DATA VOLUME AND POWER OF MULTIPLE TESTS WITH SMALL SAMPLE SIZE PER NULL

Zhiyi Chi[1]
Department of Statistics
University of Connecticut
215 Glenbrook Road, U-4120
Storrs, CT 06269, USA
zchi@stat.uconn.edu

Key Words: multiple tests, pFDR, likelihood ratio, Cramér-type large deviations.

ABSTRACT

In multiple hypothesis testing, the volume of data, defined as the number of replications per null times the total number of nulls, usually defines the amount of resource required. On the other hand, power is an important measure of performance for multiple testing. Due to practical constraints, the number of replications per null may not be large enough in terms of the difference between false and true nulls. For the case where the population fraction of false nulls is constant, we show that, as the difference between false and true nulls becomes increasingly subtle while the number of replications per null cannot increase fast enough, (1) in order to have enough chance that the data to be collected will yield some trustworthy findings, as measured by a conditional version of the positive false discovery rate (pFDR), the volume of data has to grow at a rate much faster than in the case where the number of replications per null can be large enough, and (2) in order to control the pFDR asymptotically, power has to decay to 0 in a rate highly sensitive to rejection criterion and there is no asymptotically most powerful procedures among those that control the pFDR asymptotically at the same level.

1 Introduction

Multiple hypothesis testing often faces situations where distributions under false nulls only have a subtle difference from those under true nulls. To make the difference evident, it is necessary to make repeated measurements from the distributions. As is well known, in order to attain a fixed power, the number of replications for each null, henceforth denoted by k, should be large enough. Roughly speaking, if the difference between the distributions under false nulls and those under true nulls is δ, then k should be of the same order as δ^{-2}. However, in practice, oftentimes k cannot be large enough. There are many reasons for this: the time window that allows measurements is finite, the experimental unit associated with each null can only sustain a limited number of measurements, and so on. Under this circumstance, there are two important and related issues.

[1]Research partially supported by NSF DMS 0706048 and NIH MH 68028.

First, if the underlying objective of the tests is to identify even just a few false nulls irrespective of power, so that one can get useful clues for further study, then in some cases it may be reached by testing a large number of nulls. For example, suppose a population has a small fraction of "atypical" units. Then, in order to capture at least one of them, an approach is to obtain a large sample from the population, and, for each sampled unit, determine whether to reject the null that it is typical. In this case, even though at population level, the difference between atypical and typical units may be small, there is a chance that some atypical units will "show up" with pronounced differences from typical ones, making them easy to detect. In order to increase the chance, one would hope N, the number of examined units, to be as large as possible. Oftentimes, however, the amount of resources required for the tests is in proportion to N or $V = kN$, the "volume" of data. This imposes a constraint on N and V and raises the following question: provided that k cannot be large enough, what is the minimum value of N or V in order to have desirable test results?

The answer to the question depends on what performance criterion to use for the tests. A useful criterion is pFDR $\le \alpha$, where $\alpha \in (0, 1)$ is a pre-specified level and pFDR $= E[R_0/R \,|\, R > 0]$ is known as the positive false discovery rate, with R the number of rejected nulls and R_0 that of rejected true nulls (Storey 2003). Comparing to the false discovery rate $E[R_0/(R \vee 1)]$ (Benjamini & Hochberg 1995), the pFDR is more useful when the objective is to reject *some* nulls (Chi 2007*a*, Chi & Tan 2008). In view of this, it is desirable to apply the idea of pFDR to data directly. Denote by $\boldsymbol{X}$ the data *to be* collected for the tests. Under a Bayesian framework, we propose the following variant of the pFDR criterion,

$$\mathbb{P}\left(\inf E\left[R_0/R \,|\, R > 0,\ \boldsymbol{X}\right] \le \alpha\right) \ge p, \tag{1.1}$$

where $E[R_0/R \,|\, R > 0, \boldsymbol{X}]$ is defined to be 1 if $R = 0$, α, $p \in (0, 1)$ are pre-specified constants, and the infimum is taken over all applicable multiple testing procedures that are solely based on the data; cf. (2.2). For any such procedure, once $\boldsymbol{X}$ is given, R is determined, whereas R_0 remains random, with its distribution determined by the posterior likelihoods of the truths of the nulls. This gives rise to the conditional expectation. As a result, the infimum in (1.1) is a function of $\boldsymbol{X}$. The criterion means that, with probability no less than p, the data to be collected will yield one or more rejections, which, under a future study for verification, have an expected fraction of false rejections no more than α. The minimum value of N or V will be studied under this criterion.

The second issue is straightforward, that is, even when an arbitrarily large number of nulls can be tested, power may still be an important concern. Provided k cannot be large enough, how much power can be hoped for?

The issue of minimum N or V can be thought of as a dual to the issue that given N, how small the differences between false and true nulls can be before it becomes virtually impossible to detect false nulls; see Donoho & Jin (2004) and references therein. The issue of power is more extensively studied; see Efron (2007) and references therein. However, the setup here is different. First, both issues are considered in relation to k and it is necessary to take into account the fact that the distributions of test statistics not only depend on the underlying data generating distributions, but also on k, the number of replications from the distributions for each null. Second, no sparsity is assumed for false nulls. Instead, false nulls are assumed to be increasingly similar to true nulls, while k cannot increase fast enough to compensate for this. As a result, the test statistics provide increasingly weak evidence to separate false nulls from true nulls.

All our results are obtained for the case where distributions under false nulls and those under true nulls are known and the population fraction of false nulls is known as well. In practice, especially in exploratory studies, while there may be relatively good knowledge about distributions under true nulls, oftentimes there is little knowledge about distributions under false nulls or the population fraction of false nulls. Thus, the case we consider is an ideal one and the results provide limits on what can be achieved in more realistic cases.

Section 2 covers preliminaries and identifies the quantity central to the analysis. Main results are stated in Section 3. Section 3.1 considers the asymptotics of the minimum N and V for general parametric models. Using Cramér-type large deviations, the results are established for the case where the growth of k is just a little slower than δ^{-2}. It shows that in this case, the minimum N and V have to grow much faster than in the case where k is of the same order as δ^{-2}. Sections 3.2 and 3.3 obtain refined results for tests on mean values of normal distributions with known variance and scaled gamma distributions. Section 3.4 considers the power of multiple tests as k can not increase as rapidly as δ^{-2} as $\delta \to 0$. It shows that for procedures that asymptotically control the pFDR at a given level, the power decreases to 0 and is highly sensitive to small changes in rejection criterion, and consequently, there is no asymptotically most powerful procedure among such procedures. Section 4 concludes the article with a summary and remarks. The proofs of the main results are collected in the Appendix.

2 Preliminaries

Denote by $H_1, \ldots, H_N$ the nulls. Suppose that for each H_i, a sample $X_{i1}, \ldots, X_{ik}$ is collected. Let $\eta_i = \mathbf{1}\{H_i \text{ is false}\}$. The analysis will be under the following random effects model:

$$\begin{gathered} (\eta_i, X_{i1}, \ldots, X_{ik}), \quad i \geq 1, \text{ are i.i.d. such that} \\ \mathbb{P}(\eta_i = 1) = a \text{ and} \\ \text{given } \eta_i = 0, \quad X_{i1}, \ldots, X_{ik} \text{ are i.i.d. } \sim f_0(x), \\ \text{given } \eta_i = 1, \quad X_{i1}, \ldots, X_{ik} \text{ are i.i.d. } \sim f_a(x), \end{gathered} \tag{2.1}$$

where $0 < a < 1$ is the population fraction of false nulls, and f_0, f_a are probability densities under true nulls and false nulls, respectively (Efron et al. 2001, Genovese & Wasserman 2002). In this article, we will only consider the case where a is fixed.

Following Chi & Tan (2008), a multiple testing procedure is a deterministic mapping

$$d(\boldsymbol{X}) = (d_1(\boldsymbol{X}), \ldots, d_N(\boldsymbol{X})), \tag{2.2}$$

such that H_i is rejected if and only if $d_i(\boldsymbol{X}) = 1$. Under the random effects model, $\boldsymbol{X} = \{X_{kl}\}$

and it can be shown that the criterion (1.1) can be rewritten as

$$\mathbb{P}(\text{at least one } \mathcal{E}_i(k) \text{ occurs}, \ i = 1, \ldots, N) \ge p, \tag{2.3}$$

$$\text{where} \quad \mathcal{E}_i(k) := \left\{ X_{i1}, \ldots, X_{ik} \text{ satisfy } \prod_{j=1}^{k} \frac{f_a(X_{ij})}{f_0(X_{ij})} \ge \frac{(1-a)(1-\alpha)}{a\alpha} \right\}; \tag{2.4}$$

see Section 4 for a sketch of proof.

For fixed k, the events $\mathcal{E}_i(k)$ are independent of each other and have the same probability, which depends on both k and the difference between f_0 and f_a. Suppose the difference can be parameterized by δ. For example, if $f_0 = N(\theta_0, 1)$ and $f_a = N(\theta, 1)$, then δ can be taken as $\theta - \theta_0$. Denote the common probability of $\mathcal{E}_i(k)$ by

$$p_{k,\delta}(\alpha) = \mathbb{P}(\mathcal{E}_i(k)), \quad i = 1, \ldots, N. \tag{2.5}$$

Then (2.3) is equivalent to $1 - (1 - p_{k,\delta}(\alpha))^N \ge p$, or $N \ge \ln(1-p)/\ln(1 - p_{k,\delta}(\alpha))$.

The case we will focus on is where the false nulls are increasingly similar to true nulls while k cannot increase fast enough to compensate for the decreasing δ; more specifically, $\delta \to 0$ while $k \to \infty$ at a slower rate than δ^{-2}. Then, as maybe expected, $p_{k,\delta}(\alpha) \to 0$. Provided that the growth of k makes sure $p_{k,\delta}(\alpha) > 0$, the minimum number of nulls and volume of data to satisfy (1.1) are

$$N_* = \frac{(1 + o(1))}{p_{k,\delta}(\alpha)} \ln \frac{1}{1-p}, \quad V_* = kN_* = \frac{(1 + o(1))k}{p_{k,\delta}(\alpha)} \ln \frac{1}{1-p}, \tag{2.6}$$

respectively. Thus, the main task of the analysis is to find the asymptotic of $p_{k,\delta}(\alpha)$. Note that under the random effects model,

$$p_{k,\delta}(\alpha) = (1-a)\mathbb{P}_0(\mathcal{E}_i(k)) + a\mathbb{P}_a(\mathcal{E}_i(k)), \tag{2.7}$$

where $\mathbb{P}_0$ is the probability measure under f_0 and $\mathbb{P}_a$ that under f_a.

Finally, some comments on the random effects model. It may be desirable to relax the assumption that the data distributions under false nulls are identical. To do this, one approach is to assume that under false nulls, the data obeys another random effects model, such that given $\eta_i = 1$, a parameter θ_i is first drawn from a distribution G, and then X_{i1}, …, X_{ik} are drawn from $f_{\theta_i} \ne f_0$ (Genovese & Wasserman 2002). However, by letting $f_a = \int f_\theta \, dG(\theta)$, it is seen that this model can be treated in the same way as (2.1). Another approach is to use Poisson approximation to evaluate the probability in (2.3), which does not require the distributions under false nulls be identical, and can even allow weak dependency between X_{ij} (Arratia et al. 1990). However, a full development of the Poisson approach is beyond the scope of the paper.

3 Statement of main results

Recall that a is assumed to be fixed. Henceforth, denote $Q_\alpha = (1/a - 1)(1/\alpha - 1)$.

3.1 Data volume for general multiple tests

Suppose the observations X_{ij} take values in a Euclidean space Ω and both f_0 and f_a belong to a parametric family of densities $\{f_\theta, \theta \in \Theta\}$ with respect to the Lebesgue measure dx on Ω, where Θ is an open set in $\mathbb{R}^d$. Suppose $f_0 = f_{\theta_0}$ and $f_a = f_\theta$. Let $\ell(\theta, x) = \ln f_\theta(x)$. Suppose that for each $x \in \Omega$, $\ell(\theta, x)$ is twice differentiable with

$$\dot{\ell}(\theta, x) = \left[\frac{\partial \ell(\theta, x)}{\partial \theta_1}, \ldots, \frac{\partial \ell(\theta, x)}{\partial \theta_d}\right]^T, \quad \ddot{\ell}(\theta, x) = \left[\frac{\partial^2 \ell(\theta, x)}{\partial \theta_k \partial \theta_l}\right].$$

We assume that $\{f_\theta\}$ satisfies regular conditions so that

$$E_\theta[\dot{\ell}(\theta, X)] = 0, \quad \mathrm{Var}_\theta[\dot{\ell}(\theta, X)] = -E_\theta[\ddot{\ell}(\theta, X)] = I(\theta),$$

where $I(\theta)$ is the Fisher information and E_θ and Var_θ denote the expectation and variance under f_θ, respectively. For each $\theta, \theta' \in \Theta$, by Taylor expansion,

$$\begin{aligned}
\ell(\theta', x) - \ell(\theta, x) &= \dot{\ell}(\theta, x)^T(\theta' - \theta) + \frac{(\theta' - \theta)^T \ddot{\ell}(\theta, x)(\theta' - \theta)}{2} + o(|\theta' - \theta|^2) \\
&= \dot{\ell}(\theta, x)^T(\theta' - \theta) + \frac{(\theta' - \theta)^T A(\theta, \theta', x)(\theta' - \theta)}{2},
\end{aligned}$$

where $A(\theta, \theta', x)$ is a $d \times d$ symmetric matrix. Under regular conditions, one would expect that as $\theta' \to \theta$, $E_\theta[A(\theta, \theta', X)] \to E_\theta[\ddot{\ell}(\theta, X)] = -I(\theta)$. However, for the analysis, a few stronger assumptions are needed.

Assumptions.

1. $I(\theta_0)$ is positive definite.
2. There are $C > 0$ and $r > 0$, such that $|I(\theta) - I(\theta_0)| \le C|\theta - \theta_0|$ if $|\theta - \theta_0| < r$.
3. $M_3 := \sup_{\theta \in \Theta} E_\theta |\dot{\ell}(\theta, X)|^3 < \infty$.
4. For any $\epsilon > 0$, there are positive numbers r, λ_0 and λ, such that for any θ and $\theta' \in \Theta$ with $|\theta - \theta'| < r$, if $X_1, X_2, \ldots$ are i.i.d. $\sim f_\theta$, then

$$\mathbb{P}\left(\left\|\frac{1}{k}\sum_{i=1}^k A(\theta, \theta', X_i) + I(\theta)\right\| > \epsilon\right) \le \lambda_0 e^{-\lambda k} \tag{3.1}$$

for all $k \ge 1$, where for any matrix $M = (m_{ij})$, $\|M\| = \max |m_{ij}|$.

Assumption 1 is standard. Assumption 2 holds if $I(\theta)$ is differentiable at θ_0, which along with Assumption 3 is satisfied by many parametric models. Assumption 4 is not hard to verify by using the fact that the normed quantity in (3.1) is bounded by $D_1 + D_2$, where

$$D_1 = \|h(\theta, \theta') + I(\theta)\|, \quad D_2 = \left\|\frac{1}{k}\sum_{i=1}^k A(\theta, \theta', X_i) - h(\theta, \theta')\right\|,$$

with $h(\theta,\theta') = E_\theta[A(\theta,\theta',X)]$. In fact, since $h(\theta,\theta) = -I(\theta)$, provided that $h(\theta,\theta')$ is uniformly continuous, D_1 is uniformly small for $|\theta-\theta'| \ll 1$. On the other hand, exponential inequalities can be used for D_2. For instance, if $|A(\theta,\theta',X)| \le M$ for some nonrandom $M>0$ for all θ, θ' and $X \sim f_\theta$, then Hoeffding's inequality gives $\mathbb{P}(D_2 \ge \epsilon) \le \lambda_0 e^{-\lambda k}$ for some λ_0, $\lambda > 0$ (Pollard 1984). As a concrete example, for the densities of $N(\theta,1)$, $\theta \in \mathbb{R}$, $A(\theta,\theta',x) \equiv 1$ and hence Assumption 4 is satisfied.

As $\theta - \theta_0 \to 0$, the nulls become increasingly similar. By the asymptotic theory of statistics, to attain a fixed power while keeping the same significance level for the tests, k should grow at the same order as $(\theta-\theta_0)^{-2}$. On the other hand, the results below deal with the case where k grows a little more slowly. First consider the univariate case $d=1$.

Theorem 3.1 *Let $Q_\alpha > 1$. Denote $\delta = \theta - \theta_0$ and k the number of replications per null. Suppose*

$$k = \frac{1}{\delta^2 s(\delta)}, \quad \text{such that} \quad s(\delta) \to \infty \quad \text{and} \quad \frac{s(\delta)}{\ln(1/\delta^2)} \to 0 \quad \text{as} \quad \delta \to 0. \tag{3.2}$$

Then, as $\theta \to \theta_0$,

$$p_{k,\delta}(\alpha) = (1+o(1))\sqrt{\frac{(1-a)a}{2\pi(1-\alpha)\alpha}}\,\frac{\sqrt{kI(\theta_0)}\delta}{\ln Q_\alpha}\exp\left\{-\frac{(\ln Q_\alpha)^2}{2kI(\theta_0)\delta^2}\right\}. \tag{3.3}$$

Note that $Q_\alpha > 1$ if $a + \alpha < 1$. In practice, since a is usually much less than 1 and α is small or only moderately large, the assumption $Q_\alpha > 1$ is not restrictive.

The multivariate case $d > 1$ can be derived as a corollary.

Corollary 3.1 *Let $Q_\alpha > 1$. Denote $\delta = \theta - \theta_0$. Suppose k satisfies (3.2), with δ^2 being replaced by $|\delta|^2$. Let $q(\delta) = \delta^T I(\theta_0)\delta$. Then, as $\theta \to \theta_0$,*

$$p_{k,\delta}(\alpha) = (1+o(1))\sqrt{\frac{(1-a)a}{2\pi(1-\alpha)\alpha}}\,\frac{\sqrt{kq(\delta)}}{\ln Q_\alpha}\exp\left\{-\frac{(\ln Q_\alpha)^2}{2kq(\delta)}\right\}. \tag{3.4}$$

Under the condition of Theorem 3.1, it is not hard to see $p_{k,\delta}(\alpha) \to 0$. Therefore, the minimum number of nulls N_* and the minimum volume of data V_* in order for (2.3) to be satisfied have the asympotics in (2.6), yielding

$$V_* = kN_* = (1+o(1))\ln\frac{1}{1-p}\sqrt{\frac{2\pi(1-\alpha)\alpha}{(1-a)a}}\,\frac{\sqrt{k}\ln Q_\alpha}{\sqrt{I(\theta_0)}\delta}\exp\left\{\frac{(\ln Q_\alpha)^2}{2kI(\theta_0)\delta^2}\right\}.$$

On the other hand, if k has the same order as δ^{-2}, then by the Central Limit Theorem, in order to satisfy (2.3), N_* only needs to be a large constant and V_* is of the same order as δ^{-2}. To see in which case the minimum data volume is larger, it suffices to compare the orders of $\frac{\sqrt{k}}{\delta}\exp\left\{\frac{c}{k\delta^2}\right\}$ and δ^{-2} as $\delta \to 0$, where $c > 0$ is a constant. By $k = \frac{1}{\delta^2 s(\delta)}$ with $s(\delta) \to \infty$, the ratio of the two is $\delta\sqrt{k}\exp\{\frac{c}{k\delta^2}\} = e^{cs(\delta)}/\sqrt{s(\delta)} \to \infty$. Therefore, when k cannot grow as fast as δ^{-2}, a much larger volume of data is required.

3.2 Multiple tests on means of normal distributions

Consider nulls $H_i : \theta_i = \theta_0$ for $N(\theta_i, \sigma^2)$, where σ^2 is known and under false H_i, $\theta_i = \theta$, with $\theta - \theta_0 = \delta > 0$. Without loss of generality, let $\theta_0 = 0$ and $\sigma = 1$. Then f_0 and f_a are the densities of $N(0, 1)$ and $N(\delta, 1)$, respectively. By $f_a(x)/f_0(x) = \exp(\delta x - \frac{1}{2}\delta^2)$, the event in (2.4) becomes

$$\mathcal{E}_i(k) = \left\{ \sum_{j=1}^{k} X_{ij} \ge \frac{\ln Q_\alpha}{\delta} + \frac{k\delta}{2} \right\}.$$

Under true H_i, $\sum_j X_{ij} \sim \sqrt{k}Z$, while under false H_i, $\sum_j X_{ij} \sim \sqrt{k}Z + k\delta$, where $Z \sim N(0, 1)$. Therefore, by (2.7),

$$p_{k,\delta}(\alpha) = (1-a)\bar{\Phi}\left(\frac{\ln Q_\alpha}{\sqrt{k}\delta} + \frac{\sqrt{k}\delta}{2}\right) + a\bar{\Phi}\left(\frac{\ln Q_\alpha}{\sqrt{k}\delta} - \frac{\sqrt{k}\delta}{2}\right), \tag{3.5}$$

where $\bar{\Phi}(t) = 1 - \Phi(t) = 1 - P(Z \le t)$.

Let $Q_\alpha > 1$. If $\delta \downarrow 0$ such that $k\delta^2 \to 0$, then $\frac{\ln Q_\alpha}{\sqrt{k}\delta} \pm \frac{\sqrt{k}\delta}{2} \to \infty$. Recall that, as $t \to \infty$,

$$\bar{\Phi}(t) = \Phi(-t) = (1 + o(1))\frac{e^{-t^2/2}}{\sqrt{2\pi}\, t}. \tag{3.6}$$

It is then not hard to get the asymptotic in Theorem 3.1 with fewer restrictions on (δ, k).

Corollary 3.2 *Let $Q_\alpha > 1$. Suppose $k\delta^2 \to 0$ as $\delta \to 0$. Let f_θ be the densities of $N(\theta, \sigma^2)$, with σ^2 being known. Then, as $\theta \to \theta_0$,*

$$p_{k,\delta}(\alpha) \sim \sqrt{\frac{(1-a)a}{2\pi(1-\alpha)\alpha}}\frac{\sqrt{k}\delta/\sigma}{\ln Q_\alpha} \exp\left\{-\frac{(\ln Q_\alpha)^2}{2k\delta^2/\sigma^2}\right\}, \tag{3.7}$$

$$V_* = kN_* \sim \ln\frac{1}{1-p}\sqrt{\frac{2\pi(1-\alpha)\alpha}{(1-a)a}}\frac{\sqrt{k}\ln Q_\alpha}{\delta/\sigma} \exp\left\{\frac{(\ln Q_\alpha)^2}{2k\delta^2/\sigma^2}\right\}. \tag{3.8}$$

The rapid increase of minimum data volume is illustrated in Figure 3.2(A), which graphs $\log_{10}(V_t/V_2)$ versus $t \in [0, 1]$ for $\delta = 0.1$, 0.2, and 0.4, where V_t is the right hand side of (3.8) with $k = \delta^{-t}$. For the plot, $a = 5\%$, $\alpha = 0.4$ and $p = 0.9$. Even at the log scale, the increase in the minimum data value is apparent.

3.3 Multiple tests on scales of Gamma distributions

Denote by Gamma(a, b) the Gamma distribution with shape parameter a and scale parameter b. Multiple tests on the scales of Gamma distributions have been used as a case of study

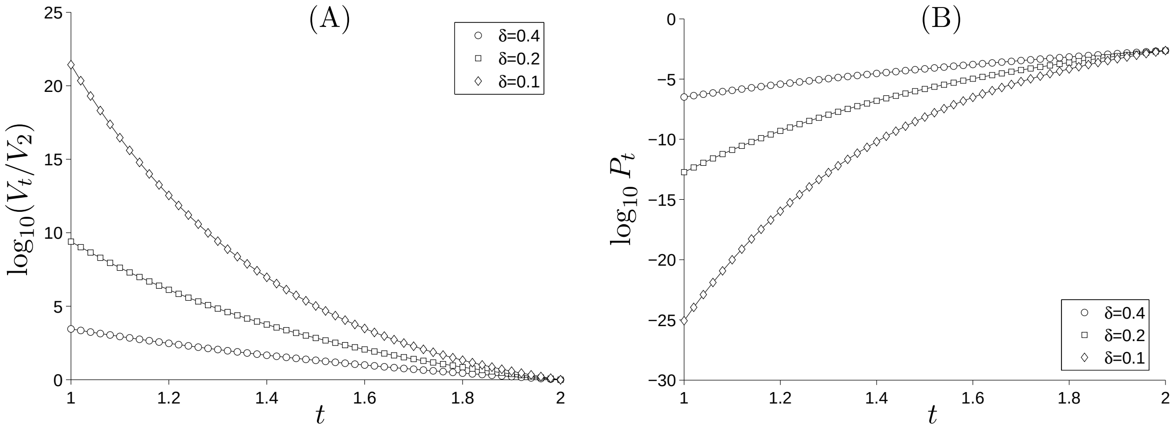

Figure 1: Minimum data volume and power for tests on mean values of $N(\delta, 1)$ when $k = \delta^{-t}$, $t \in [1, 2]$; see details in Sections 3.2 and 3.4.

in the literature (Donoho & Jin 2004). Fix $\nu > 0$. Let $f_0(x)$ be the density of Gamma$(\nu, 1)$ and $f_a(x)$ that of Gamma$(\nu, 1 + \delta)$, where $\delta > 0$. Then

$$f_0(x) = \frac{x^{\nu-1}e^{-x}}{\Gamma(\nu)}, \quad f_a(x) = f_\delta(x) = \frac{x^{\nu-1}e^{-x/(1+\delta)}}{\Gamma(\nu)(1+\delta)^\nu}, \quad x > 0.$$

By $f_a(x)/f_0(x) = (1 + \delta)^{-\nu}e^{\delta x/(1+\delta)}$, the event in (2.4) becomes

$$\mathcal{E}_i(k) = \left\{ \sum_{j=1}^{k} X_{ij} \geq c_k \right\}, \quad \text{with } c_k := \frac{[k\nu \ln(1+\delta) + \ln Q_\alpha](1+\delta)}{\delta}. \tag{3.9}$$

Under true H_i, $\sum_j X_{ij} \sim$ Gamma$(k\nu, 1)$; under false H_i, $\sum_j X_{ij} \sim$ Gamma$(k\nu, 1 + \delta)$. By (2.7), to get the asymptotics of N_* and V_*, the main step is to get the asymptotics of the probability of $\{S \geq c_k\}$ for S following Gamma$(k\nu, 1)$ or Gamma$(k\nu, 1 + \delta)$. Since the tail probabilities under Gamma distributions are available in detail, the asymptotics can be attained for a much wider range of values of k than for the general case. The results are as follows; see Section A.3 for a proof.

Theorem 3.2 *Let f_0 and f_a be as above and $Q_\alpha > 1$. Suppose*

$$(\delta, k) \to (0, \infty) \;\; \textit{such that} \;\; k\delta \to \infty, \; k\delta^2 \to 0. \tag{3.10}$$

Then, denoting $\psi(t) = t - \frac{t^2}{2} - \ln(1 + t)$ for $t > -1$,

$$p_{k,\delta}(\alpha) = (1 + o(1))\sqrt{\frac{(1-a)a}{2\pi(1-\alpha)\alpha}}\frac{\sqrt{k\nu}\delta}{\sqrt{\ln Q_\alpha}} \exp\left\{ -\frac{(\ln Q_\alpha)^2}{2k\nu\delta^2} - k\nu\psi\left(\frac{\ln Q_\alpha}{k\nu\delta}\right) \right\}. \tag{3.11}$$

3.4 Asymptotics of power

For fixed δ and k, power can be analyzed using previous results (Signorovitch 2006, Storey 2007, Chi 2008). Under the setup here, since $(\delta, k) \to (0, \infty)$, the asymptotics of power are of interest. To avoid subtleties that a finite number of nulls may cause, we consider power under the situation where arbitrarily many nulls can be tested. For any procedure, let N_a and $R_a = R - R_0$ denote the numbers of false nulls and rejected false nulls, respectively. Then, provided the limit below exists,

$$\text{power}_\infty = \lim_{N\to\infty} E[R_a/N_a], \tag{3.12}$$

characterizes the power of the procedure when $N \gg N_*$. We compare the powers of different procedures when they control the pFDR around or below the same level. For $N \gg N_*$, the pFDR of a procedure can be characterized by

$$\text{pFDR}_\infty = \lim_{N\to\infty} E[R_0/R \,|\, R > 0]. \tag{3.13}$$

As the limits in (3.12) and (3.13) are defined for fixed δ and k, we use $\text{power}_\infty(\delta, k)$ and $\text{pFDR}_\infty(\delta, k)$ to indicate the dependency and consider the asymptotics of the quantities as $(\delta, k) \to (0, \infty)$. Fix $\alpha \in (0, 1)$. First consider the thresholding procedure with cut-off α,

$$d_i^*(\boldsymbol{X}) = \mathbf{1}\left\{\mathbb{P}(\eta_i = 0 \,|\, \boldsymbol{X}) \le \alpha\right\}, \quad i = 1, 2, \ldots,$$

i.e., d^* rejects H_i if and only $\mathbb{P}(\eta_i = 0 \,|\, \boldsymbol{X}) \le \alpha$. Denote by $\text{power}^*_\infty(\delta, k)$ and $\text{pFDR}^*_\infty(\delta, k)$ the asymptotic power and pFDR of d^*, respectively.

Proposition 3.1 *Suppose $(\delta, k) \to (0, \infty)$ such that*

$$p_{k,\delta}(\alpha) \to 0 \quad \textit{while staying positive, and} \tag{3.14}$$

$$p_{k,\delta}(\alpha_1) = o(p_{k,\delta}(\alpha)) \quad \textit{for any} \quad 0 < \alpha_1 < \alpha, \tag{3.15}$$

Then d^* has the following property

$$\begin{gathered}\textit{for any fixed } \delta > 0 \textit{ and } k \ge 1\textit{, the limits in (3.12) and (3.13) exist,}\\ \textit{and } R_a/N_a \xrightarrow{\text{P}} \text{power}_\infty \textit{ as } N \to \infty.\end{gathered} \tag{3.16}$$

Moreover,

$$\text{power}^*_\infty(\delta, k) = (1 + o(1))\frac{(1-\alpha)p_{k,\delta}(\alpha)}{a}, \quad \text{pFDR}^*_\infty(\delta, k) = (1 + o(1))\alpha. \tag{3.17}$$

We use d^* as a baseline to compare other procedures that satisfy the basic property (3.16) while asymptotically controlling the pFDR.

Proposition 3.2 *Let $(\delta,k)\to(0,\infty)$ as in Proposition 3.1. Let d be a procedure satisfying (3.16) with $\overline{\lim}\,\mathrm{pFDR}_\infty(\delta,k)\le\alpha$. If $\mathrm{power}_\infty(\delta,k)\ge\mathrm{power}^*_\infty(\delta,k)$ for all (δ,k), then for any $\alpha_2>\alpha$,*

$$\mathrm{power}_\infty(\delta,k)\le(1+o(1))\frac{p_{k,\delta}(\alpha_2)}{a},\quad \mathrm{pFDR}_\infty(\delta,k)=(1+o(1))\alpha. \tag{3.18}$$

It is not hard to see that provided $Q_\alpha>1$, the $p_{k,\delta}(\alpha)$ given in Theorems 3.1 and 3.2 satisfies (3.14) and (3.15) and therefore the above results apply. Since by Proposition 3.1, $p_{k,\delta}(\alpha_2)$ is of the same order as the power of a thresholding procedure with cut-off α_2, Proposition 3.2 basically says that for any procedure satisfying (3.16) with $\overline{\lim}\,\mathrm{pFDR}_\infty(\delta,k)\le\alpha$, its power is dominated up to a constant factor by a thresholding procedure with a cut-off just a little bit above α. In view of this, one question is whether there is a most powerful procedure among those that satisfy (3.16) and $\overline{\lim}\,\mathrm{pFDR}_\infty(\delta,k)\le\alpha$, and in particular, whether d^* is such one. As seen next, in general the answer is no. Given $c>0$, let d be a procedure such that for each (δ,k), its cut-off is $\alpha+ck\delta^2$, i.e.

$$d_i(\boldsymbol{X})=\mathbf{1}\left\{\mathbb{P}(\eta_i=0\,|\,\boldsymbol{X})\le\alpha+ck\delta^2\right\}.$$

Proposition 3.3 *Under the random effects model (2.1), let (δ,k) be as in Theorem 3.1. Suppose $Q_\alpha>1$. Given $M>1$, let $c=(1-\alpha)\alpha I(\theta_0)\ln M/\ln Q_\alpha$. Then d satisfies (3.16) and $\overline{\lim}\,\mathrm{pFDR}_\infty(\delta,k)\le\alpha$, while $\mathrm{power}_\infty(\delta,k)=(M+o(1))\mathrm{power}^*_\infty(\delta,k)$.*

More generally, there are no asymptotically most powerful procedures that satisfy (3.16) and $\overline{\lim}\,\mathrm{pFDR}_\infty(\delta,k)\le\alpha$.

As an illustration, consider multiple testing for the mean values of $N(\theta,1)$ as in Section 3.2. Figure 3.2(B) shows the dependency of the asymptotic power of d^* on (δ,k). Under the same parameters as in panel (A), it graphs $\log_{10}P_t$, $t\in[1,2]$, where P_t is $(1-\alpha)/\alpha$ times the right hand side of (3.7) with $k=\delta^{-t}$. From Proposition 3.1, we know $\mathrm{power}^*_\infty(\delta,k)=(1+o(1))P_t$ as $\delta\to0$ and $k=\delta^{-t}$. The rapid decrease of power as $\delta\to0$ is clear. We next illustrate how the asymptotic power of a thresholding procedure can be arbitrarily increased by a small change in cut-off. As seen from (3.5), for any δ and k, $\mathrm{power}^*_\infty(\delta,k)=\bar\Phi\left(\frac{\ln Q_\alpha}{\sqrt{k}\delta}-\frac{\sqrt{k}\delta}{2}\right)$ and the thresholding procedure with cut-off $\alpha+ck\delta^2$ has $\mathrm{power}_\infty(\delta,k)=\bar\Phi\left(\frac{\ln Q_{\alpha+ck\delta^2}}{\sqrt{k}\delta}-\frac{\sqrt{k}\delta}{2}\right)$. As $(\delta,k)\to(0,\infty)$ with $k\delta^2\to0$, the difference between the cut-offs α and $\alpha+ck\delta^2$ tends to 0. It is not hard to get that for both procedures, $\mathrm{pFDR}_\infty(\delta,k)\to\alpha$. On the other hand, by (3.6), the ratio of their asymptotic powers is

$$\begin{aligned}&(1+o(1))\exp\left\{\left(\frac{\ln Q_{\alpha+ck\delta^2}}{\sqrt{k}\delta}-\frac{\sqrt{k}\delta}{2}\right)^2-\left(\frac{\ln Q_\alpha}{\sqrt{k}\delta}-\frac{\sqrt{k}\delta}{2}\right)^2\right\}\\ =&(1+o(1))\exp\left\{\frac{(\ln Q_{\alpha+ck\delta^2})^2-(\ln Q_\alpha)^2}{k\delta^2}\right\}=(1+o(1))\exp\left\{-\frac{2c\ln Q_\alpha}{1-\alpha}\right\}.\end{aligned}$$

Therefore, by increasing c, the power of the second thresholding procedure is arbitrarily many times higher than d^*.

4 Summary and remarks

This article studies the issues of minimum data volume and power when $k = o(\delta^{-2})$, i.e., the number of repeated measurements for each null is much smaller than the squared differences between false and true nulls. It shows that in this case, in order to meet a pFDR based performance criterion, the minimum data volume has to grow much faster than in the case where k is of the same order as δ^{-2}. It also shows how fast power will decay to 0 and the sensitivity of the power to small changes in rejection rules.

The results are essentially due to the fact that when k is not large enough, evidence against true nulls can only come from values of test statistics far away from the "normal" ones. When k increases more slowly than δ^{-2} but faster than δ^{-1}, such values can be treated as moderate deviations (Dembo & Zeitouni 1998), which can yield the log-growth rate of the minimum data volume but nevertheless may not be accurate enough to give the growth rate itself. On the other hand, the article does not consider the case where k is only of the order of δ^{-1}. Analysis in this case seems to require the large deviations principle and can be quite subtle (Chi 2007*b*, Dembo & Zeitouni 1998).

References

Arratia, R., Goldstein, L. & Gordon, L. (1990), 'Poisson approximation and the Chen-Stein method', *Statist. Sci.* **5**(4), 403–434. With comments and a rejoinder by the authors.

Benjamini, Y. & Hochberg, Y. (1995), 'Controlling the false discovery rate: a practical and powerful approach to multiple testing', *J. R. Stat. Soc. Ser. B Stat. Methodol.* **57**(1), 289–300.

Chi, Z. (2007*a*), 'On the performance of FDR control: constraints and a partial solution', *Ann. Statist.* **35**(4), 1409–1431.

Chi, Z. (2007*b*), 'Sample size and positive false discovery rate control for multiple testing', *Electronic J. Statist* **1**, 77–118.

Chi, Z. (2008), 'False discovery rate control with multivariate p-values', *Electronic J. Statist* **2**, 368–411.

Chi, Z. & Tan, Z. (2008), 'Positive false discovery proportions for multiple testing: intrinsic bounds and adaptive control', *Statistica Sinica* **18**(3), 837–860.

Dembo, A. & Zeitouni, O. (1998), *Large Deviations Techniques And Applications*, 2 edn, Springer-Verlag, New York.

Donoho, D. & Jin, J. (2004), 'Higher criticism for detecting sparse heterogeneous mixtures', *Ann. Statist.* **32**(3), 962–994.

Efron, B. (2007), 'Size, power, and false discovery rates', *Ann. Statist.* **35**(4), 1351–1377.

Efron, B., Tibshirani, R., Storey, J. D. & Tusher, V. G. (2001), 'Empirical Bayes analysis of a microarray experiment', *J. Amer. Statist. Assoc.* **96**(456), 1151–1160.

Genovese, C. & Wasserman, L. (2002), 'Operating characteristics and extensions of the false discovery rate procedure', *J. R. Stat. Soc. Ser. B Stat. Methodol.* **64**(3), 499–517.

Nagaev, S. V. (1979), 'Large deviations of sums of independent random variables', *Ann. Probab.* **7**(5), 745–789.

Pollard, D. (1984), *Convergence of stochastic processes*, Springer Series in Statistics, Springer-Verlag, New York.

Signorovitch, J. E. (2006), Multiple testing with an empirical alternative hypothesis, Technical Report 60, Harvard University Biostatistics Working Paper Series, Boston.

Storey, J. D. (2003), 'The positive false discovery rate: a Bayesian interpretation and the q-value', *Ann. Statist.* **31**(6), 2012–2035.

Storey, J. D. (2007), 'The optimal discovery procedure: a new approach to simultaneous significance testing', *J. R. Stat. Soc. Ser. B Stat. Methodol.* **69**(1), 1–22.

Appendix: technical details

A.1 Proof for the equivalence of criteria (1.1) and (2.3)

We sketch a proof that under the random effects model (2.1), the criterion (1.1) can be rewritten as (2.3), where the infimum in (1.1) is taken over procedures satisfying (2.2). For more details, see Chi & Tan (2008).

For any procedure $d(\boldsymbol{X})$ as in (2.2), $R = \sum_{i=1}^N d_i(\boldsymbol{X})$ and $R_0 = \sum_{i=1}^N \mathbf{1}\{\eta_i = 0\}\, d_i(\boldsymbol{X})$. Given $\boldsymbol{X}$, if $R > 0$, then, as $d_i(\boldsymbol{X})$ are now determined,

$$E\left[R_0/R \,|\, \boldsymbol{X}\right] = \frac{1}{R}\sum_{i=1}^N d_i(\boldsymbol{X})\mathbb{P}(\eta_i = 0 \,|\, \boldsymbol{X}) \geq \min_{i=1}^N \mathbb{P}(\eta_i = 0 \,|\, \boldsymbol{X}),$$

with equality if and only if d only rejects H_i with the smallest $\mathbb{P}(\eta_i = 0 \,|\, \boldsymbol{X})$. On the other hand, if $R = 0$, then by definition, $E[R_0/R \,|\, R > 0, \boldsymbol{X}] = 1$. Note that by Bayes rule,

$$\mathbb{P}(\eta_i = 0 \,|\, \boldsymbol{X}) = \mathbb{P}(\eta_i = 0 \,|\, X_{ij},\, j = 1, \ldots, k) = \left[1 + \frac{a}{1-a}\prod_{j=1}^k \frac{f_a(X_{ij})}{f_0(X_{ij})}\right]^{-1}. \tag{A.1}$$

It is then seen that the criterion (1.1) can be rewritten as (2.3).

A.2 Proofs for general multiple tests

Recall that by Bikjalis' theorem (Nagaev 1979), there is an absolute constant $\beta > 0$, such that for any $Z_1, Z_2, \ldots$ i.i.d. with $EZ_1 = 0$, $\mathrm{Var}(Z_1) = \sigma^2 > 0$ and $E|Z_1|^3 < \infty$,

$$\left|\bar{\Phi}(t) - \mathbb{P}\left(\frac{1}{\sigma\sqrt{k}}\sum_{i=1}^{k} Z_i \ge t\right)\right| \le \frac{\beta E|Z_1|^3}{\sigma^3\sqrt{k}(1+|t|^3)}, \quad k = 1, 2, \ldots. \tag{A.2}$$

Proof of Theorem 3.1. For $\theta \in \Theta \subset \mathbb{R}$, let $\delta = \theta - \theta_0$. Then

$$\ell(\theta, x) - \ell(\theta_0, x) = \dot{\ell}(\theta_0, x)\delta + \frac{A(\theta_0, \theta, x)\delta^2}{2} \tag{A.3}$$

$$= \dot{\ell}(\theta, x)\delta - \frac{A(\theta, \theta_0, x)\delta^2}{2}. \tag{A.4}$$

According to (2.6), we need to compute $p_{k,\delta}(\alpha)$. By (2.7),

$$p_{k,\delta}(\alpha) = (1-a)P_{\theta_0}(E_k) + aP_\theta(E_k), \tag{A.5}$$

where P_θ is the k-fold product of the probability measure with density f_θ and E_k is the event $\{(X_1, \ldots, X_k) : \sum_{i=1}^k [\ell(\theta, X_i) - \ell(\theta_0, X_i)] \ge \ln Q_\alpha\}$. Under f_{θ_0}, $\dot{\ell}(\theta_0, X_i)$ are i.i.d. with mean 0 and variance $I(\theta_0)$. Given $\epsilon > 0$, define events

$$G_k = \left\{\left|\frac{1}{k}\sum_{i=1}^{k} A(\theta_0, \theta, X_i) + I(\theta_0)\right| \le \epsilon\right\}.$$

Denote $Z_i = \dot{\ell}(\theta_0, X_i)$. By (A.3), $F_- \cap G_k \subset E_k \cap G_k \subset F_+ \cap G_k$, where, for $\theta \ne \theta_0$,

$$F_\pm = \left\{\frac{\mathrm{sign}(\delta)}{\sqrt{kI(\theta_0)}}\sum_{i=1}^{k} Z_i \ge u_\pm\right\} \quad \text{with} \quad u_\pm = \frac{\ln Q_\alpha + \frac{1}{2}k(I(\theta_0) \mp \epsilon)\delta^2}{\sqrt{kI(\theta_0)}\,|\delta|}.$$

Without loss of generality, we only consider the case $\theta > \theta_0$. Then

$$P_{\theta_0}(F_-) - P_{\theta_0}(G_k^c) \le P_{\theta_0}(E_k) \le P_{\theta_0}(F_+) + P_{\theta_0}(G_k^c). \tag{A.6}$$

By (A.2) and Assumption 3,

$$\left|\bar{\Phi}(u_\pm) - P_{\theta_0}(F_\pm)\right| \le \frac{\beta M_3}{\sqrt{k}\, I(\theta_0)^{3/2}(1+|u_\pm|^3)}.$$

We need the following results.

Lemma A.1 *If k satisfies (3.2), then, as $\delta \to 0$,*

$$\bar{\Phi}(u_\pm) = (1+o(1))\frac{e^{-u_\pm^2/2}}{\sqrt{2\pi}u_\pm}, \tag{A.7}$$

$$\frac{1}{\sqrt{k}(1+|u_\pm|^3)} = o(\bar{\Phi}(u_\pm)), \tag{A.8}$$

$$P_{\theta_0}(G_k^c) = o(\bar{\Phi}(u_\pm)). \tag{A.9}$$

Assume Lemma A.1 is true for now. By (A.6)–(A.9), there is $r_k \to 0$, such that

$$(1-r_k)\frac{e^{-u_-^2/2}}{\sqrt{2\pi}u_-} \le P_{\theta_0}(E_k) \le (1+r_k)\frac{e^{-u_+^2/2}}{\sqrt{2\pi}u_+}.$$

Since $k\delta^2 \to 0$, $u_- \sim u_+ \sim \frac{\ln Q_\alpha}{\sqrt{kI(\theta_0)}\,\delta}$. On the other hand,

$$u_\pm^2 = \frac{(\ln Q_\alpha)^2}{kI(\theta_0)\delta^2} + \frac{(I(\theta_0)\mp\epsilon)\ln Q_\alpha}{I(\theta_0)} + \frac{(I(\theta_0)\mp\epsilon)^2 k\delta^2}{4I(\theta_0)}.$$

By Assumption 1, $I(\theta_0) > 0$. Since $\epsilon > 0$ is arbitrary and $k\delta^2 \to 0$, we then get

$$P_{\theta_0}(E_k) = (1+o(1))\frac{\sqrt{kI(\theta_0)}\,\delta}{\sqrt{2\pi}\ln Q_\alpha}\exp\left\{-\frac{(\ln Q_\alpha)^2}{2kI(\theta_0)\delta^2} - \frac{\ln Q_\alpha}{2}\right\}. \tag{A.10}$$

With similar argument, now applied to $\dot\ell(\theta, X_i)$ under f_θ,

$$P_\theta(E_k) = (1+o(1))\frac{\sqrt{kI(\theta)}\delta}{\sqrt{2\pi}\ln Q_\alpha}\exp\left\{-\frac{(\ln Q_\alpha)^2}{2kI(\theta)\delta^2} + \frac{\ln Q_\alpha}{2}\right\},$$

where $+\frac{1}{2}\ln Q_\alpha$ in the exponential is due to $-\frac{1}{2}A(\theta,\theta_0,x)\delta^2$ in (A.4). By Assumption 2, there are constants $C > 0$ and $r > 0$, such that for $|\delta| < r$,

$$\left|\frac{1}{kI(\theta)\delta^2} - \frac{1}{kI(\theta_0)\delta^2}\right| \le \frac{C}{k|\delta| I^2(\theta_0)}.$$

Since $k\delta \to \infty$, it follows that

$$P_\theta(E_k) = (1+o(1))\frac{\sqrt{kI(\theta_0)}\delta}{\sqrt{2\pi}\ln Q_\alpha}\exp\left\{-\frac{(\ln Q_\alpha)^2}{2kI(\theta_0)\delta^2} + \frac{\ln Q_\alpha}{2}\right\}. \tag{A.11}$$

Combining (A.5), (A.10), (A.11), and $\exp\{\frac{\ln Q_\alpha}{2}\} = \sqrt{\frac{(1-a)(1-\alpha)}{a\alpha}}$, (3.3) then follows. □

Proof of Lemma A.1. Because $u_\pm \to \infty$ as $\delta \to 0$, (A.7) follows from (3.6). To show (A.8), it suffices to show $\sqrt{k}u_\pm^2 e^{-u_\pm^2/2} \to \infty$ as $\delta \to 0$, or, equivalently, $\ln k - u_\pm^2 + 4\ln u_\pm \to \infty$. Because $u_\pm$ is of the same order as $\frac{1}{\sqrt{k}\delta}$ and $k\delta^2 \to 0$, it is seen the above asymptotic follows if $\frac{1}{k\delta^2} = o(\ln k)$, or $(k\ln k)\delta^2 \to \infty$. Now by $s(\delta) \to \infty$ and $s(\delta) = o(\ln(1/\delta))$,

$$(k\ln k)\delta^2 = \frac{1}{\delta^2 s(\delta)}\left(2\ln\frac{1}{\delta} - \ln s(\delta)\right)\delta^2 \to \infty.$$

To show (A.9), let $\lambda > 0$ be as in (3.1). Then $P_{\theta_0}(G_k^c)$ is of the same order as $e^{-\lambda k}$. By (A.7), it suffices to show $u_\pm^2 = o(k)$. Since $u_\pm^2$ is of the same order as $1/(k\delta^2)$ and $k\delta \to \infty$, the last claim is proved. □

Proof of Corollary 3.1. In place of (A.3) and (A.4), we have

$$\ell(\theta, x) - \ell(\theta_0, x) = \dot{\ell}(\theta_0, x)^T\delta + \frac{\delta^T A(\theta_0, \theta, x)\delta}{2} = \dot{\ell}(\theta, x)^T\delta - \frac{\delta^T A(\theta, \theta_0, x)\delta}{2}.$$

Let $e = \delta/|\delta|$. Under f_{θ_0}, $\dot{\ell}(\theta_0, X_i)^T e$ are i.i.d. with mean 0 and variance $v(\theta_0) = e^T I(\theta_0)e > 0$; under f_θ, $\dot{\ell}(\theta, X_i)^T e$ are i.i.d. with mean 0 and variance $v(\theta) = e^T I(\theta)e$. Applying the proof of Theorem 3.1 to $\dot{\ell}(\theta_0, X_i)^T e$ and $\dot{\ell}(\theta, X_i)^T e$ yields

$$p_{k,\delta}(\alpha) \sim \sqrt{\frac{(1-a)a}{2\pi(1-\alpha)\alpha}} \frac{\sqrt{kv(\theta_0)}\,|\delta|}{\ln Q_\alpha} \exp\left\{-\frac{(\ln Q_\alpha)^2}{2kv(\theta_0)\,|\delta|^2}\right\}.$$

Since $v(\theta_0)|\delta|^2 = \delta^T I(\theta_0)\delta$, (3.4) then follows. □

A.3 Proofs for multiple tests on Gamma distributions

We next prove Theorem 3.2. Denote by $G_k(x)$ the upper tail probability of Gamma$(k\nu, 1)$, i.e. $G_k(x) = \frac{1}{\Gamma(k\nu)}\int_x^\infty s^{k\nu-1}e^{-s}\,ds$, $x > 0$. As noted in Section 3.3, the main step is to find the asymptotics of $G_k(c_k)$ and $G_k(d_k)$, where c_k is defined in (3.9) and $d_k = \frac{c_k}{1+\delta}$.

To find the asymptotic of $G_k(c_k)$, first, by power expansion of $\ln(1+\delta)$, for $\delta \in (-1, 1)$,

$$c_k = k\nu + \frac{\ln Q_\alpha}{\delta} + k\nu\delta \sum_{j=0}^\infty \frac{(-\delta)^j}{(j+1)(j+2)} + \ln Q_\alpha,$$

$$d_k = k\nu + \frac{\ln Q_\alpha}{\delta} + k\nu\delta \sum_{j=0}^\infty \frac{(-1)^{j-1}\delta^j}{j+2}.$$

Because $k\delta \to \infty$ while $k\delta^2 \to 0$, it is seen that in each of the sums, every term is of an infinitesimal order of its previous one. Let

$$z = k\nu, \quad s = z(1+t), \quad b = \ln Q_\alpha. \tag{A.12}$$

With the variable substitutions,

$$G_k(c_k) = \frac{z^z e^{-z}}{\Gamma(z)} \underbrace{\int_{\frac{b}{z\delta}+D(\delta,z)}^\infty (1+t)^{z-1}e^{-zt}\,dt}_{I(z,\delta)}, \quad G_k(d_k) = \frac{z^z e^{-z}}{\Gamma(z)} \underbrace{\int_{\frac{b}{z\delta}+L(\delta,z)}^\infty (1+t)^{z-1}e^{-zt}\,dt}_{J(z,\delta)},$$

where

$$D(\delta, z) = \delta r(\delta) + \frac{b}{z}, \text{ with } r(\delta) = \sum_{j=0}^\infty \frac{(-\delta)^j}{(j+1)(j+2)}, \tag{A.13}$$

$$L(\delta, z) = \delta\bar{r}(\delta) + \frac{b}{z}, \text{ with } \bar{r}(\delta) = -\sum_{j=0}^\infty \frac{(-\delta)^j}{j+2}. \tag{A.14}$$

The main step is to show

$$I(z,\delta) \sim \frac{\delta}{b} \exp\left\{-\frac{b^2}{2z\delta^2} - \frac{b}{2} - z\psi\left(\frac{b}{z\delta}\right)\right\}, \tag{A.15}$$

$$J(z,\delta) \sim \frac{\delta}{b} \exp\left\{-\frac{b^2}{2z\delta^2} + \frac{b}{2} - z\psi\left(\frac{b}{z\delta}\right)\right\}. \tag{A.16}$$

Assume the two formulas are true for now. By Stirling's formula, $\frac{z^z e^{-z}}{\Gamma(z)} = (1+o(1))\sqrt{\frac{z}{2\pi}}$. Then by (A.15) and (A.16),

$$G_k(c_k) \sim \sqrt{\frac{z}{2\pi}}\frac{\delta}{b} \exp\left\{-\frac{b^2}{2z\delta^2} - \frac{b}{2} - z\psi\left(\frac{b}{z\delta}\right)\right\},$$
$$G_k(d_k) \sim \sqrt{\frac{z}{2\pi}}\frac{\delta}{b} \exp\left\{-\frac{b^2}{2z\delta^2} + \frac{b}{2} - z\psi\left(\frac{b}{z\delta}\right)\right\}.$$

Since $p_{k,\delta}(\alpha) = (1-a)G_k(c_k) + aG_k(d_k)$ and (A.12),

$$p_{k,\delta}(\alpha) \sim \sqrt{\frac{(1-a)a}{2\pi(1-\alpha)\alpha}}\frac{\sqrt{k\nu}\delta}{\sqrt{\ln Q_\alpha}} \exp\left\{-\frac{(\ln Q_\alpha)^2}{2k\nu\delta^2} - k\nu\psi\left(\frac{\ln Q_\alpha}{k\nu\delta}\right)\right\}.$$

The proof is complete by (2.6).

The rest of the section is devoted to the proof of (A.15) and (A.16). Observe $r(\delta) \to 1/2$ and $\bar{r}(\delta) \to -1/2$ as $\delta \to 0$. By (3.10),

$$z\delta = \nu k\delta \to \infty, \quad z\delta^2 = \nu k\delta^2 \to 0. \tag{A.17}$$

It is then not hard to check that $D(\delta, z) \sim \delta/2$. Also, for any $z > 0$, $(1+t)^{z-1}e^{-zt}$ is strictly decreasing in $t > 0$. Given $0 < \epsilon \ll 1$, using (A.17) again,

$$\begin{aligned} I_\epsilon(z,\delta) &:= \int_{\frac{b}{z\delta}+D(\delta,z)}^{\epsilon} (1+t)^{z-1}e^{-zt}\,dt \ge \int_{\frac{2b}{z\delta}}^{\frac{3b}{z\delta}} (1+t)^{z-1}e^{-zt}\,dt \\ &\ge \left(1+\frac{3b}{z\delta}\right)^{z-1} e^{-3b/\delta}\left(\frac{b}{z\delta}\right) \\ &\overset{(a)}{\ge} \exp\left\{\left[\frac{3b}{z\delta} - \frac{1}{2}\left(\frac{3b}{z\delta}\right)^2\right](z-1) - \frac{3b}{\delta}\right\}\frac{b}{z\delta} \ge \exp\left\{-\frac{C}{z\delta^2}\right\}\frac{b}{z\delta} \end{aligned}$$

for some $C > 0$, where (a) is due to $\ln(1+x) \ge x - x^2/2$ for $x > 0$. Therefore, $I_\epsilon(z,\delta)^{1/z} \to 1$. On the other hand,

$$\left(\int_\epsilon^\infty (1+t)^{z-1}e^{-zt}\,dt\right)^{1/z} \to \sup_{t\ge\epsilon}(1+t)e^{-t} < 1.$$

As a result, for any $\epsilon > 0$, $I(z,\delta) \sim I_\epsilon(z,\delta)$. Since ϵ is arbitrary, it follows that we can replace $(1+t)^{z-1}$ in the integrand to $(1+t)^z$ to get

$$I(z,\delta) \sim \int_{\frac{b}{2\delta}+D(\delta,z)}^{\epsilon} (1+t)^z e^{-zt}\,dt = \int_{\frac{b}{2\delta}+D(\delta,z)}^{\epsilon} e^{-z\varphi(t)}\,dt, \tag{A.18}$$

where $\varphi(t) = t - \ln(1+t)$. By $\varphi'(t) = \frac{t}{1+t}$, $\varphi(t)$ is a strictly increasing function from $(0,\infty)$ onto $(0,\infty)$ with smooth inverse $\varphi^{-1}(u)$. On the other hand, $\varphi(t) = \frac{t^2}{2} + O(t^3)$, as $t \downarrow 0$. As a result, as $u \to 0+$, $\varphi^{-1}(u) = (1+o(1))\sqrt{2u}$ and hence

$$(\varphi^{-1})'(u) = \frac{1}{\varphi'(\varphi^{-1}(u))} = 1 + \frac{1}{\varphi^{-1}(u)} = \frac{1+o(1)}{\sqrt{2u}} \quad \text{as } u \to 0.$$

By (A.18) and the arbitrariness of $\epsilon > 0$ as well as the above properties of φ,

$$I(z,\delta) \sim \int_{\varphi(\frac{b}{z\delta}+D(\delta,z))}^{\varphi(\epsilon)} \frac{e^{-zu}}{\sqrt{2u}}\,du \sim \int_{\varphi(\frac{b}{z\delta}+D(\delta,z))}^{\infty} \frac{e^{-zu}}{\sqrt{2u}}\,du = I_1.$$

By variable substitution $u = v/z$,

$$I_1 = \frac{1}{\sqrt{z}} \int_{z\varphi(\frac{b}{z\delta}+D(\delta,z))}^{\infty} \frac{1}{\sqrt{2v}} e^{-v}\,dv.$$

Since $z\delta D(\delta,z) \to \infty$ and $D(\delta,z) \to 0$, by $\varphi(t) \sim t^2/2$ as $t \to 0$,

$$z\varphi\left(\frac{b}{z\delta} + D(\delta,z)\right) \sim \frac{z}{2}\left(\frac{b}{z\delta}\right)^2 = \frac{b^2}{2z\delta^2} \to \infty. \tag{A.19}$$

Recall that for any a, $\int_x^\infty t^a e^{-t}\,dt \sim x^a e^{-x}$, as $x \to \infty$. Then by (A.19)

$$\begin{aligned} I_1 &\sim \frac{1}{\sqrt{z}} \frac{1}{\sqrt{2z\varphi\left(\frac{b}{z\delta}+D(\delta,z)\right)}} \exp\left\{-z\varphi\left(\frac{b}{z\delta}+D(\delta,z)\right)\right\} \\ &\sim \frac{\delta}{b} \exp\left\{-z\varphi\left(\frac{b}{z\delta}+D(\delta,z)\right)\right\}. \end{aligned}$$

Because $\psi(t) = \varphi(t) - \frac{t^2}{2}$,

$$z\varphi\left(\frac{b}{z\delta}+D(\delta,z)\right) = \frac{z}{2}\left(\frac{b}{z\delta}+D(\delta,z)\right)^2 + z\psi\left(\frac{b}{z\delta}+D(\delta,z)\right).$$

First, by (A.17),

$$\begin{aligned} \frac{z}{2}\left(\frac{b}{z\delta}+D(\delta,z)\right)^2 &= \frac{b^2}{2z\delta^2} + \frac{bD(\delta,z)}{\delta} + \frac{z(D(\delta,z))^2}{2} \\ &= \frac{b^2}{2z\delta^2} + \frac{b}{\delta}\left(\delta r(\delta) + \frac{b}{z}\right) + \frac{z}{2}\left(\delta r(\delta) + \frac{b}{z}\right)^2 = \frac{b^2}{2z\delta^2} + \frac{b}{2} + o(1). \end{aligned}$$

Second, since $\psi'(x) = \varphi'(x) - x = 1 - \frac{1}{1+x} - x = -\frac{x^2}{1+x}$, by Taylor expansion and (A.13)

$$z\psi\left(\frac{b}{z\delta} + D(\delta, z)\right) - z\psi\left(\frac{b}{z\delta}\right) = zD(\delta, z)\psi'\left(\frac{b}{z\delta} + \xi D(\delta, z)\right) = \frac{z\delta}{2}\left(\frac{b}{z\delta}\right)^2 = o(1).$$

As a result,

$$z\varphi\left(\frac{b}{z\delta} + D(\delta, z)\right) = \frac{b^2}{2z\delta^2} + \frac{b}{2} + z\psi\left(\frac{b}{z\delta}\right) + o(1)$$

and hence by $I(z, \delta) \sim I_1$, (A.15) then follows. By similar argument, it can be shown that

$$\begin{aligned} J(z, \delta) &\sim \frac{1}{\sqrt{z}} \frac{1}{\sqrt{2z\varphi\left(\frac{b}{z\delta} + L(\delta, z)\right)}} \exp\left\{-z\varphi\left(\frac{b}{z\delta} + L(\delta, z)\right)\right\} \\ &\sim \frac{\delta}{b} \exp\left\{-z\varphi\left(\frac{b}{z\delta} + L(\delta, z)\right)\right\}, \end{aligned}$$

which leads to (A.16).

A.4 Proofs for the asymptotics of power

A basic fact to use is that under the random effects model (2.1), $\mathbb{P}(\eta_i = 0 \mid \boldsymbol{X})$ are i.i.d. and by (A.1), given $\delta > 0$ and k, for any $\alpha \in (0, 1)$, the probability of $\{\mathbb{P}(\eta_i = 0 \mid \boldsymbol{X}) \le \alpha\}$ is

$$p_{k,\delta}(\alpha) = (1 - a)P_0(E_k(\alpha)) + aP_a(E_k(\alpha)), \tag{A.20}$$

where P_0 and P_a are the probability distributions under true and false nulls, respectively, and $E_k(\alpha) = \left\{\prod_{j=1}^k \frac{f_a(X_j)}{f_0(X_j)} \ge Q_\alpha\right\}$ with $X_1, \ldots, X_k$ being i.i.d.

Proof of Proposition 3.1. For fixed N,

$$R = \sum_{i=1}^N d_i^*(\boldsymbol{X}), \quad R_0 = \sum_{i=1}^N d_i^*(\boldsymbol{X})(1 - \eta_i), \quad R_a = \sum_{i=1}^N d_i^*(\boldsymbol{X})\eta_i.$$

Given $\delta > 0$ and k, since $d_i^*(\boldsymbol{X}) = \mathbf{1}\{\mathbb{P}(\eta_i = 0 \mid \boldsymbol{X}) \le \alpha\}$, by (A.20) and the Weak Law of Large Numbers (WLLN), $R/N \xrightarrow{\text{P}} p_{k,\delta}(\alpha) > 0$. Similarly, $R_0/N \xrightarrow{\text{P}} (1 - a)P_0(E_k(\alpha))$, $R_a/N \xrightarrow{\text{P}} aP_a(E_k(\alpha))$ and $N_a/N \to a$. Property (3.16) can then be proved. In particular,

$$\text{power}_\infty(\delta, k) = P_a(E_k(\alpha)), \quad \text{pFDR}^*_\infty(\delta, k) = \frac{(1 - a)P_0(E_k(\alpha))}{p_{k,\delta}(\alpha)}. \tag{A.21}$$

To show (3.17), given $\boldsymbol{X}$ with $R > 0$,

$$\begin{aligned} E\left[R_0/R \,|\, \boldsymbol{X}\right] &= \frac{1}{R}\sum_{i=1}^{N} E\left[\mathbf{1}\left\{\mathbb{P}(\eta_i = 0 \,|\, \boldsymbol{X}) \le \alpha\right\}(1-\eta_i) \,|\, \boldsymbol{X}\right] \\ &= \frac{1}{R}\sum_{i=1}^{N} \mathbf{1}\left\{\mathbb{P}(\eta_i = 0 \,|\, \boldsymbol{X}) \le \alpha\right\}\mathbb{P}(\eta_i = 0 \,|\, \boldsymbol{X}) \\ &\le \frac{1}{R}\sum_{i=1}^{N} \alpha\mathbf{1}\left\{\mathbb{P}(\eta_i = 0 \,|\, \boldsymbol{X}) \le \alpha\right\} = \alpha. \end{aligned}$$

Since $p_{k,\delta}(\alpha) > 0$, $\mathbb{P}(d_i^*(\boldsymbol{X}) > 0$ for at least one $i = 1, \ldots, N) > 0$. Therefore, the conditional expectation of R_0/R over $\boldsymbol{X}$ with $R > 0$ is well defined, giving $E[R_0/R \,|\, R > 0] \le \alpha$. Thus $\mathrm{pFDR}^*_\infty(\delta, k) \le \alpha$ for all (δ, k). On the other hand, given $\beta < \alpha$,

$$\begin{aligned} E[R_0/R \,|\, \boldsymbol{X}] &\ge \frac{1}{R}\sum_{i=1}^{N} E[\mathbf{1}\left\{\beta \le \mathbb{P}(\eta_i = 0 \,|\, \boldsymbol{X}) \le \alpha\right\}(1-\eta_i) \,|\, \boldsymbol{X}] \\ &\ge \frac{\beta}{R}\sum_{i=1}^{N} \mathbf{1}\left\{\beta \le \mathbb{P}(\eta_i = 0 \,|\, \boldsymbol{X}) \le \alpha\right\}. \end{aligned}$$

Under the random effects model and the WLLN,

$$\sum_{i=1}^{N} \mathbf{1}\left\{\beta \le \mathbb{P}(\eta_i = 0 \,|\, \boldsymbol{X}) \le \alpha\right\} = (1 + o_p(1))[p_{k,\delta}(\alpha) - p_{k,\delta}(\beta)]N,$$

where $o_p(1)$ stands for some sequence of random variables $\xi_N \xrightarrow{\mathrm{P}} 0$ as $N \to \infty$. Taking expectation over $\boldsymbol{X}$ with $R > 0$ and then letting $N \to \infty$,

$$\mathrm{pFDR}^*_\infty(\delta, k) \ge \frac{\beta[p_{k,\delta}(\alpha) - p_{k,\delta}(\beta)]}{p_{k,\delta}(\alpha)}.$$

Let $(\delta, k) \to (0, \infty)$ while satisfying (3.14) and (3.15). Then $\overline{\lim}\,\mathrm{pFDR}^*_\infty(\delta, k) \ge \beta$. Since β is arbitrary, $\mathrm{pFDR}^*_\infty(\delta, k) \to \alpha$, showing the second half of (3.17). Finally, combining this with (A.20) and (A.21), the first half of (3.17) follows. □

Proof of Proposition 3.2. Let d be a procedure more powerful than d^* while satisfying (3.16) and $\overline{\lim}\,\mathrm{pFDR}_\infty(\delta, k) \le \alpha$. Let (δ, k) be fixed first. Given $0 < \alpha_1 < \alpha < \alpha_2$, let

$$\begin{aligned} R^{(1)} &= \#\{i : \mathbb{P}(\eta_i = 0 \,|\, \boldsymbol{X}) < \alpha_1,\ d_i(\boldsymbol{X}) = 1\}, \\ R^{(2)} &= \#\{i : \alpha_1 \le \mathbb{P}(\eta_i = 0 \,|\, \boldsymbol{X}) \le \alpha_2,\ d_i(\boldsymbol{X}) = 1\}, \\ R^{(3)} &= \#\{i : \mathbb{P}(\eta_i = 0 \,|\, \boldsymbol{X}) > \alpha_2,\ d_i(\boldsymbol{X}) = 1\}. \end{aligned}$$

Then $R = R^{(1)} + R^{(2)} + R^{(3)}$ and for any $\boldsymbol{X}$ with $R > 0$,

$$E\left[R_0/R \,|\, \boldsymbol{X}\right] = \frac{1}{R}\sum_{i=1}^{N} d_i(\boldsymbol{X})\mathbb{P}(\eta_i = 0 \,|\, \boldsymbol{X}) \geq \frac{\alpha_1 R^{(2)} + \alpha_2 R^{(3)}}{R}. \tag{A.22}$$

Since d satisfies (3.16), by the WLLN, $R_a = (a + o_p(1))\text{power}_\infty(\delta, k)N$ as $N \to \infty$. By the assumption and (3.17), $\text{power}_\infty(\delta, k) \geq \text{power}^*_\infty(\delta, k) = (1 - \alpha + o(1))p_{k,\delta}(\alpha)/a$. Since $R \geq R_a$, R is at least of the same order as $p_{k,\delta}(\alpha)N$. On the other hand, since

$$R^{(1)} \leq \#\{i : \mathbb{P}(\eta_i = 0 \,|\, \boldsymbol{X}) < \alpha_1\} = (1 + o_p(1))p_{k,\delta}(\alpha_1)N,$$

by (3.15), $R^{(1)} = o_p(1)R$ and so $R^{(2)} + R^{(3)} = (1 + o_p(1))R$. Therefore,

$$\frac{\alpha_1 R^{(2)} + \alpha_2 R^{(3)}}{R} = (1 + o_p(1))\frac{\alpha_1 R^{(2)} + \alpha_2 R^{(3)}}{R^{(2)} + R^{(3)}} = (1 + o_p(1))\left[\alpha_1 + (\alpha_2 - \alpha_1)\frac{R^{(3)}}{R}\right].$$

Combine this with (A.22). Taking expectation over $\boldsymbol{X}$ and letting $N \to \infty$ yield

$$\text{pFDR}_\infty(\delta, k) \geq \alpha_1 + (\alpha_2 - \alpha_1)\varlimsup_{N\to\infty} E[\, R^{(3)}/R \,|\, R > 0\,].$$

Let $(\delta, k) \to (0, \infty)$. As $\varlimsup \text{pFDR}_\infty(\delta, k) \leq \alpha$ by the assumption and $\alpha_1 < \alpha$ is arbitrary, the second half of (3.18) follows. Furthermore, the above inequality implies $\varlimsup_N E[R^{(3)}/R \,|\, R > 0] = o(1)$. Since for each fixed (δ, k), $R^{(1)} = o_p(1)R$ and $N_a = (a + o_p(1))N$, it then follows that, as $(\delta, k) \to (0, \infty)$, $\lim_N E[R/N_a] = \lim_N E[(R^{(2)} + R^{(3)})/N_a] = (1 + o(1))\lim_N E[R^{(2)}/N_a]$. Since $R^{(2)}$ is no greater than the number of nulls with $\mathbb{P}(\eta_i = 0 \,|\, \boldsymbol{X}) \leq \alpha_2$, which is $(1 + o_p(1))p_{k,\delta}(\alpha_2)N$,

$$\text{power}_\infty(\delta, k) \leq \lim_{N\to\infty} E\left[\frac{R}{N_a}\right] = (1 + o(1))\lim_{N\to\infty} E\left[\frac{R^{(2)}}{N_a}\right] \leq (1 + o(1))\frac{p_{k,\delta}(\alpha_2)}{a}.$$

Therefore, $\text{power}_\infty(\delta, k)$ satisfies (3.18). □

Proof of Proposition 3.3. Denote $\alpha_k = \alpha + ck\delta^2$. By the WLLN, d satisfies (3.16). For each (δ, k), d is a thresholding procedure, so $\text{pFDR}_\infty(\delta, k) \leq \alpha_k$. Then by $k\delta^2 \to 0$, d satisfies $\varlimsup \text{pFDR}_\infty(\delta, k) \leq \alpha$. Given (δ, k), following the same argument that leads to (A.11),

$$\text{power}_\infty(\delta, k) = (1 + o(1))\frac{\sqrt{kI(\theta_0)}\delta}{\sqrt{2\pi}\ln Q_{\alpha_k}}\exp\left\{-\frac{(\ln Q_{\alpha_k})^2}{2kI(\theta_0)\delta^2} + \frac{\ln Q_{\alpha_k}}{2}\right\}.$$

Since $Q_{\alpha_k} \to Q_\alpha$, to get $\text{power}_\infty(\delta, k) = (M + o(1))\text{power}^*_\infty(\delta, k)$ as $(\delta, k) \to (0, \infty)$, it boils down to showing

$$\exp\left\{-\frac{(\ln Q_{\alpha_k})^2}{2kI(\theta_0)\delta^2}\right\} = (1 + o(1))M\exp\left\{-\frac{(\ln Q_\alpha)^2}{2kI(\theta_0)\delta^2}\right\}.$$

By Taylor expansion,

$$\ln Q_{\alpha_k} - \ln Q_\alpha = \ln \frac{1-\alpha_k}{1-\alpha} - \ln \frac{\alpha_k}{\alpha} = -\frac{ck\delta^2}{(1-\alpha)\alpha} + O((k\delta^2)^2).$$

As a result,

$$\frac{(\ln Q_{\alpha_k})^2}{2kI(\theta_0)\delta^2} = \frac{(\ln Q_\alpha)^2}{2kI(\theta_0)\delta^2} - \frac{c \ln Q_\alpha}{(1-\alpha)\alpha I(\theta_0)} + O(k\delta^2).$$

By the definition of c, the result follows.

Finally, we show that among procedures that satisfy (3.16) and $\overline{\lim}\, \mathrm{pFDR}_\infty(\delta, k) \le \alpha$, no one is asymptotically the most powerful. It suffices to show that for any such procedure d that is more powerful than d^*, there is yet another one more powerful than d. First, by diagonal argument and the first part of (3.18), there is a decreasing $\alpha_k \to \alpha$, such that $\mathrm{power}_\infty(\delta, k) \le 2p_{k,\delta}(\alpha_k)/\alpha$ for large k. Now we use the same construction as above. Let $\alpha'_k = \alpha_k + c_k k\delta^2$, with $c_k = (1-\alpha_k)\alpha_k I(\theta_0) M / \ln Q_{\alpha_k}$, where $M > 0$. The thresholding procedure using α'_k as cut-offs satisfy the conditions of Proposition 3.2. It is seen that as long as M is large enough, the power of this new procedure will be greater than $4p_{k,\delta}(\alpha_k)/\alpha$, and hence at least twice as large as $\mathrm{power}_\infty(\delta, k)$. □