 38    | 39    | 0.1190        |
| $n$ | $\rho$ | $\pi_{10}$ | $\lambda_{75}$ | $\hat{\mathbf{FDR}}$ | $\pi_{ij}(0.18)$ |
|-----|-------|----------|-----------|----------------|----------------|
| 14  | 0.00  | 0.7172   | 0.3000    | 0.1421         | 0.1910         |
| 14  | 0.10  | 0.7080   | 0.5020    | 0.1402         | 0.2080         |
| 14  | 0.20  | 0.7173   | 0.5260    | 0.1432         | 0.2320         |
| 14  | 0.30  | 0.6965   | 0.4780    | 0.1412         | 0.2310         |
| 14  | 0.40  | 0.7045   | 0.4930    | 0.1421         | 0.2180         |
| 14  | 0.50  | 0.6993   | 0.4860    | 0.1408         | 0.2180         |
| 14  | 0.60  | 0.7034   | 0.4830    | 0.1413         | 0.2280         |
| 14  | 0.70  | 0.6954   | 0.4910    | 0.1447         | 0.2500         |
| 14  | 0.80  | 0.7107   | 0.4900    | 0.1378         | 0.2220         |
| 16  | 0.00  | 0.7989   | 0.8680    | 0.1419         | 0.1670         |
| 16  | 0.10  | 0.7924   | 0.6950    | 0.1420         | 0.2370         |
| 16  | 0.20  | 0.7870   | 0.6880    | 0.1432         | 0.2270         |
| 16  | 0.30  | 0.7882   | 0.6940    | 0.1426         | 0.2350         |
| 16  | 0.40  | 0.7926   | 0.7020    | 0.1420         | 0.2270         |
| 16  | 0.50  | 0.7871   | 0.6940    | 0.1427         | 0.2420         |
| 16  | 0.60  | 0.7966   | 0.7050    | 0.1439         | 0.2350         |
| 16  | 0.70  | 0.7967   | 0.7060    | 0.1423         | 0.2250         |
| 16  | 0.80  | 0.7884   | 0.6780    | 0.1422         | 0.2150         |

Table 5: Average power, $\lambda_{75}$ power, empirical FDR, and $\Pr(FDF > 0.18)$ at fixed effect size=1.25, FDR=15%, $r=5\%$ and 2000 simultaneous tests, for sample sizes 14 and 16 and correlation varies over 0 to 80% in increments of 10%, with block size 100.
Table 6: Excerpted results from a simulation study modelling micro-array studies, \( m = 54,675 \).

| Eff Sz | \( E[M_m] \) | \( n \) | FDR | \( \pi_{av,m} \) | \( \pi_\text{oracle} \) | \( \pi_\text{lower} \) | \( \pi_{av,m} \) |
|--------|-------------|-------|------|----------------|----------------|----------------|----------------|
| 0.60   | 100         | 100   | 0.15 | 0.444         | 0.683          | 0.683          | 0.681          |
| 0.60   | 100         | 110   | 0.15 | 0.444         | 0.763          | 0.763          | 0.762          |
| 0.60   | 100         | 120   | 0.15 | 0.444         | 0.826          | 0.826          | 0.825          |
| 0.60   | 100         | 130   | 0.15 | 0.444         | 0.874          | 0.874          | 0.874          |
| 0.60   | 100         | 140   | 0.15 | 0.444         | 0.910          | 0.910          | 0.910          |
| 0.60   | 1000        | 70    | 0.15 | 0.640         | 0.662          | 0.665          | 0.662          |
| 0.60   | 1000        | 80    | 0.15 | 0.743         | 0.761          | 0.764          | 0.761          |
| 0.60   | 1000        | 90    | 0.15 | 0.805         | 0.835          | 0.836          | 0.834          |
| 0.60   | 1000        | 100   | 0.15 | 0.815         | 0.887          | 0.889          | 0.887          |
| 0.60   | 1000        | 100   | 0.15 | 0.815         | 0.924          | 0.925          | 0.924          |
| 0.60   | 2000        | 60    | 0.15 | 0.616         | 0.640          | 0.647          | 0.640          |
| 0.60   | 2000        | 70    | 0.15 | 0.732         | 0.752          | 0.757          | 0.752          |
| 0.60   | 2000        | 80    | 0.15 | 0.817         | 0.832          | 0.836          | 0.832          |
| 0.60   | 2000        | 90    | 0.15 | 0.864         | 0.888          | 0.891          | 0.888          |
| 0.60   | 2000        | 100   | 0.15 | 0.870         | 0.927          | 0.929          | 0.927          |
| 0.80   | 100         | 60    | 0.15 | 0.444         | 0.717          | 0.717          | 0.718          |
| 0.80   | 100         | 70    | 0.15 | 0.444         | 0.835          | 0.836          | 0.837          |
| 0.80   | 100         | 80    | 0.15 | 0.444         | 0.909          | 0.909          | 0.908          |
| 0.80   | 100         | 90    | 0.15 | 0.630         | 0.653          | 0.656          | 0.654          |
| 0.80   | 100         | 100   | 0.15 | 0.794         | 0.816          | 0.818          | 0.815          |
| 0.80   | 1000        | 60    | 0.15 | 0.816         | 0.907          | 0.908          | 0.907          |
| 0.80   | 2000        | 40    | 0.15 | 0.727         | 0.747          | 0.753          | 0.747          |
| 0.80   | 2000        | 50    | 0.15 | 0.857         | 0.875          | 0.879          | 0.876          |
| 1.00   | 100         | 40    | 0.15 | 0.444         | 0.725          | 0.726          | 0.726          |
| 1.00   | 100         | 50    | 0.15 | 0.444         | 0.886          | 0.886          | 0.885          |
| 1.00   | 100         | 60    | 0.15 | 0.734         | 0.754          | 0.756          | 0.753          |
| 1.00   | 100         | 70    | 0.15 | 0.816         | 0.915          | 0.916          | 0.914          |
| 1.00   | 100         | 80    | 0.15 | 0.814         | 0.830          | 0.835          | 0.830          |
| 1.00   | 100         | 90    | 0.15 | 0.814         | 0.830          | 0.835          | 0.830          |

IST average power, oracle power, lower bound and simulated average power for a selection of effect sizes, values of \( E[M_m] \), FDR, and \( n \).
Table 7: Excerpted results from a simulation study modelling micro-array studies, $m = 54,675$, for various values of effect sizes, values of $E[M_m]$, FDR, and $n$. Shown are the $\lambda$-power at $\lambda = 75\%$ and at $90\%$ from CLT and from simulations, $\lambda_{SM}(\pi_m)$ and sample size ratio. The IST average power is also shown for comparison.
Table 8: Excerpted results from a simulation study modelling GWA studies, $m = 1,000,000$. IST average power, oracle power, lower bound and simulated average power for a selection of effect sizes, values of $\mathbb{E}[M_m]$, FDR, and $n$. 

| Eff Sz | $\mathbb{E}[M_m]$ | n | FDR | $\hat{\pi}_L$ | $\hat{\pi}_{AV,m}$ | $\hat{\pi}_{PB}$ | $\pi_o$ | $\hat{\pi}_{AV,m}$ |
|--------|------------------|----|-----|----------------|-------------------|----------------|--------|-------------------|
| 0.08   | 400              | 7800 | 0.01 | 0.610 | 0.612 | 0.612 | 0.612 |
| 0.08   | 400              | 8400 | 0.01 | 0.679 | 0.690 | 0.691 | 0.691 |
| 0.08   | 400              | 9000 | 0.01 | 0.705 | 0.757 | 0.758 | 0.757 |
| 0.08   | 400              | 9600 | 0.01 | 0.709 | 0.813 | 0.813 | 0.813 |
| 0.08   | 400              | 10200 | 0.01 | 0.709 | 0.858 | 0.858 | 0.857 |
| 0.08   | 400              | 10800 | 0.01 | 0.709 | 0.893 | 0.893 | 0.893 |
| 0.08   | 400              | 11400 | 0.01 | 0.709 | 0.921 | 0.921 | 0.921 |
| 0.28   | 400              | 650  | 0.01 | 0.624 | 0.626 | 0.626 | 0.626 |
| 0.28   | 400              | 750  | 0.01 | 0.687 | 0.704 | 0.704 | 0.705 |
| 0.28   | 400              | 750  | 0.01 | 0.707 | 0.770 | 0.770 | 0.771 |
| 0.28   | 400              | 800  | 0.01 | 0.709 | 0.824 | 0.824 | 0.824 |
| 0.28   | 400              | 850  | 0.01 | 0.709 | 0.868 | 0.868 | 0.868 |
| 0.28   | 400              | 900  | 0.01 | 0.709 | 0.902 | 0.902 | 0.902 |
| 0.28   | 400              | 950  | 0.01 | 0.709 | 0.928 | 0.928 | 0.929 |
| 0.68   | 400              | 120  | 0.01 | 0.668 | 0.676 | 0.676 | 0.677 |
| 0.68   | 400              | 160  | 0.01 | 0.709 | 0.912 | 0.912 | 0.911 |
| 0.08   | 1000             | 7500 | 0.01 | 0.651 | 0.652 | 0.652 | 0.651 |
| 0.08   | 1000             | 8000 | 0.01 | 0.715 | 0.716 | 0.716 | 0.716 |
| 0.08   | 1000             | 8500 | 0.01 | 0.769 | 0.771 | 0.771 | 0.772 |
| 0.08   | 1000             | 9000 | 0.01 | 0.803 | 0.818 | 0.818 | 0.818 |
| 0.08   | 1000             | 9500 | 0.01 | 0.813 | 0.856 | 0.856 | 0.856 |
| 0.08   | 1000             | 10000 | 0.01 | 0.814 | 0.888 | 0.888 | 0.888 |
| 0.08   | 1000             | 10500 | 0.01 | 0.814 | 0.913 | 0.913 | 0.913 |
| 0.28   | 1000             | 600  | 0.01 | 0.622 | 0.623 | 0.623 | 0.623 |
| 0.28   | 1000             | 640  | 0.01 | 0.689 | 0.689 | 0.690 | 0.689 |
| 0.28   | 1000             | 680  | 0.01 | 0.746 | 0.747 | 0.747 | 0.748 |
| 0.28   | 1000             | 720  | 0.01 | 0.791 | 0.797 | 0.797 | 0.797 |
| 0.28   | 1000             | 760  | 0.01 | 0.810 | 0.838 | 0.838 | 0.838 |
| 0.28   | 1000             | 800  | 0.01 | 0.813 | 0.872 | 0.873 | 0.873 |
| 0.28   | 1000             | 840  | 0.01 | 0.814 | 0.900 | 0.900 | 0.900 |
| 0.28   | 1000             | 880  | 0.01 | 0.814 | 0.923 | 0.923 | 0.923 |
| 0.68   | 1000             | 120  | 0.01 | 0.751 | 0.752 | 0.752 | 0.753 |

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Table 9: Excerpted results from a simulation study modelling GWA studies, \( m = 1,000,000 \). Shown are the \( \lambda \)-power at \( \lambda = 75\% \) and at 90% from CLT and from simulations, \( \lambda_{S/M}(\pi_{pi}) \) and samplesize ratio. The IST average power is also shown for comparison.