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Learning false discovery rates by fitting sigmoidal threshold functions

Titre: Estimation du taux de fausse découverte par ajustement de fonctions sigmoïdales

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Abstract: False discovery rates (FDR) are typically estimated from a mixture of a null and an alternative distribution. Here, we study a complementary approach proposed by Rice and Spiegelhalter (2008) that uses as primary quantities the null model and a parametric family for the local false discovery rate. Specifically, we consider the half-normal decay and the beta-uniform mixture models as FDR threshold functions. Using simulations and analysis of real data we compare the performance of the Rice-Spiegelhalter approach with that of competing FDR estimation procedures. If the alternative model is misspecified and an empirical null distribution is employed the accuracy of FDR estimation degrades substantially. Hence, while being a very elegant formalism, the FDR threshold approach requires special care in actual application.

Résumé : Le taux de fausse découverte (FDR) est habituellement estimé en utilisant un mélange de deux distributions, la distribution nulle et la distribution alternative. Dans cet article nous étudions une proposition de Rice et Spiegelhalter (2008), qui utilisent comme point de départ une distribution nulle et une famille parametrique de courbes sigmoïdes pour le FDR. Dans ces familles nous considerons les modèles half-normal decay et beta-uniform mixture. Nous utilisons des simulations et des données réelles pour comparer l'idée de Rice et Spiegelhalter avec des méthodes établies. Nos analyses montrent que si la distribution alternative est mal spécifiée et si une estimation empirique de la distribution nulle est appliquée, on voit une dégradation substantielle de la précision de l'estimation du FDR. Donc, bien que le formalisme proposé soit assez élégant, il est nécessaire de l'appliquer avec une diligence particulière.

Keywords: False discovery rate, multiple testing, model misspecification
Mots-clés : FDR, Taux de fausse découverte, tests multiples, mauvaise spécification des modèles
AMS 2000 subject classifications: 62J15 (pairwise and multiple comparisons)

1. Introduction

Statistical techniques for multiple testing have become indispensable in the analysis of modern high-dimensional data [1]. One of the most prominent approaches uses false discovery rates (FDR) as a measure of error and for determining test thresholds. A precursor of the FDR approach was presented in [7] but only with the seminal work of Benjamini and Hochberg [2] FDR was firmly established in the statistical community.

FDR estimation and control is best understood from a combined Bayesian-frequentist perspective [3]. In this view, the data are modeled by a two-component mixture and local FDR is defined as the Bayesian posterior probability of the null model given the observed value of a test statistic. In an interesting comment Rice and Spiegelhalter [6] reverse the traditional view prevalent in FDR estimation. Rather than assuming a null and alternative model to derive FDR curves they

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proceed by specification of a null model plus a parametric family for the local FDR threshold function. The advantage of this procedure is that the alternative model needs not to be specified explicitly and that at the same time monotonicity of FDR is automatically enforced.

Here, we investigate the Rice-Spiegelhalter approach by studying two different choices of threshold functions and considering two settings for the separation of null and alternative mixture components. Using simulation and analysis of four data sets we also provide a comparison with competing FDR estimation algorithms.

The remainder of the paper is as follows. First, we revisit the background for FDR estimation using mixture models and local FDR threshold curves. Next, we describe two simple models for threshold curves, the beta-uniform mixture (BUM) and the half-normal decay (HND) model. Subsequently, we study the performance of the approach both for a prespecified null model and for empirical null model estimation.

2. False discovery rate estimation via threshold curves

Estimation of false discovery rates (FDR) typically starts by fitting a two-component mixture model to the observed test statistics [3]. This mixture consists of a null model f_0 and an alternative component f_A from which the "interesting" cases are assumed to be drawn. In the following we use a general test statistic $y \geq 0$, with large values of y indicating an "interesting" and small values close to zero an "uninteresting" case. Examples for y include absolute z-scores $|z|$, absolute correlations $|r|$ or $1-p$, i.e the complement of p-values. We can write the mixture model in terms of densities as

$$f(y) = \eta_0 f_0(y) + (1-\eta_0) f_A(y)$$

and using distributions as

$$F(y) = \eta_0 F_0(y) + (1-\eta_0) F_A(y)\,.$$

The parameter η_0 is the true proportion of the null features. The statistic y corresponds, e.g., to 1 - p-value or the absolute value of a z-score or of a correlation coefficient [9]. >From a given mixture model the local FDR (=fdr) is obtained by

$$\begin{aligned} \mathrm{fdr}(y) &= \mathrm{Prob}(\text{“not interesting”}|Y=y) \\ &= \eta_0 \frac{f_0(y)}{f(y)} \end{aligned} \tag{1}$$

and the tail-area-based FDR (=Fdr), also known as q-value, is defined by

$$\begin{aligned} \mathrm{Fdr}(y) &= \mathrm{Prob}(\text{“not interesting”}|Y \geq y) \\ &= \eta_0 \frac{1-F_0(y)}{1-F(y)}\,. \end{aligned} \tag{2}$$

Most (if not all) proposed procedures for determining Fdr and fdr values can be characterized according to the strategies employed for estimation of the underlying densities and distributions - for an overview see [9, 3]. For reasons of identifiability of the mixture model the alternative component is assumed to vanish near the orgin and hence it follows that $\mathrm{fdr}(0)=1$. Similarly, by construction we have $\mathrm{Fdr}(0)=\eta_0$ as $F \to F_0$ for small y.

An alternative approach to FDR estimation is presented by [6] who suggest to view the null model f_0 plus the fdr curve defined by $\text{fdr}(y)$ as the primary objects, rather than the two densities $f_0(y)$ and $f_A(y)$. >From Eq. **1** we obtained the marginal distribution

$$f(y) = \frac{\eta_0 f_0(y)}{\text{fdr}(y)} \tag{3}$$

which is here represented as a function of the null model and the local FDR. Similarly, the alternative component is given by

$$f_A(y) = \frac{\eta_0}{1-\eta_0} \frac{1-\text{fdr}(y)}{\text{fdr}(y)} f_0(y)\,.$$

Furthermore, as $f(y)$ is a density with $\int_0^\infty f(y)dy = 1$ we get the relationship

$$\eta_0 = \left(\int_0^\infty \frac{f_0(y)}{\text{fdr}(y)} dy \right)^{-1}. \tag{4}$$

As a consequence, specifying $f_0(y)$ together with $\text{fdr}(y)$ is equivalent to the standard two-component formulation, but with η_0 and $f_A(y)$ viewed as derived rather than primary quantities. Eq. **3** also plays an important role in the `fdrtool` algorithm for FDR estimation (cf. [9], page 10, algorithm step 7). In particular, in `fdrtool` the function $\text{fdr}(y)$ is estimated nonparametrically and modeled by a step-function.

In the present work we study the estimation of FDR using two continuous variants of threshold curves for $\text{fdr}(y)$. Specifically, we consider the half-normal decay (HND) model by [6] and the beta-uniform mixture (BUM) model of [5]. A further motivation for our study is the recent comparison by [4] who found that the discrete fdr function obtained by the `fdrtool` algorithm may lead to a bias and thus is open to further improvement.

3. Models for fdr threshold curves

We now discuss two simple local FDR threshold functions $\text{fdr}(y)$. There are two natural properties for such a curve. First, the function should be monotonically decreasing, so the FDR values lead to the same ranking as the raw statistics y. Second, on a z-score scale the shape of the curve should be sigmoidal ranging from $\text{fdr}(0) = 1$ onwards to $\text{fdr}(y \to \infty) = 0$. The beta-uniform mixture (BUM) and the half-normal decay (HND) model, as well as their generalizations, satisfy these criteria.

3.1. Beta-uniform mixture (BUM) model

The BUM model was proposed in the context of FDR estimation from p-values [5]. We define the model based on a random variable $Y \in [0,1]$ with uniform distribution as null model. The density is therefore

$$f_0(y) = 1$$

and the corresponding distribution

$$F_0(y) = y\,.$$

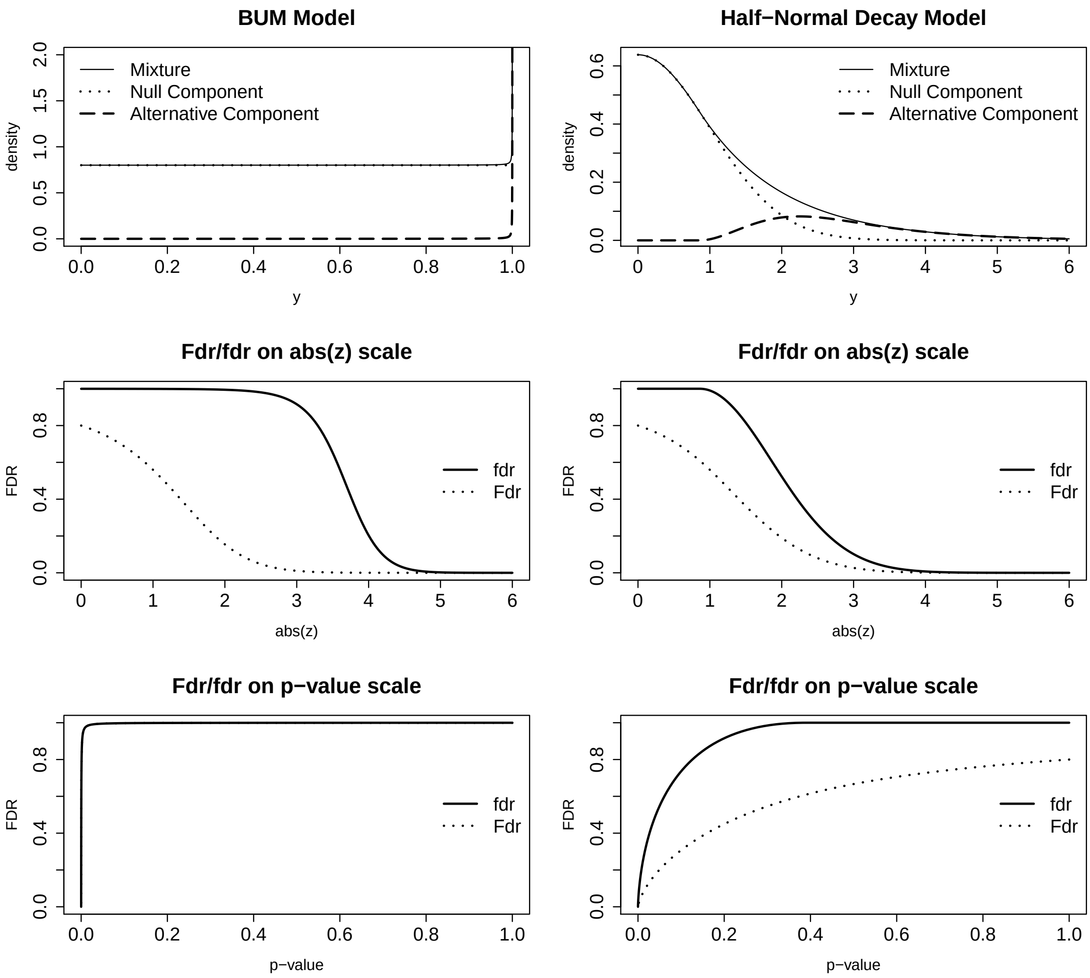


Figure 1: Examples of the BUM and HND model for $\eta_0 = 0.8$. The first row shows the corresponding joint, null and alternative densities. The second row displays the fdr and Fdr values on the standard normal z-score scale. The third row shows fdr and Fdr values on the p-value scale.

The BUM fdr function is given as a one parameter family

$$\mathrm{fdr}^{\mathrm{BUM}}(y|s) = \frac{s}{s + a(1-s)(1-y)^{a-1}} .$$

Note that a is not a parameter but a small constant so that approximately $\mathrm{fdr}^{\mathrm{BUM}}(0|s) = 1$ (we use $a = 0.001$ throughout). From Eq. **4** we find the identity

$$\eta_0 = s$$

which greatly facilitates the interpretation of the parameter s. The marginal density in the BUM model is therefore (Eq. **3**)

$$f(y) = \eta_0 + a(1-\eta_0)(1-y)^{a-1}\,.$$

Similarly, the alternative density is

$$f_A(y) = a(1-y)^{a-1}$$

and the distribution

$$F_A(y) = 1-(1-y)^a\,.$$

The resulting marginal distribution is

$$F(y) = \eta_0 y + (1-\eta_0)(1-(1-y)^a)$$

which leads with Eq. **2** to the following expression for the q-value

$$\mathrm{Fdr}(y) = \frac{\eta_0}{\eta_0 + (1-\eta_0)(1-y)^{a-1}}$$

which has $\mathrm{Fdr}(0) = \eta_0$ as required.

The BUM model can also be trivially reformulated using p-values ($y(p) = 1-p$). Alternatively, as null statistic one may also use standard normal z-scores with $y(z) = 2\Phi(|z|)-1$ where Φ is the standard normal distribution function. The Fdr and fdr curves are invariant against reparameterization, i.e. $\mathrm{Fdr}(z) = \mathrm{Fdr}(y(z))$ and $\mathrm{fdr}(z) = \mathrm{fdr}(y(z))$. The marginal density is computed as $f(z) = \eta_0 f_0(z)/\mathrm{fdr}(y(z))$ and thus requires as additional factor the volume element (which is hidden here in the transformation from $f_0(y)$ to $f_0(z)$).

In Fig. **1** the BUM model and the associated Fdr and fdr values are shown for $\eta_0 = 0.8$ both on a p-value scale and on a standard normal z-score scale.

3.2. Half-normal decay (HND) model

The half-normal decay model is first described by Rice and Spiegelhalter [6]. Its starting point is the random variable Y drawn from standard half-normal distribution Thus, the observations $y \in [0,\infty]$ have null density

$$f_0(y) = \sqrt{\frac{2}{\pi}}e^{-y^2/2}$$

and corresponding distribution function

$$F_0(y) = 2\Phi(y)-1\,.$$

The local FDR curve is given by a one parameter family

$$\mathrm{fdr}^{\mathrm{HND}}(y|s) = \begin{cases} 1 & \text{for } y \le s \\ e^{-(y-s)^2/2} & \text{for } y > s\,. \end{cases}$$

The parameter s has a natural interpretation as cut-off threshold below which there are no "interesting" cases. This specification of null model and fdr curve results in

$$\eta_0 = \left(2\Phi(s) - 1 + \sqrt{\frac{2}{\pi}} e^{-s^2/2 - \log s}\right)^{-1}.$$

This equation is invertible, hence the parameter s has a one-to-one correspondence to the proportion of the null features η_0. In the HND model the marginal density is

$$f(y) = \begin{cases} \eta_0 \sqrt{\frac{2}{\pi}} e^{-y^2/2} & \text{for } y \le s \\ \eta_0 \sqrt{\frac{2}{\pi}} e^{s^2/2 - ys} & \text{for } y > s \end{cases}$$

and the alternative density

$$f_A(y) = \begin{cases} 0 & \text{for } y \le s \\ \frac{\eta_0}{1-\eta_0} \sqrt{\frac{2}{\pi}} (e^{s^2/2 - ys} - e^{-y^2/2}) & \text{for } y > s\,. \end{cases}$$

Finally, the marginal distribution function is

$$F(y) = \begin{cases} \eta_0 (2\Phi(y) - 1) & \text{for } y \le s \\ \eta_0 \left(2\Phi(s) - 1 + \sqrt{\frac{2}{\pi}} e^{s^2/2 - \log s} (e^{s^2} - e^{-sy})\right) & \text{for } y > s \end{cases}$$

which together with $F_0(y)$ allows to compute the tail-area-based Fdr by applying Eq. **2**.

The HND may also be expressed in terms of p-values, using the transformation $y = \Phi^{-1}(1 - p/2)$. In Fig. **1** the HND model for $\eta_0 = 0.8$ (or equivalently $s = 0.862$) is shown and contrasted with the notably different BUM model.

3.3. Generalizations and problem of confounding

The BUM and HND fdr threshold functions are one parameter families indexed by the parameter s which in both models has a one-to-one mapping onto the true proportion of null hypotheses η_0. To allow for more flexibility it is useful to introduce additional parameters, either in the null density $f_0(y)$ or in the fdr function fdr(y). For example, if the null model is misspecified then an additional variance parameter is often all that is needed to extend the model [3]. On the other hand, if the alternative density is not flexible enough this may be fixed by introducing additional parameters into the fdr curve.

Here, we will employ both the BUM and HND model with an additional scale parameter σ in the null model. Specifically, we assume that the null density is a normal $N(0, \sigma^2)$ with mean zero and variance σ^2 so that for the HND model $y = |z/\sigma|$ and for BUM $y = 2\Phi(|z/\sigma|) - 1$, where z is the observed test statistic.

In generalizing null models and fdr functions particular care is necessary because of potential confounding of parameters, especially if the null model and the fdr threshold function are extended simultaneously. For example, the local fdr curve of the standard HND model has an inflection point at $z_0 = s+1$ with fdr value $e^{-1/2} \approx 0.6$ and slope $-e^{-1/2} \approx -0.6$. The extended HND model with additional scale parameter σ in the null model leads to an fdr curve with inflection point $z_0 = s+\sigma$ with fdr value $-e^{-1/2} \approx 0.6$ and slope $-\sigma e^{-1/2} \approx -0.6\sigma$. Thus, the scale parameter of the null model directly determines the slope of the fdr curve at its inflection point, which implies that scale and slope parameters are confounded.

3.4. Empirical null

In a setting with a large number of multiple tests is is possible to employ an empirical null model [3]. Specifically, instead of assuming a theoretical null density with some fixed parameter σ it is possible (and often beneficial) to estimate it from data . As in the present framework the marginal density is a completely specified low-dimensional family given by the null density and the fdr function (Eq. **3**), the empirical null can be obtained in a straightforward fashion by maximum likelihood estimation.

4. Results

We present results from the analysis of synthetic data, followed by a reanalysis of four data sets from [6].

4.1. Setup of simulation study

In order to evaluate the accuracy of the FDR threshold approach we conducted computer simulations. For the data generation we followed the simulation setup for z scores described in [9]:

- Data $x_1, \ldots, x_{200}$ were drawn from a from a mixture of the normal distribution $N(\mu = 0, \sigma^2 = 4)$ with the symmetric uniform alternatives $U(-10,-5)$ and $U(5,10)$ and a null proportion of $\eta_0 = 0.8$.
- The sampling was repeated $B = 1000$ times.

The alternative density of this model does not match the implied alternative density f_A of neither the BUM nor the HND parameterizations. Thus, with this simulation setup we investigate how well the fdr threshold model performs under misspecification. Note that this mixture model corresponds to a scenario where null and non-null features are well separated.

In addition, we also simulated data for a scenario where the alternative and the null model are overlapping:

- Setup as above but with $U(-10,-2)$ and $U(2,10)$ as alternative distribution.

This scenario leads to a marginal density that is similar in shape as the native HND model.

In the subsequent step of comparison of resulting FDR values and model parameters we employed two different strategies for fitting the parameters for the HND and BUM models

1. External estimation: the parameters of the fdr threshold model σ and s (or equivalently η_0) are estimated using `fdrtool` [8] and plugged into the corresponding equations of the BUM and HND models. This allows to directly compare the FDR values computed by `fdrtool` with that of BUM and HND.

2. Empirical null model: the parameters of fdr threshold model are estimated by maximizing the marginal likelihood of the BUM and HND models. We refer to these estimated models as BUM-native and HND-native. This allows to evaluate the effect of misspecification on parameter estimation.

In each case we computed for all $B = 1000$ repetitions the Fdr and fdr values of all $m = 200$ hypotheses and compared these estimates with the true Fdr and fdr values as given by the true known mixture model.

4.2. Results from simulation study

In Fig. **2** the results from the comparison of true and estimated FDR values are shown using the following abbreviations for the investigated algorithms: fdrtool-a, fdrtool-b, and fdrtool-c correspond to using the `fdrtool` software [8, 9], with option `cutoff.method` set to `fndr`, `pct0`, and `locfdr`, respectively (note that fdrtool-a is the default method); BUM and HND denote the two fdr threshold methods with null model given by fdrtool-a; and BUM-native and HND-native correspond to the two fdr threshold methods with empirical null model.

The results can be summarized as follows. For local FDR (first column in Fig. **2**) the HND model improves over `fdrtool` . As fdrtool-a uses exactly the same null model as HND this shows that the step function used to model the local FDR in `fdrtool` may be improved by suitable smoothing. Intriguingly, however, HND-native exhibits a dramatic reduction of accuracy in fdr estimation if the null and alternative are well separated (upper left image). On the other hand, if the null and the alternative are overlapping the HND-native approach performs well (albeit with a large variance). The BUM models performs worst, both with and without empirical null model. For tail-area based FDR (second column in Fig. **2**) both BUM and HND perform similar as `fdrtool` . However, there is again a drastic reduction in accuracy for HND-native and BUM-native in the case of clear separation of null and alternative density (upper right image). HND-native performs very well in the overlapping scenario.

Fig. **3** shows the accuracy of the estimated null models for fdrtool-a, fdrtool-b, fdrtool-c, BUM-native, and HND-native. In the first column box-plots for the estimated null proportion $\hat{\eta}_0$ are shown. With the true value of $\eta_0 = 0.8$ it is evident that BUM-native always overestimates η_0 whereas HND-native mostly underestimates η_0. Likewise, the second column shows that the scale parameter σ is also always overestimated by BUM-native and mostly underestimated by HND-native. In comparison, `fdrtool` overestimates both η_0 and σ only slightly. As in Fig. **2** we also clearly see the impact of the misspecification on HND-native. If the null and alternative densities are clearly separated the HND-native model is not appropriate but in the more difficult case of overlapping mixture components HND-native performs rather well.

In summary, we find the HND model works well for both Fdr and fdr estimation if the correct parameters for the null model are being supplied. HND-native estimation of the empirical null requires that model and data are not misspecified. In contrast, the BUM model is only suited for Fdr estimation and empirical null estimation failed for both investigated scenarios.

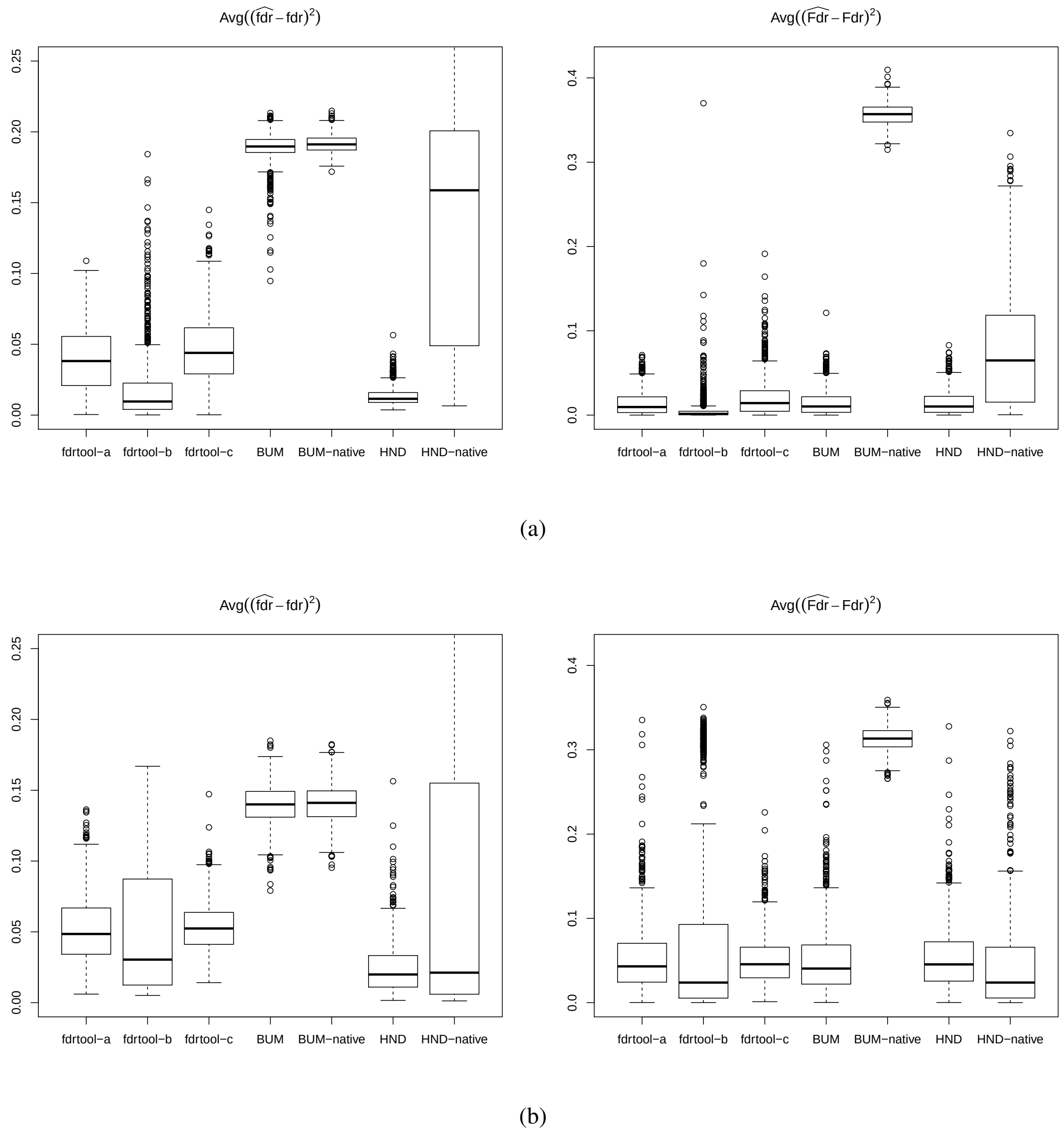
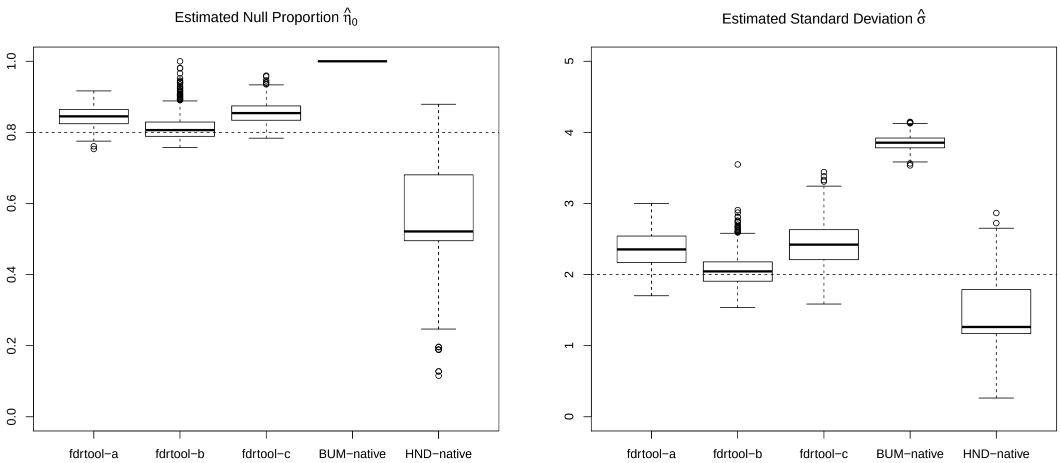
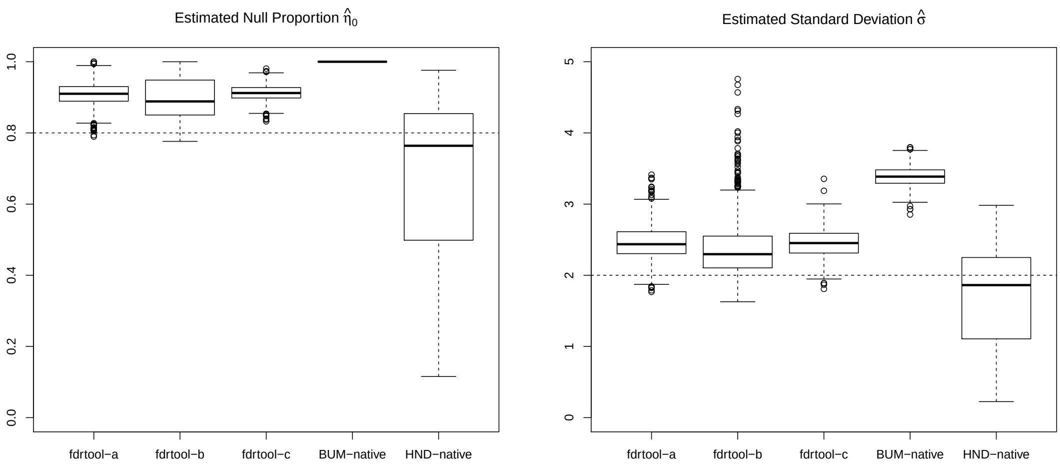


Figure 2: Comparison of the accuracy of fdr and Fdr estimates for the simulated data: (a) well separated case, and (b) overlapping scenario.



(a)



(b)

Figure 3: Comparison of the accuracy of parameter estimates for the simulated data: a) well separated case, and (b) overlapping scenario.

TABLE 1. *Parameter estimates obtained for four real data sets.*

	Prostate	Education	BRCA	HIV
$\hat{\eta}_0$:				
fdrtool-a	0.9855	0.9671	1	0.9587
BUM-native	1	1	1	0.9984
HND-native	0.9829	0.9536	1	0.9370
$\hat{\sigma}$:				
fdrtool-a	1.0649	1.7204	1.5730	0.7999
BUM-native	1.1350	1.9911	1.4313	0.9220
HND-native	1.0588	1.6810	1.4311	0.7652

4.3. Analysis of real data

In their original paper Rice and Spiegelhalter analyzed for four experimental data sets concerning prostate cancer, education (mathematics competency), breast cancer and HIV [6]. We refer to this paper for details and biological background of the data.

Tab. **1** shows the estimates of the model parameters σ and η_0 obtained by BUM-native and HND-native in comparison with the fdrtool-a algorithm. In agreement with the simulations BUM-native performs rather poorly, and HND-native underestimates relative to fdrtool-a. However, in these data examples the fdrtool-a and HND-native are in broad agreement, which implies that here the implicit alternative density of the HND model is appropriate.

5. Conclusion

FDR estimation by direct modeling the fdr threshold curve is a very elegant procedure. We have investigated this procedure using two parametric models for the fdr function and explored its robustness with respect to misspecification of data and model with regard to estimation of local and tail-area based FDR.

The original motivation for proposing this approach in [6] was a preference of fully explicit modeling over using (supposedly) adhoc approaches. However, as our study shows, a full specified model such as HND, and even more so BUM, runs a severe risk of misspecification. In such a case, semi- or nonparametric approaches such as [9] or [4] are in our view preferable, especially if the number of hypotheses is large.

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