False discovery rate envelopes

Tomáš Mrkvička* and Mari Myllymäki†

1*Faculty of Economics, University of South Bohemia, Studentská 13, České Budějovice, 37001, Czech Republic.
2 Natural Resources Institute Finland (Luke), Latokartanonkaari 9, Helsinki, FI-00790, Finland.

*Corresponding author(s). E-mail(s): mrkvicka.toma@gmail.com;
Contributing authors: mari.myllymaki@luke.fi;
†These authors contributed equally to this work.

Abstract
False discovery rate (FDR) is a common way to control the number of false discoveries in multiple testing. There are a number of approaches available for controlling FDR. However, for functional test statistics, which are discretized into \( m \) highly correlated hypotheses, the methods must account for changes in distribution across the functional domain and correlation structure. Further, it is of great practical importance to visualize the test statistic together with its rejection or acceptance region. Therefore, the aim of this paper is to find, based on resampling principles, a graphical envelope that controls FDR and detects the outcomes of all individual hypotheses by a simple rule: the hypothesis is rejected if and only if the empirical test statistic is outside of the envelope. Such an envelope offers a straightforward interpretation of the test results, similarly as the recently developed global envelope testing which controls the family-wise error rate. Two different adaptive single threshold procedures are developed to fulfill this aim. Their performance is studied in an extensive simulation study. The new methods are illustrated by three real data examples.

Keywords: functional linear model, global envelope test, local spatial correlation, multiple testing, resampling

1 Introduction

1.1 Motivation and overview
Nowadays, functional test statistics appear in many applications, for example, in spatial statistics, functional regression, and neuroimaging. A wealth of literature can be found for multiple comparison testing, in particular for micro-arrays applications. However, new challenges arise with functional applications: (i) the functional test statistics are highly correlated over the functional domain, (ii) the distribution of test statistic can change across the domain and even (iii) the correlation of the test statistic can change across the functional domain. Further, the distribution of the functional test statistic is rarely known; therefore, nonparametric methods are often required. With the functional domain, also the visualization of the test statistic, together with its rejection or acceptance region, is of great practical importance.

Recently, we developed a global envelope test (Myllymäki et al, 2017) which provides a global envelope, i.e., the acceptance region for testing with a functional test statistic, under the control
of family-wise error rate (FWER). This method relies on resampling to obtain the distribution of the test statistic under the null hypothesis in the presence of the high correlation of the test statistics across the functional domain. Using rank based ordering of functional statistics as the basis, the method handles the changes of the distribution and correlation across the functional domain. Further, the acceptance region is visualized in the space of the functional test statistics: the parts of the functional domain where the observed test statistics lies outside of the envelope show the reasons for the rejection of the tested global null hypothesis. This direct visualization helps the user to interpret the results in more details, especially because resampling allows to use of any test statistics and not just the conventional standardized test statistics. Consequently, this method allows for a very general application while controlling FWER. Our aim in this paper is to define a procedure that does the same job while controlling the false discovery rate (FDR). To the best of our knowledge, none of the available FDR methods provide such direct visualization with the test result.

Indeed, in functional tests, it is often essential not only to know if the global test is significant but also to estimate the whole domain which is responsible for the rejection, i.e., the local inference. A very popular and powerful control for local inference is the FDR. An attempt to introduce the FDR control to the infinite-dimensional case was made by Olsen et al (2021) as an extension of the FDR procedure of Benjamini and Hochberg (1995). However, this procedure is a step-down procedure, whereby it has no direct visualization. Further, Benjamini and Hochberg (1995) method was overcome by newer FDR procedures.

For the purpose of estimating all alternative hypotheses, the FDR control was defined first in Benjamini and Hochberg (1995). More specifically, the difference between FDR and FWER can be seen from Table 1 of outcomes when testing m hypotheses. The FWER is defined to be \( P(V \geq 1) \), whereas FDR is defined to be \( E(Q) \), where \( Q = \frac{V}{\rho} \) whenever \( \rho > 0 \), and \( Q = 0 \) if \( \rho = 0 \). Clearly, FWER provides more strict control than FDR. Only in the case of all hypothesis being true null (i.e. \( m_0 = m \)), the FDR control implies FWER control (Benjamini and Hochberg, 1995).

Since Benjamini and Hochberg (1995) many theoretical achievements have been made for FDR. Benjamini and Hochberg (1995) proved that their linear step-up procedure controls the FDR for independent test statistics. The subsequent article of Benjamini and Yekutieli (2001) established the control of FDR for test statistics with more general dependence structures, such as positive regression dependence. Benjamini and Hochberg (2000) and Benjamini et al (2006) defined adaptive step-up procedures, which include the estimation of the number of true null hypotheses. Storey (2002) defined another adaptive one-step procedure for controlling FDR.

Since our aim is to define a very general FDR procedure, we stick to the resampling-based methods. The first resampling based procedure was defined in Yekutieli and Benjamini (1999), where the FDR conditional on \( S = s \) (see Table 1) was estimated. This was criticized by Storey and Tibshirani (2001), and they proposed a resampling method for estimating FDR based on the estimation of the number of true null hypotheses for a single threshold rejection rule. Ge et al (2003) then rephrased this procedure. Dudoit et al (2008) defined a Bayes posterior resampling FDR control under the assumption of a mixture model, which assumes that the distributions of all true null statistics are equal and the distributions of all false null statistics are equal. Romano et al (2008) constructed a bootstrap procedure to estimate critical values in a step-down FDR procedure; this method requires bootstrapping the whole data set, which makes its applicability limited. Finally, Ge et al (2008) proposed a resampling procedure based on the step-down procedure of Westfall and Young (1993), which requires the subset pivotality and relies on the assumption that the joint distribution of statistics from the true nulls is independent of the joint distribution of statistics from the false nulls. Since our goal is direct visualization and step-down procedures cannot be used for this purpose, the methods of Yekutieli and Benjamini (1999) and Storey and Tibshirani (2001) can be adapted to our aim.

The following software can be used for the computation of FDR: The R/Bioconductor package

---

Table 1 Possible outcomes from m hypothesis tests

|                | Accept | Reject | Total |
|----------------|--------|--------|-------|
| True null hypothesis | U      | V      | m_0   |
| False null hypothesis | T      | S      | m_1   |
| Total           | W      | ρ      | m     |
multtest (Gilbert et al, 2009) contains the procedures of Benjamini et al (2006) and Dudoit et al (2008). The package fdrtool (Strimmer, 2008) offers the unified approach for the computation of FDR by a semiparametric method allowing for parametric modeling of tests interdependencies. The FDR has further been modeled by many parametric approaches, see Strimmer (2008) and the references therein. The R/Bioconductor package qvalue (Storey et al, 2021) determines the q-value of Storey (2002) for given pointwise p-values. The q-value gives the scientist a multiple hypothesis testing measure for each observed statistic with respect to FDR. This corresponds to the multiple testing adjusted p-value in the FWER sense. Implementation of the FDR envelopes proposed in this work is provided in the development version of the R library GET (Myllymäki and Mrkvička, 2020) available at https://github.com/myllym/GET.

1.2 A comparison of FWER and FDR envelopes: a motivational example

To illustrate the merits of the FDR global envelopes, we explore linear trends in annual water temperature curves sampled at the water level of Rimov reservoir in the Czech republic every day from 1979 to 2014 (Figure 1, top). Viewing the observations as daily samples of functional data, we fit the model

$$y_i(k) = \beta_0(k) + \beta_1(k)(i - 1978) + e(k), \quad (1)$$

where $y_i(k)$ is the water temperature at day $k$, $k = 1,\ldots,365$, in year $i$, $i = 1979,\ldots,2014$, $\beta_0(k)$ and $\beta_1(k)$ are model parameters, and $e(k)$ denotes the error. To test the null hypothesis

$$\beta_1(k) = 0 \quad \text{for all } k = 1,\ldots,365, \quad (2)$$

we use the estimator of the regression coefficient, i.e. $\hat{\beta}_1(k)$, as our test statistic following the methodology proposed in Mrkvička et al (2021). Then 7000 resamples of the test statistic were obtained under the null hypothesis using simple permutation of raw functional data. We utilized the R packages GET (Myllymäki and Mrkvička, 2020) and pppvalue (Xu and Reiss, 2020b,a) to compute the three different tests explained below.

Figure 1 (middle) shows the output of the global extreme rank length (ERL) envelope test (Myllymäki et al, 2017; Narisetty and Nair, 2016; Mrkvička et al, 2020) on testing the global null hypothesis (2) under the FWER control. The global ERL test shows the behavior of $\hat{\beta}_1(k)$ estimated from the data in comparison to the 95% global envelope constructed from the permutations and detects a significant increase in temperature for 24 days around the 120th day of the year (21 days). So it directly identifies the reason for the rejection (increase), and further, it expresses the evolution of the variability of the test statistic under the null hypothesis via the global envelope. It also specifies the amount of the increase over the threshold given by the global envelope. However, the global envelope is not designed for local inference. Therefore, the step-down method of Westfall and Young (1993) can be more powerful, but only if many permutations are used. The step-down p-values (Xu and Reiss, 2020a) are shown in Figure 1 (bottom). Using 7000 permutations, we could obtain significant increases (or decreases) for 17 days. Repeating the experiment for 2000 permutations, the results of the FWER (ERL) and FDR envelopes produced rather the same results, but none of the FWER adjusted step-down p-values were below 0.05. Thus, the step-down procedure requires plenty of permutations, and it provides only visualization of p-values.

Both the global ERL test as well as the step-down method control FWER. The aim of this paper is to employ the FDR control instead, retain the direct visualization (single-step methods) and not require plenty of permutations. For example, in applications in spatial statistics or neuroimaging, the simulations of the null model can be rather complex computationally or in terms of memory. Figure 2 shows an FDR envelope proposed in this work (IATSE algorithm presented in Section 4.1). The test controlling FDR rejected null hypotheses in springtime, around the 120th day of the year as the FWER envelope test, but additionally also in summertime around the 180th day of the year. The null hypothesis was rejected for 35 days in total under FDR control.

1.3 Outline of the work

Because the data are assumed to be highly dependent, and the aim is to use the envelope for any
functional test statistic, nonparametric resampling methods will be used. We also assume a general model for alternative hypotheses, since, e.g., in functional permutation tests, the differences between groups of functions will range from zero (null hypothesis) to small (alternative hypothesis) and large ones (alternative hypothesis). Since our aim is to develop an FDR envelope that allows for direct visualization, we will concentrate on a single threshold multiple testing procedure, such as developed by Storey (2002) or Yekutieli and Benjamini (1999).

We will propose two new two-stage procedures, with the basis in the algorithm of Storey (2002) to estimate FDR for a given rejection region. Essential new features of our algorithms are the following: 1) an estimate of the probability that a hypothesis is a true null which works well for highly dependent hypotheses, and 2) defining the rejection regions, for which the FDR is estimated, using a new min-max envelope. As such we will obtain an envelope which (a) allows for direct visualization, (b) is directly able to identify all the false hypotheses under the control of FDR, (c) is not sensitive to the change of the distribution of the test statistic across the functional domain, and (d) is not sensitive to the change of the correlation structure across the functional domain.

The setup for multiple hypothesis testing and the proposed rejection (and acceptance) regions are described in Section 2 and 3. Section 4 proposes two algorithms for the FDR envelopes together with q-value definition for them. An extension of this method for the case where nuisance parameters have to be estimated is introduced in Appendix A. Section 5 contains a thorough simulation study comparing the performance of proposed methods with several FDR alternatives. The advantage of direct visualization is emphasized by a data example in Section 6. An example from spatial statistics with a two-dimensional test statistic studying local spatial correlation is presented in Section 7. Conclusions are given in Section 8.

2 Multiple hypothesis testing

Assume the functional hypothesis testing problem, with hypotheses $H_x$, $x \in \mathbb{R}^d$, which is discretized into $m$ hypotheses. Assume now that all $H_x$ are simple hypotheses. The discretization can be arbitrary; equidistances are not required. Thus we assume
that we are testing $m$ hypotheses $H_k$, $k = 1, \ldots, m$, simultaneously. Denote $H_k = 0$ if the $k$-th hypothesis is a true null hypothesis and $H_k = 1$ if the $k$-th hypothesis is a false null hypothesis. The sets $\mathcal{M}_0 = \{k : H_k = 0\}$ and $\mathcal{M}_1 = \{k : H_k = 1\}$ are unknown and the aim is to estimate them. Let us denote by $m_0 = |\mathcal{M}_0|$ and $m_1 = |\mathcal{M}_1|$ the numbers of true and false hypotheses. The number of rejected hypotheses $\rho$ is observed together with the number of not rejected hypotheses $W$. On the other hand, the numbers of rejected and not rejected true null hypotheses $V$ and $U$ and the numbers of rejected and not rejected false null hypotheses $S$ and $T$ are not observed (see Table 1).

Every single test $k$ is tested by the statistic $T_k$. The vector of the statistics, $\mathbf{T} = (T_1, \ldots, T_m)$, can have an arbitrary distribution. The marginal distributions of $T_k$, $k = 1, \ldots, m$, can be interdependent and the distribution of $T_k$ can change across $k$. Also the interdependence can vary across $k$. A usual approach is to consider the parametric statistics as $t, F, \ldots$, but since such a parametric statistic can change its marginal distribution across $k$, we will switch to rank statistics of these parametric statistics. Obviously, when the statistic changes its marginal distribution, the simultaneous tests will be blind to alternatives that occur for $k$ with smaller variability of test statistic $\mathbf{T}$; the rank statistics overcome this problem.

When $\mathcal{R}$ denotes the rejection region in a single test, $P(T \in \mathcal{R} | H = 0)$ is called the type I error rate and is controlled by a predetermined level $\alpha$. On the other hand, $P(T \notin \mathcal{R} | H = 1)$ is called the type II error rate and is not controlled.

In multiple testing, the problem of controlling the type I error is more complex, and it is generalized in several ways. The most common is FWER, where the probability of at least one type I error is controlled, i.e., $\text{FWER} = P(V \geq 1)$. But also, per comparison error rate can be defined as $\text{PCER} = E(V)/m$ or per family error rate $\text{PFER} = E(V)$. In functional setting, Pini and Van'tini (2017) recently introduced the interval-wise error rate in order to control the type I error for each subinterval of the functional domain. All the above-mentioned controls are designated to control the existence of rejection of a true null hypothesis, whereas the famous FDR was introduced in order to determine $\mathcal{M}_0$ and $\mathcal{M}_1$. The natural way to control FDR would be by $E(V/\rho)$, but the case of division by zero has to be treated. Therefore, the first definition of FDR (Benjamini and Hochberg, 1995) was $\text{FDR}= E(V/\rho) | \rho > 0) \mathbb{P}(\rho > 0)$. Then Storey (2002) defined positive false discovery rate by $\text{pFDR}= E(V/\rho) | \rho > 0)$, which controls error rate when positive findings occurred.

The rejection region for the multiple hypothesis test can be given by a step-up procedure, subsequently rejecting the hypothesis from the smallest $p$-values, as proposed by Benjamini and Hochberg (1995). Such rejection region is estimated to fulfill the FDR control. If an opposite approach is taken, it is possible to estimate FDR or pFDR for a general fixed rejection region $\Gamma = (R_1, \ldots, R_m)$.

Storey (2002) proposed to use a single value threshold $\gamma$ as a natural rejection region for the continuous statistics $T_k$. While we would like to use rank statistics, this approach brings many ties and has to be refined. For example, assume that the null hypothesis is resampled $s$ times. Then the single test statistic can achieve only ranks from 1 to $s$. Consequently, the single threshold rejection region can also obtain only these values, and the corresponding estimated FDR values can be rather sparse, leading to only approximate control. For this purpose, we will define new acceptance regions based on the global rank envelope (Myllymäki et al., 2017).

We note that the problem of ties in $p$-values for non-resampling algorithms was also discussed recently in the literature (Chen et al., 2018; Chen, 2020). They assumed that the test statistic comes from a given discrete distribution.

### 3 Continuous min-max envelope

In our earlier works, summarized in Myllymäki and Mrkvička (2020), we have defined several global envelopes, which are appropriate in the case of the FWER control, where it is desired to construct the envelopes together with the data and simulated functions in order to get the exact Monte Carlo test in the Barnard sense (Barnard, 1963). Here we introduce a new min-max envelope which is a continuous version of the rank envelope proposed in Myllymäki et al. (2017), and use it as the basis of our FDR envelopes.

We will estimate the FDR for a given rejection region $\Gamma$ which corresponds to the acceptance region determined by the envelope $\mathcal{E}$. We introduce
a new, continuously enlarging envelope that is controlled by a single parameter, similarly as it is in the classical constant rejection rule (Storey, 2002). However, our continuous min-max envelope reflects the shape of the distribution of the test function under the complete null hypothesis.

Assume now, that we have s resamples of the complete null hypothesis, i.e. m0 = m, which gives us s test vectors \( T_i = (T_{i1}, \ldots, T_{im}), i = 1, \ldots, s \).

Let us define the lower and upper bounds of the envelope \( E \) for the two-sided alternative hypotheses. For \( \gamma \) being an integer, \( \gamma = 1, 2, 3, \ldots, \lfloor s/2 \rfloor \), the bounds are defined by

\[
E_{\gamma, k}^\text{low} = \min \gamma \{ T_{ik} : i = 1, \ldots, s \},
\]

\[
E_{\gamma, k}^\text{upp} = \max \gamma \{ T_{ik} : i = 1, \ldots, s \}
\]

for \( k = 1, \ldots, m \), where \( \min \gamma \) and \( \max \gamma \) denote the \( \gamma \)-th smallest and largest values, respectively. For a non-integer \( \gamma > 1 \), we define the bounds of \( E_{\gamma} \) as the average of neighboring integer \( \gamma s \):

\[
E_{\gamma, k}^\text{low} = E_{\lceil \gamma \rceil, k}^\text{low} + (\gamma - \lceil \gamma \rceil) \cdot (E_{\lceil \gamma \rceil + 1, k}^\text{low} - E_{\lceil \gamma \rceil, k}^\text{low}),
\]

\[
E_{\gamma, k}^\text{upp} = E_{\lceil \gamma \rceil, k}^\text{upp} - (\gamma - \lceil \gamma \rceil) \cdot (E_{\lceil \gamma \rceil, k}^\text{upp} - E_{\lceil \gamma \rceil + 1, k}^\text{upp}).
\]

For \( 0 < \gamma < 1 \), we define the envelope \( E_{\gamma} \) as an extension of \( E_1 \):

\[
E_{\gamma, k}^\text{low} = E_{1, k}^\text{low} + \log \gamma \cdot (E_{1, k}^\text{upp} - E_{1, k}^\text{low}),
\]

\[
E_{\gamma, k}^\text{upp} = E_{1, k}^\text{upp} - \log \gamma \cdot (E_{1, k}^\text{upp} - E_{1, k}^\text{low}).
\]

The definition for the one-sided alternatives can be obtained accordingly by omitting the lower or upper part.

### 4 FDR estimation

This section describes algorithms for FDR estimation from s resamples of the complete null hypothesis. We adopt the Storey (2002) approach of estimation FDR, rather than the Benjamini and Hochberg (1995) approach of estimation of rejection region. This allows us to estimate FDR for a general global envelope \( E \), which represents the acceptance region corresponding to the rejection region \( \Gamma \). The advantage of our proposed algorithms is that they make no assumptions on the correlation structure of the test statistics and also not on the false null hypotheses. The only assumption here is that the true null hypotheses are simple.

For a fixed \( \Gamma \), we can observe only \( \rho(\Gamma) \), the number of positives, together with the corresponding numbers of acceptances, \( W(\Gamma) \). The number of false positives \( V(\Gamma) \) is not observable, but it can be estimated.

Storey and Tibshirani (2001) showed that

\[
\mathbb{E}\left[ \frac{V(\Gamma)}{\rho(\Gamma)} \right] \approx \frac{\mathbb{E} V(\Gamma)}{\max(\rho(\Gamma), 1)} = \pi_0 \frac{\mathbb{E} \rho_0(\Gamma)}{\max(\rho(\Gamma), 1)},
\]

(3)

where \( \rho_0(\Gamma) \) is the number of positives under complete null hypothesis. In order to estimate the probability that a hypothesis is true null, \( \pi_0 \), Storey and Tibshirani (2001) proposed to choose a smaller rejection region \( \Gamma' \) and compute

\[
\hat{\pi}_0 = \frac{W(\Gamma')}{\mathbb{E} W_0(\Gamma')}. \quad (4)
\]

When working with highly correlated data, this estimator of \( \pi_0 \) has a significant drawback: the histogram of \( p \)-values observed under null hypothesis is not uniform, which is assumed by the method (Storey and Tibshirani, 2003). This feature causes the estimator to fail for any choice of \( \Gamma' \), even for the smoothing method defined in Storey and Tibshirani (2003). Also, Xie et al (2005) claimed that estimation of \( \pi_0 \) is a challenging problem. In non-resampling approaches, the choice of \( \Gamma' \) attracted many researchers in order to define so-called adaptive FDR procedures based on the Storey estimator (4) (e.g. Liang and Nettleton, 2012; Heesen and Janssen, 2016). However, since these procedures are still based on the basic Storey estimator, we searched for another estimator of \( \pi_0 \), which would not require the uniformity of \( p \)-values. Hwang (2011) compared several estimators from which the lowest slope method developed by Benjamini and Hochberg (2000) and the mean of differences method (Hsueh et al, 2003) seem to be the best in the dependent case, but Hwang (2011) did not include in the comparison the two-stage approach of Benjamini et al (2006). The two-stage method was compared to the method of Benjamini and Hochberg (2000) in Benjamini et al (2006), and it was found to be significantly better. Also, this two-stage approach satisfies the conservative estimation of \( \pi_0 \) under the independence of all hypotheses. For these reasons, we utilize the \( \pi_0 \) estimation of this two-stage approach of Benjamini et al (2006), which is defined in the
following algorithm, in one of our proposed algorithms, and we also use the algorithm as the reference method in the simulation study. In our second algorithm, we use another estimator for $\pi_0$, and we prove its strong conservativeness without further assumptions.

Adaptive two-stage procedure of Benjamini et al (2006) (ATS):
1. Use the linear step-up procedure at level $\alpha^* = \alpha/(1 + \alpha)$. Let $r$ be the number of rejected hypotheses. If $r = 0$ do not reject any hypothesis and stop; if $r = m$ reject all $m$ hypotheses and stop; otherwise continue.
2. Let $\hat{\pi}_0 = (m - r)/m$.
3. Use the linear step-up procedure with $\alpha' = \alpha/\hat{\pi}_0$.

The linear step-up procedure uses $m$ $p$-values \{\(p_1, \ldots, p_m\)\} corresponding to the $m$ hypotheses and the ordered $p$-values $\{p[1] \leq p[2] \leq \cdots \leq p[m]\}$. It rejects $k$ hypotheses corresponding to the first $k$ smallest $p$-values, where $k = \max\{i : p[i] \leq i\alpha/m\}$. If such $k$ does not exist, it rejects no hypothesis.

In the first step of the algorithm, the numbers of rejections are estimated assuming that $\pi_0 = 1$. In the second step, an estimate for $\pi_0$ is found, and the third step finds the rejections utilizing the estimate of $\pi_0$.

4.1 Two-stage resampling procedures for FDR envelopes

We can now, in the two-stage procedure, replace the linear step-up procedure with the procedure of Storey and Tibshirani (2001) applied to our rejection regions of Section 3. The resulting adaptive two-stage resampling-based procedure (ATSE) defined in the following algorithm has a global envelope representation corresponding to the rejection region $\Gamma_\gamma$.

As the estimate of $\mathbb{E} \rho(\Gamma_\gamma)$ in the steps 1. and 3. of the algorithm we use

$$\mathbb{E} \rho(\Gamma_\gamma) \cong m \hat{\gamma}, \quad (5)$$

where $\Gamma_\gamma$ is the rejection region corresponding to $\mathcal{E}_\gamma$ as defined in Section 3 and $\hat{\gamma}$ is the pointwise adaptive two-stage envelope (ATSE):
1. Find the largest rejection region $\Gamma_{\gamma^*}$ for which

$$\frac{\mathbb{E} \rho(\Gamma_{\gamma^*})}{\max(\rho(\Gamma_{\gamma^*}), 1)} \leq \alpha/(1 + \alpha).$$

Let $r$ be the number of rejected hypotheses for $\Gamma_{\gamma^*}$. If $r = 0$, do not reject any hypothesis, take $\Gamma_{\gamma} = \Gamma_{\gamma^*}$ and stop; if $r = m$, reject all $m$ hypotheses, take $\Gamma_{\gamma} = \Gamma_{\gamma^*}$ and stop; otherwise continue.
2. Let $\tilde{\pi}_0 = (m - r)/m$.
3. Find the largest rejection region $\Gamma_{\gamma}$ for which

$$\frac{\mathbb{E} \rho(\Gamma_{\gamma})}{\max(\rho(\Gamma_{\gamma}), 1)} \leq \alpha/\tilde{\pi}_0.$$ 

$p$-value corresponding to $\Gamma_{\gamma}$. That is,

$$\hat{\gamma} = \begin{cases} 2\gamma/s & \text{in the two-sided case} \\ \gamma/s & \text{in the one-sided case}. \end{cases} \quad (6)$$

Note that there is equality in Equation (5) for an integer $\gamma$. A formula similar to (5) was used in Storey (2002) and Storey and Tibshirani (2003) for a given threshold $p$.

Instead of using the idea of ATS algorithm to estimate $\pi_0$, it is also possible to use the following iterative adaptive two-stage envelope (IATSE) algorithm.

The expectations in steps 1. and 3. of the IATSE algorithm are calculated according to Equation (5) similarly as in the ATS algorithm. Note here that the ATSE method controls the estimate of $\pi_0$ by assuming a greater significance level in the first step, in the same way as the ATS algorithm of Benjamini et al (2006). On the other hand, the IATSE method adds the expected number of false null hypotheses to the estimate of $\pi_0$.

The IATSE algorithm is motivated by the following conservative, iterative estimate of $\hat{\pi}_0$:

$$\hat{\pi}_0^1 = m - r + m\hat{\gamma}^*$$

and

$$\hat{\pi}_0^l = m - r + \hat{\pi}_0^{l-1}\hat{\gamma}^*.$$ 

The limit of this iterative procedure is according to the sum of geometrical sequence equal to

$$(m - r)/(1 - \hat{\gamma}^*).$$

**Theorem 1** The estimate (7) of the IATSE algorithm is a conservative estimate of $\pi_0$. 


Iterative adaptive two-stage envelope (IATSE):
1. Find the largest rejection region \( \Gamma_{\gamma^*} \) for which
\[
\frac{\mathbb{E} \rho^0(\Gamma_{\gamma^*})}{\max(\rho(\Gamma_{\gamma^*}), 1)} \leq \alpha.
\]
Let \( r \) be the number of rejected hypotheses for \( \Gamma_{\gamma^*} \). If \( r = 0 \), do not reject any hypothesis, take \( \Gamma_{\gamma} = \Gamma_{\gamma^*} \) and stop; otherwise continue.
2. Let \( \tilde{\gamma}^* \) be the pointwise \( p \)-value corresponding to \( \Gamma_{\gamma^*} \) defined according to the Formula (6) and
\[
\tilde{\pi}_0 = \min \left( 1, \frac{(m - r)/m}{1 - \tilde{\gamma}^*} \right).
\]
3. Find the largest rejection region \( \Gamma_{\gamma} \) for which
\[
\frac{\mathbb{E} \rho^0(\Gamma_{\gamma})}{\max(\rho(\Gamma_{\gamma}), 1)} \leq \alpha/\tilde{\pi}_0.
\]

**Proof** It suffices to prove that \( \mathbb{E} \frac{(m - r)/m}{1 - \tilde{\gamma}^*} \geq \pi_0 \). Denote now \( \beta_k \) the probability of the error of the second kind for any \( k \)-th hypothesis which is false.
\[
\mathbb{E} \frac{(m - r)/m}{1 - \tilde{\gamma}^*} = \frac{(m - m_0 \tilde{\gamma}^* + \sum_{k \in \mathcal{M}_1} (1 - \beta_k))/m}{1 - \tilde{\gamma}^*} = \frac{(m - m_0 \tilde{\gamma}^* + \sum_{k \in \mathcal{M}_1} (1 - \beta_k))/m}{1 - \tilde{\gamma}^*} = \pi_0 + \sum_{k \in \mathcal{M}_1} \frac{(1 - \beta_k)/m}{1 - \tilde{\gamma}^*} \geq \pi_0.
\]

\( \Box \)

Since the strong control of our whole procedures can be studied only under independence assumptions of test statistics (similarly as in Liang and Nettleton, 2012), which is not realistic in functional setting, we resort on checking the control by an extensive simulation study. Note here that the strong control of the ATS algorithm was also proven for independent hypotheses only (Benjamini et al, 2006).

Appendix A contains an algorithm for FDR estimation in case the null hypothesis is not simple, but some nuisance parameters are estimated, which is an extension of the proposed algorithms. Appendix B contains further algorithms and their modifications that incorporate the dependence of the test statistics in the FDR estimation and which can be used for envelope construction. These algorithms were used in the simulation study for comparison with the proposed algorithm, but they did not perform as well as the algorithms proposed in this section.

### 4.2 q-values

The \( q \)-value related to the hypothesis \( H_k, k = 1, \ldots, m \), is the size of the test still rejecting \( H_k \) while controlling FDR. In the case of FDR envelopes, this size corresponds to the \( \tilde{\gamma} \) value that defines the largest possible envelope (i.e., smallest possible rejection region) such that the hypothesis \( H_k \) is rejected. Formally,
\[
q_k = \inf \{ \tilde{\gamma} : T_k \in \Gamma_{\gamma} \}.
\]

Yekutieli and Benjamini (1999) noted that it is advantageous to use adjusted \( p \)-values in multiple hypothesis testing because then the level of the test does not have to be determined in advance. The same can be said about \( q \)-values in the context of FDR control.

### 5 Simulation study

A simulation study was performed to investigate the FDR control and power of different FDR methods listed in Table 2. We include some methods with parametric and nonparametric pointwise \( p \)-values to stress differences between them. We show some methods with known \( \pi_0 \) in order to check the problem of \( \pi_0 \) estimation by comparing it to the method with unknown \( \pi_0 \). The ATS method is included as the reference method, the best one we have found from the literature. ST, YB, YBu, IATSE-YB, IATSE-YBu, ATSE, and IATSE are included in the comparison as candidates for the best FDR envelope. The methods YB, YBu, IATSE-YB, IATSE-YBu, which incorporate the dependence of the test statistics, are described in Appendix B.

The FDR methods were investigated for detecting the difference between two groups of functions, where each group had ten observations. The functions in the groups were generated from Gaussian, Student’s \( t_1 \) or bimodal random processes on \([0, 1]\) with means \( \mu_1(k) \) and \( \mu_2(k) \) for the two groups, respectively. We considered 11 different mean function combinations for the two groups. As a null case, we considered the ‘no differences’ case where
Table 2  Multiple testing methods with FDR control investigated in the simulation study

| Short name | Description |
|------------|-------------|
| ATSp       | ATS (Benjamini et al, 2006) with parametric \( p \)-values |
| ATS        | ATS (Benjamini et al, 2006) with non-parametric \( p \)-values |
| STp        | Storey and Tibshirani (2003) with parametric \( p \)-values |
| ST         | Storey and Tibshirani (2003) with non-parametric \( p \)-values |
| STp/\( \pi_0 \) | Storey and Tibshirani (2003) with parametric \( p \)-values and known \( \pi_0 \) |
| ST/\( \pi_0 \) | Storey and Tibshirani (2003) with non-parametric \( p \)-values and known \( \pi_0 \) |
| YB         | Yekutieli and Benjamini (1999) (with \( \pi_0 = 1 \)) |
| YBu        | Yekutieli and Benjamini (1999) \('u\'-version with \( \beta = 0.05 \) (with \( \pi_0 = 1 \)) |
| IATSE-YB   | Yekutieli and Benjamini (1999) \('u\'-version complemented with \( \pi_0 \) estimation |
| IATSE-YBu  | Yekutieli and Benjamini (1999) \('u\'-version complemented with \( \pi_0 \) estimation |
| ATSE       | FDR envelope using the ATSE algorithm |
| IATSE      | FDR envelope using the IATSE algorithm |

both groups had mean zero. Further, we considered three cases named 'Abrupt', 'Fluctuating' and 'Soft', where the first group had zero mean, while the mean in the second group deviated from zero in different ways and on different sub-intervals of \([0, 1]\). Finally, a case of 'Bumps' was considered where both mean functions are positive on \([0, 0.66]\), and 0 otherwise. The mean functions slightly differ on \([0, 0.66]\). More precisely, the mean functions are specified in Table 3 and visualized in Figure C1 of Appendix C. The Gaussian process was constructed as \( Z_i(k) = \mu_i(k) + e(k) \), where \( i = 1, 2 \) and \( e(k), k \in [0, 1] \), are the Gaussian errors with the standard deviation \( \sigma_Z \) and the exponential covariance function with the scale parameter \( \phi_Z = 0 \) (independent case), 0.1 or 0.5. In the case of Student’s \( t_1 \) distribution, the error was obtained from two independent standard Gaussian errors with the same covariance as \( e(k) \). In the bimodal case, the error was obtained by transforming \( e(k) \) as \( e_b(k) = \text{sign}(e(k)) \cdot \frac{2}{3} | e(k) |^{1/5} \). Different values were considered for \( \sigma_Z \) as specified in Table 3. The choices were different for different mean functions in order to reach the powers of the methods in a reasonable range.

We first compared all the methods of Table 2 with the resolution \( m = 200 \), such that \( k \) obtained \( m \) equidistant values on \([0, 1]\). We did the comparison for different numbers of resamples \( s = 100, 500, 1000, 2000, 5000\), for all 11 models explained in Table 3 with the Gaussian, \( t_1 \) and bimodal errors and with the three strengths of correlation determined by \( \phi_Z = 0, 0.1, 0.5 \), in total for \( 3 \cdot 3 \cdot 11 \cdot 5 = 495 \) cases. To test the hypothesis of no difference in the means of the two groups, we used the functional \( F \)-statistic (the vector of \( F \)-values calculated for each \( k \)). The chosen \( F \)-statistics allows to compute also parametric \( p \)-values and compare the performance of parametric and non-parametric FDR methods (see Table 2). Note that the nonparametric methods are not limited to the \( F \)-statistic, but other statistics, which can be more easily interpreted, can be used (see Section 6).

Each case was repeated 2000 times, and for each repetition, we calculated the FDR, i.e., the number of falsely rejected hypotheses divided by the total number of rejections. Also, the proportion of rejected hypotheses from the known true positives as a measure of power was calculated. The mean FDR and power as well as their standard errors, \( \sigma_{\text{FDR}} \) and \( \sigma_{\text{power}} \), were then calculated from the 2000 repetitions. In the following, we summarize the relevant findings from the simulation study. The rest of the results are given in Appendix C.

Figure 3 shows the mean FDR (\( \pm 2 \cdot \sigma_{\text{FDR}} \)) for Models 1 (complete null model), 4, 5 and 11 with Gaussian errors. First, the results show that ST and STp methods are highly liberal for correlated cases. This liberality is caused by the \( \pi_0 \) estimation: the ST methods with known \( \pi_0 \) are not liberal. Some repetition for ST and STp even fell down due to the non-uniform distribution of pointwise \( p \)-values. Namely, tens of repetitions fell down for correlation 0.1, and hundreds fell down for correlation 0.5; these cases were excluded from the results. The results also show the liberality of all YB methods for the complete null model (Model 1) with correlated errors. The liberality of YB and YBu methods is then suppressed for Model 5 because the methods do not consider the estimation of
Adding the estimation of π₀ into YB methods, i.e., using IATSE-YB and IATSE-YBu methods causes the return to liberalism also in cases where π₀ < 1, particularly for Models 4 and 11. Due to these observed liberalities, we concentrate our further comparison only on ATSp, ATS, ATSE, and IATSE methods, whose estimated mean FDR was satisfactory for all models.

The power of non-liberal methods is shown for Models 2, 4, and 11 in Figure 4. Here we can observe, especially for Model 2, that the parametric ATS achieves the highest power, which is only reached by nonparametric methods by applying at least 5000 permutations. The IATSE method seems to be the most powerful from nonparametric methods, which is more apparent for small numbers of permutations s. The number of resamples is not a negligible feature of the test since, for example, in spatial statistics, the resampling of a test statistic can be costly in terms of time.

The advantage of the parametric method is clearly lost when the errors are not Gaussian since the parametric p-values assume the Gaussianity. Figure 5 shows that if the assumptions of parametric p-values are not fulfilled, the parametric method can achieve either strong liberalty or strong conservativeness.

The above experiment suggests that the IATSE method is a universal method for FDR control. Namely, it does not require knowing the test statistic distribution, it was conservative in all studied cases, conservativeness of its π₀ estimation was proven, and it allows for graphical interpretation using the envelopes. Further, it tends to have a little bit tighter control of FDR than ATS and ATSE, as it can be seen from Figure 6 where the FDR control is studied with respect to increasing resolution m for the Gaussian error case. This figure also shows that the increased resolution has no influence on the FDR control of these three methods when the number of resamples is large enough to distinguish the extreme pointwise p-values.

6 Population growth example

Figure 7 (left) shows population growth, defined here as the population at the end of the year divided by the population at the beginning of the year, in years from 1960 to 2014 in Africa, Asia, Europe, and North America, and Latin America, total in 112 countries with more than one million inhabitants in 1950 (Nagy et al, 2017; Dai et al, 2020). Figure 7 (right) shows the GDP of every country in the study discounted to the 1960 USD. The discounting was performed according to USD inflation. The data was obtained from the World Bank. The missing values of the GDP of a country were extrapolated using the closest known ratio of the GDP of the country and the median GDP in that year. The missing values of GDP were interpolated using linear interpolation of the two closest ratios.

We explore the functional general linear model (GLM) for the population growth across years 1960-2014 with categorical covariate (continent), continuous covariate (GDP), and interactions (GDP with respect to the continent). For this purpose, we applied three tests, and on each of them, we applied the proposed FDR control (IATSE) to obtain all years which are significant for the studied covariate. We follow the graphical functional GLM testing procedure introduced for FWER control in Mrkvička et al (2021).

### Table 3

Mean functions µ₁(k) and µ₂(k), k ∈ [0, 1], used in the simulation study. The equations for the bumps are

\[ µ₁^\text{bump}(k) = 3 \cdot (5 + 2) \cdot k \cdot (1 - k)^{5+2} \]

and

\[ µ₂^\text{bump}(k) = 3 \cdot (5 + 6) \cdot k \cdot (1 - k)^{5+6} \]

for k < 0.66, and 0 otherwise. Different values were considered for the parameters of the mean functions (Parameters) leading to different proportions of the true nulls (m₀/m). The final row gives the standard deviation of the Gaussian error, σ₂, used for the Gaussian and bimodal errors.

| Model | Name            | 1   | 2-4 | 5-7 | 8-10 | 11  |
|-------|-----------------|-----|-----|-----|------|-----|
|       | No diff.        | Abru|     |     |      |     |
| µ₁(k) |                 | 0   | 0   | 0   |      |     |
| µ₂(k) |                 | 0   | 1 for s ∈ (0, a), | max(0, sin(bk) - k) |      |     |
|       |                 |     | 0 otherwise | exp\{-((k - 0.5)^2/(2σ²)} |      |     |
|       | Parameters      |     | a = 0.05, 0.20, 0.50 | b = 20, 50, 100 |      |     |
|       | m₀/m            | 1   | 0.95, 0.8, 0.5 | 0.65, 0.67, 0.67 |      |     |
| σ₂    | 0.5             | 0.5 | 0.3  |     | 0.3  | 0.05 |
First, to test the effect of the continent, we assume the main effects model

\[
\text{population growth} \sim \text{Continent} + \text{GDP},
\]

and we used the test statistic

\[
\beta_{\text{Cont}} = (\beta_{\text{Cont}}^{1,1960}, \ldots, \beta_{\text{Cont}}^{1,2014}, \beta_{\text{Cont}}^{2,1960}, \ldots, \beta_{\text{Cont}}^{2,2014}, \beta_{\text{Cont}}^{3,1960}, \ldots, \beta_{\text{Cont}}^{3,2014}, \beta_{\text{Cont}}^{4,1960}, \ldots, \beta_{\text{Cont}}^{4,2014}),
\]

where \(\beta_{\text{Cont}}^{i,j}\) are the parameters of the univariate GLM model for year \(i\), computed with condition \(\sum_{j=1}^{4} \beta_{\text{Cont}}^{i,j} = 0\). The advantage of this test statistic with respect to the \(F\) statistic is that we directly test which continents differ from the mean. The permutations were obtained by the standard Freedman and Lane (1983) procedure, i.e. permuting residuals under the null model (population growth \(\sim\) GDP). The graphical output of the IATSE algorithm is shown in Figure 8. Here, for better interpretation, instead of showing \(\beta_{\text{Cont}}\) only, we show the fitted curve for every continent, i.e. the intercept \(\beta_{0i}\) and mean effect of GDP, \(\beta_{i}^{\text{GDP}} \cdot \text{mean}(\text{GDP})_i\), are added to every \(\beta_{\text{Cont}}^{j,i}\). The output also shows the 95% FDR envelope together with the red points that identify the years and continents, which are significantly different from the fitted mean curve under FDR control. The output shows higher population growth in Africa from 1965 onwards, in Asia for years up to 1974, and in Latin America for years up to 1965. Further, it shows lower population growth for Europe and North America. One could assume that this would be caused by different GDPs in the continents, but...
Figure 4 The mean power ($\pm 2 \cdot \sigma_{\text{Power}}$ given by bars around dots) of four methods of Table 2 for Model 2, 4 and 11 with Gaussian error and $m = 200$.

Figure 5 The mean FDR ($\pm 2 \cdot \sigma_{\text{FDR}}$ given by bars around dots) of four methods of Table 2 for Model 1 and 2 with Gaussian error, heavy tailed error ($t$) and bimodal error for $s = 5000$ and $m = 200$.

GDP is treated here as a nuisance factor. Also, the second test shows only a little importance of the main effect of GDP.

Second, to test the effect of the GDP, we assumed the same main effects model as above and we used simply the test statistic

$$\beta_{\text{GDP}} = (\beta_{\text{GDP} 1960}, \ldots, \beta_{\text{GDP} 2014}).$$

(9)

The graphical output of the IATSE algorithm is shown in Figure 9. The FDR envelope shows, in this case, rather decreasing variability of the test statistics, which makes no problem to the procedure itself, but it is worth noting for the interpretation. The main effect of GDP is significant only between the years 2004 and 2009.

Third, to test the effect of the interactions, we assume the factorial model

$$\text{population growth} \sim \text{Continent} \ast \text{GDP},$$
and we used the test statistic

$$\beta^I = (\beta_{1,1960}^I, \ldots, \beta_{1,2014}^I, \beta_{2,1960}^I, \ldots, \beta_{2,2014}^I, \beta_{3,1960}^I, \ldots, \beta_{3,2014}^I, \beta_{4,1960}^I, \ldots, \beta_{4,2014}^I)$$

where $\beta_{1,i}^I, \ldots, \beta_{4,i}^I$ are interaction parameters of the univariate GLM model for year $i$, computed with condition $\sum_{j=1}^4 \beta_{j,i}^I = 0$. The permutations of residuals from the null model (population growth $\sim$ Continent + GDP) was used. The graphical output of the IATSE algorithm is shown in Figure 10. It provides rich interpretability of the interaction component. The population growth of countries in Africa is significantly positively influenced by GDP up to 1974, whereas it is significantly less influenced than the whole world from 1998 onwards. The population growth of Asian countries is more positively influenced by GDP than the whole world from 1996 onwards. The same holds for Europe and North America. On the other hand, the population growth in Latin American countries is negatively influenced by GDP up to 1974.

We also applied ATS to the test vectors (8), (9) and (10). ATS rejected one year less than the FDR envelope in total, and it gave no information about the reasons (direction) of rejection and variability of the test statistic under the null. Definitely, the results of FDR envelope presented in Figures 8, 9 and 10 are much richer and allow for interpreting the results in much deeper detail than the results...
Mean population growth in different continents with 95% FDR envelope for $\beta_{\text{Cont}}$

Figure 8 Test for the main effect of the continent, given the GDP (in 1960 USD) as a nuisance factor. The IATSE algorithm was used for FDR control with 5000 permutations. Red color is used to highlight the (significant) years where the data function ($\hat{\beta}_0^i + \hat{\beta}_i^{\text{GDP}} \cdot \text{mean}(\text{GDP}_i) + \hat{\beta}_{j,i}^{\text{Cont}}$, $i = 1960, \ldots, 2014, j = 1, 2, 3, 4$) goes outside the 95% FDR envelope. The central function is given by $\hat{\beta}_0^i + \hat{\beta}_i^{\text{GDP}} \cdot \text{mean}(\text{GDP}_i)$.

provided by ATS or other non-graphical FDR algorithm which gives only $q$-values or the rejections as an output. For comparison, if the $F$-statistic is used instead of the test vector (8) and (10), we obtain even less information from the test. This $F$-test of the main effect of the continent just rejected the hypotheses for all years, and this test of the interaction effect rejected the hypotheses for the years 1960-1982, 1988, and 1995-2014.

The envelopes of Figures 9 and 10 are rather fluctuating due to fluctuations in the GDB values 7. To reduce the fluctuation of these envelopes the standardised beta coefficients can be used instead of beta coefficients in Formulas 9 and 10. Since the standardisation has no effect on the significance of these envelopes, we prefer the simpler versions.

7 Local spatial correlation

In spatial statistics, it is a relevant question to ask in what regions two random fields are correlated. This question was studied nonparametrically in Viladomat et al (2014), where the pointwise local p-values were obtained. Viladomat et al (2014) did not perform any adjustment for multiple testing. The aim of this section is to show the possibility of FDR control in a 2D example with the use of our proposed FDR envelopes.

Assume that we observe two random fields $\Phi$ and $\Psi$ in the observation window $W \subset \mathbb{R}^2$. Let $X$ be the set of sampling locations where the values of $\Phi$ are observed. $X$ can be either random or non-random, depending on the design of the experiment. We denote by $\Phi(X)$ the vector of values of $\Phi$ observed at sampling points $X$, and similarly for $\Psi(X)$.
The functional test statistic describing the local correlation at a location \( u \in W \) can be calculated as

\[
\hat{r}_b(u) = \frac{\sum_{x \in X} w_b(u-x)(\Phi(x)-\Psi(x))(\Psi(x)-\Psi(x))}{\sqrt{\sum_{x \in X} w_b(u-x)(\Phi(x)-\Phi(x))^2}}.
\]  

(11)

where \( w_b(s) \) is a kernel with bandwidth \( b \) (we have used a Gaussian kernel with bandwidth equal to its standard deviation),

\[
\Phi(x) = \frac{\sum_{x \in X} w_b(u-x)(\Phi(x))}{\sum_{x \in X} w_b(u-x)},
\]

and

\[
Psi(x) = \frac{\sum_{x \in X} w_b(u-x)(\Psi(x))}{\sum_{x \in X} w_b(u-x)}.
\]

The asymptotic behavior of \( \hat{r}_b \) is unknown; therefore, resampling under the null model of independence has to be performed. Viladomat et al (2014) proposed to obtain resamples \( \Psi^* \) by smoothing the permuted values \( \Psi(x) \) in order to obtain a smoothed empirical variogram that matches its counterpart for \( \Psi \). Mrkvička et al (2021) proposed the random shift method with a variance correction for the test statistic instead. They showed that random shifts are more powerful in assessing the global correlation. However, for assessing the local correlation, the number of points used to calculate \( \hat{r}_b(u) \) would have to be used in the mentioned variance correction. Since for local correlation, this issue would have to be investigated, we use the Viladomat et al (2014) proposal instead.

For the illustration we use the covariates observed in the tropical forest plot of area 1000 m \( \times \) 500 m in Barro Colorado Island (Hubbell et al, 2005; Condit, 1998; Hubbell et al, 1999). This data set is accompanied with many covariates but, for the purpose of illustration, we study only the dependence of the first two covariates, i.e., Aluminium (Al) and Boron (B) observed on a 50 \( \times \) 25 grid with equally spaced observations (see Figure 11, top). The global correlation (a single Pearson’s correlation coefficient) between the two covariates is approximately \(-0.41\), which is significant according to the Viladomat et al (2014) global test of independence (\( p \approx 0.031 \)). We then applied the described local independence test (with \( b = 100 \)) to find all regions with significant local correlations. The results in Figure 11 (bottom) show that there are significant positive local correlations in the middle of the image, whereas on the left and right side of the image, there are significant negative local correlations.

8 Discussion

The aim of this work was to find a good method for determining the FDR envelope. For this purpose, we defined two alternatives, namely ATSE and IATSE. These algorithms are based on the idea of Storey and Tibshirani (2001), but the estimation methods of \( \pi_0 \) introduced in Storey (2002) and Storey and Tibshirani (2003) were found to be unsatisfactory for highly dependent test statistics which arise in functional data analysis. Therefore, the proposed algorithms are supplied with different \( \pi_0 \) estimates. Based on our study, these two methods perform as well as the ATS algorithm, which we have found to be the best from the literature, both in terms of being close to the nominal FDR level and the power. The simulation study also suggests that the IATSE algorithm is a little bit more powerful than the ATS algorithm, especially for lower numbers of replicates. It can be seen as an advantage when the simulation of the replicates is time-consuming as it can be, e.g., in
spatial statistics. We also investigated resampling methods capturing the dependence between tests; unfortunately, the only method applicable in the required wide generality turned out to be rather liberal if the method was made to be adaptive, i.e., when the estimate of $\pi_0$ was considered in the algorithm.

Since our proposed methods construct the rejection region from resamples and their pointwise ranks, these methods are robust with respect to changes in the distribution of the test statistic along its domain. This is not the case for the methods using the parametric $p$-values, which require the homogeneity of the test statistic across the domain. The same can be said for the homogeneity of the correlation structure of the test statistic along its domain.

The population growth example (Section 6) shows the interpretation advantages of FDR envelopes with respect to pure $q$-values, which can be obtained from other FDR methods without graphical interpretation. The local independence test (Section 7) shows the possibility of applying the FDR envelope in the 2D case in spatial statistics. The greatest advantages of our proposed methods are the graphical interpretation, its generality, and its easy application via the R package GET (Myllymäki and Mrkvička, 2020). The generality of our methods includes that the methods can be used with any test statistic without knowing its distribution, the distribution of the test statistic can vary along its domain, and the autocorrelation of the test statistic can also vary.

The method of Storey and Tibshirani (2003) was promoted in the context of permutation tests in genetics studies, where the dependence between the test statistics is not as strong as in functional data analysis. For this method, Jiao and Zhang (2008) and Xie et al (2005) proposed to estimate $E\rho^0(\Gamma)$ only from those hypotheses which are true null for the resampling approach. Obviously, it is impossible to know the true null hypotheses, and therefore they used only hypotheses which are not rejected for the data. The reason to avoid false null
hypotheses was the increase of variance for false null with respect to true null. Since our rejection region, $\Gamma_\gamma$, is not a constant number, as it is usually assumed, but it is constructed from resampling of the whole test vector under the complete null hypothesis, $\Gamma_\gamma$ is adapted to this increased variability (see, e.g., Figure 9). This means that the whole problem of the Storey and Tibshirani (2001) procedure discussed in Jiao and Zhang (2008) and Xie et al (2005) is overcome by our construction of $\Gamma_\gamma$.

Our proposed methods are defined under the assumption of simple null hypothesis testing. Additionally, we introduced an algorithm based on these methods and the quadratic Monte Carlo scheme, which makes the FDR envelopes valid also for composite null hypotheses (see Appendix A). The performance of this algorithm with respect to neglecting the compositeness of the null hypothesis will be studied in the future.

Acknowledgements

T.M. was financially supported by the Grant Agency of the Czech Republic (project number 19-04412S), and M.M. by the Academy of Finland (project numbers 295100, 306875, 327211). The BCI forest dynamics research project was founded by S.P. Hubbell and R.B. Foster and is now managed by R. Condit, S. Lao, and R. Perez under the Center for Tropical Forest Science and the Smithsonian Tropical Research in Panama. Numerous organizations have provided funding, principally the U.S. National Science Foundation and hundreds of field workers have contributed. The Barro Colorado Island soils data set was collected and analyzed by J. Dalling, R. John, K. Harms, R. Stallard, and J. Yavitt, with support from National Science Foundation, grants DEB021104, DEB021115, DEB0212284, DEB0212818 and OISE 0314581, Smithsonian Tropical Research Institute.
and Center for Tropical Forest Science. The authors thank Mikko Kuronen (Luke) for his remarks on an earlier version of the manuscript.

**Appendix A  Composite null hypothesis**

When the null hypothesis is not simple, but some nuisance parameters are estimated, the estimate (5) of the main document will be biased, and thus the estimate of FDR will also be biased. In such case, an adjusted estimate of $\mathbb{E}\rho^0(\Gamma_\gamma)$ can be performed in a similar manner as for Monte Carlo methods controlling FWER (Dao and Genton, 2014; Baddeley et al, 2017).

Assume that the null hypothesis has a parameter $\theta$, which needs to be estimated in order to obtain simulations from the null hypothesis, e.g., for a goodness-of-fit test with a functional test statistic. To estimate $\mathbb{E}\rho^0(\Gamma_\gamma)$ a theoretical density of $\hat{\theta}$ estimator can be used:

$$\mathbb{E}\rho^0(\Gamma_\gamma) = \int \mathbb{E}(\rho^0(\Gamma_\gamma) \mid \hat{\theta}) p(\hat{\theta}) d\hat{\theta}.$$ 

For $p(\hat{\theta})$, an asymptotic distribution of $\hat{\theta}$ or, more preferably, a two-stage Monte Carlo scheme (Baddeley et al, 2017) can be used.

---

**(Quadratic) Two-stage Monte Carlo estimate of $\mathbb{E}\rho^0(\Gamma_\gamma)$:**

1. Estimate $\hat{\theta}$.
2. Simulate $s_1$ simulations from the fitted model with $\hat{\theta}$.
3. Estimate $\hat{\theta}_i$, $i = 1, \ldots, s_1$, for every simulation.
4. Simulate $s_2$ simulations from $\hat{\theta}_i$ for every $i$, $i = 1, \ldots, s_1$.
5. Compute $\mathbb{E}(\rho^0(\Gamma_\gamma) \mid \hat{\theta}_i)$ for every $i$ via

$$\mathbb{E}\rho^0(\Gamma_\gamma \mid \hat{\theta}_i) \approx \frac{1}{s_2} \sum_{j=1}^{s_2} \rho_j^0(\Gamma_\gamma),$$

where $\rho_j^0(\Gamma_\gamma)$ is the number of rejections produced by $\Gamma_\gamma$ on the $j$-th simulation from $\hat{\theta}_i$.
6. Estimate $\mathbb{E}\rho^0(\Gamma_\gamma)$ by average of $\mathbb{E}(\rho^0(\Gamma_\gamma) \mid \hat{\theta}_i)$.

Thus, this algorithm requires $s$ simulations for constructing $\Gamma_\gamma$ and $s_1 \cdot s_2$ simulations for computing the expectation $\mathbb{E}\rho^0(\Gamma_\gamma)$. Since the quadratic Monte Carlo method is used to approximate the expectation, the numbers $s_1$ and $s_2$ can be small, and the whole algorithm will not be too computational.

---

**Appendix B  Incorporating dependence of the test statistics in the FDR estimation**

Yekutieli and Benjamini (1999) provided a resampling method under the assumption of subset pivotality and independence of null and alternative hypotheses in order to handle the dependence between test statistics. Schwartzman and Lin (2011) showed that correlation may increase the bias and variance of the FDR estimators substantially in comparison to the independent case. In order to solve this issue, some authors modeled the correlation, e.g., Sun and Cai (2009) modeled the correlation by a hidden Markov model and, on the other hand, Romano et al (2008) modeled the correlation via bootstrapping of the original data. Since we do not want to rely on model assumptions, only the method of Yekutieli and Benjamini (1999) is usable. Inspired by it, we also investigate the adaptive FDR versions of Yekutieli and Benjamini (1999) estimators for correlated test statistics.

Let us first describe the original Yekutieli and Benjamini (1999) procedure which is based on $p$-values, in our case resampling $p$-values, and which consists of one step only. The FDR for a given threshold $p$ (defining the rejection region $\Gamma$) is estimated by

$$\mathbb{E} \left[ \frac{V(p)}{p(p)} \right] \approx EQ^*(p),$$

where

$$Q^*(p) = 0 \quad \text{if} \quad \rho^0(p) = 0,$$

$$Q^*(p) = 1 \quad \text{if} \quad \rho^0(p) > 0 \text{ and } p(p) - \rho^u_0(p) < mp,$$

$$Q^*(p) = \frac{\rho^0(p)}{\rho^0(p) - mp + p(p)} \quad \text{if} \quad \rho^0(p) > 0 \text{ and } p(p) - \rho^u_0(p) \geq mp.$$
Here $\rho(p)$ is the number of rejections with the threshold $p$, i.e., $|\{k : p_k \leq p\}|$, $\rho^0(p)$ is the number of rejections with the threshold $p$ of resampled data, i.e., $|\{k : p_k^* \leq p\}|$. The resampled data are obtained here under the complete null hypothesis, similarly as our envelopes $\mathcal{E}$. Finally, $V(p)$ is the number of false rejections with the threshold $p$.

Yekutieli and Benjamini (1999) also defined a more conservative estimate with

$$
Q_u^*(p) = 0 \quad \text{if} \quad \rho^0(p) = 0,
$$

$$
Q_u^*(p) = 1 \quad \text{if} \quad \rho^0(p) > 0 \quad \text{and} \quad \rho(p) - \rho_u^0(p) < 0,
$$

$$
Q_u^*(p) = \frac{\rho^0(p)}{\rho^0(p) - \rho_u^0(p) + \rho(p)} \quad \text{if} \quad \rho^0(p) > 0 \quad \text{and} \quad \rho(p) - \rho_u^0(p) > 0.
$$

Here $\rho_u^0(p)$ is defined as $1-\beta$ quantile of $\rho^0(p)$, where Yekutieli and Benjamini (1999) used $\beta = 0.05$.

Since we do not assume independence of null and alternative hypotheses, these estimators are theoretically not valid. Indeed, resampling approximates the marginal distribution of $V(p)$, but not the conditional distribution of $V(p)$ given $\rho(p) = r$.

We anyway modified these algorithms to our setting with rejection region $\Gamma_\gamma$ and replaced steps 1. and 3. of the ATSE and IATSE algorithms with it. This defines four new adaptive FDR estimators, which should handle the dependence between the test statistics. We do not provide a rigorous definition of these algorithms since they are found to be liberal in the simulation study. Note here only that we performed two independent sets of resamples here, first for obtaining $\Gamma_\gamma$ and second for estimating $Q^*(\Gamma_\gamma)$ and $Q_u^*(\Gamma_\gamma)$.

Appendix C Results of the simulation study

Here we complete the results of the simulation study of Section 5 of the main document. For the details of the simulation study setup, we refer to Section 5 of the main document. In particular, Table 2 there explains the methods that were compared in the simulation study (shown in all plots on the y-axis), and Table 3 explains the considered models. Figure C1 visualises the mean functions of Table 3. In all figures below, $s$ denotes the number of resamples, and $\phi_Z$ is the correlation parameter of the error term.

Figures C2, C3 and C4 present the mean FDR for the case of Gaussian error for the models ((2, 3), (6, 7) and (8, 9, 10), respectively) that were not shown in the main document. Figures C5, C6 and C7 present the mean power for the case of Gaussian error for the models ((3, 11), (6, 7), and (8, 9, 10), respectively) that were not shown in the main document. In these and the following figures, the results are only shown for the four methods (ATS, ATSp, ATSE, and IATSE) that had reasonable FDR levels. Finally, Figures C8, C9 and C10 show the comparison of the performance of the methods with respect to the different error structures for the rest of the models not shown in the main document.

References

Baddeley A., Hardegen A., Lawrence T., et al: On two-stage Monte Carlo tests of composite hypotheses. Computational Statistics & Data Analysis 114:75 – 87 (2017). https://doi.org/10.1016/j.csda.2017.04.003

Barnard G., A.: Discussion of professor Bartlett’s paper. Journal of the Royal Statistical Society Series B (Methodological) 25:294 (1963)

Benjamini Y., Hochberg Y.: Controlling the false discovery rate: A practical and powerful approach to multiple testing. Journal of the Royal Statistical Society Series B (Methodological) 57(1):289–300 (1995). URL http://www.jstor.org/stable/2346101

Benjamini Y., Hochberg Y.: On the adaptive control of the false discovery rate in multiple testing with independent statistics. Journal of Educational and Behavioral Statistics 25(1):60–83 (2000). https://doi.org/10.3102/10769986025001060

Benjamini Y., Yekutieli D.: The control of the false discovery rate in multiple testing under dependency. Ann Statist 29(4):1165–1188 (2001). https://doi.org/10.1214/aos/1013699998

Benjamini Y., Krieger AM., Yekutieli D.: Adaptive linear step-up procedures that control the false discovery rate. Biometrika 93(3):491–507 (2006). URL https://ideas.repec.org/a/oup/biom/
Figure C1  Mean functions in the simulation study for the second group for 'Abrupt', 'Fluctuating' and 'Soft' with different parameter values and for both groups for 'Bumps' (see Table 3).

biomet/v93y2006i3p491-507.html

Chen X.: False discovery rate control for multiple testing based on discrete p-values. Biometrical Journal 62(4):1060–1079 (2020). https://doi.org/10.1002/bimj.201900163

Chen X., Doerge RW., Heyse JF.: Multiple testing with discrete data: Proportion of true null hypotheses and two adaptive FDR procedures. Biometrical Journal 60(4):761–779 (2018). https://doi.org/10.1002/bimj.201700157

Condit R.: Tropical Forest Census Plots. Springer-Verlag and R. G. Landes Company, Berlin, Germany, and Georgetown, Texas, (1998)

Dai W., Mrkvička T., Sun Y., et al: Functional outlier detection and taxonomy by sequential transformations. Computational Statistics & Data Analysis 149:106,960 (2020). https://doi.org/10.1016/j.csda.2020.106960

Dao NA., Genton MG.: A Monte Carlo adjusted goodness-of-fit test for parametric models describing spatial point patterns. Journal of Computational and Graphical Statistics 23:497–517 (2014). https://doi.org/10.1080/10618600.2012.760459

Dudoit S., Gilbert HN., van der Laan MJ.: Resampling-based empirical bayes multiple testing procedures for controlling generalized tail probability and expected value error rates: Focus on the false discovery rate and simulation study. Biometrical Journal 50(5):716–744 (2008). https://doi.org/10.1002/bimj.200710473

Freedman D., Lane D.: A nonstochastic interpretation of reported significance levels. Journal
Figure C2 The mean FDR ($\pm 2 \cdot \sigma_{FDR}$ given by bars around dots) of the different methods for Model 2 and 3 with Gaussian error and $m = 200$.

of Business and Economic Statistics 1(4):292–298 (1983). URL http://www.jstor.org/stable/1391660

Ge Y., Dudoit S., Speed TP.: Resampling-based multiple testing for microarray data analysis. Test 12:1 – 77 (2003).

Ge Y., Sealfon SC., Speed TP.: Some step-down procedures controlling the false discovery rate under dependence. Statistica Sinica 18(3):881–904 (2008). URL http://www.jstor.org/stable/24308521

Gilbert HN., Pollard KS., van der Laan MJ., et al: Resampling-based multiple hypothesis testing with applications to genomics: New developments in the r/bioconductor package multtest. UC Berkeley Division of Biostatistics Working Paper Series Working Paper 249 (2009).

Heesen P., Janssen A.: Dynamic adaptive multiple tests with finite sample fdr control. Journal of Statistical Planning and Inference 168:38 – 51 (2016). https://doi.org/10.1016/j.jspi.2015.06.007,

Hsueh H., Chen JJ., Kodell RL.: Comparison of methods for estimating the number of true null hypotheses in multiplicity testing. Journal of Biopharmaceutical Statistics 13(4):675–689 (2003). https://doi.org/10.1081/BIP-120024202

Hubbell SP., Foster RB., O’Brien ST., et al: Light gap disturbances, recruitment limitation, and tree diversity in a neotropical forest. Science 283:554–557 (1999).

Hubbell SP., Condit R., Foster RB.: Barro Colorado forest census plot data. (2005). URL https://ctfsarnbharvardedu/webatlas/datasets/bci
Figure C3 The mean FDR ($\pm 2 \cdot \sigma_{\text{FDR}}$ given by bars around dots) of the different methods for Model 6 and 7 with Gaussian error and $m = 200$.

Hwang YT.: Comparisons of estimators of the number of true null hypotheses and adaptive FDR procedures in multiplicity testing. Journal of Statistical Computation and Simulation 81(2):207–220 (2011). https://doi.org/10.1080/00949650903260855

Jiao S., Zhang S.: On correcting the overestimation of the permutation-based false discovery rate estimator. Bioinformatics 24(15):1655–1661 (2008). https://doi.org/10.1093/bioinformatics/btn310

Liang K., Nettleton D.: Adaptive and dynamic adaptive procedures for false discovery rate control and estimation. Journal of the Royal Statistical Society: Series B (Statistical Methodology) 74(1):163–182(2012). https://doi.org/10.1111/j.1467-9868.2011.01001.x

Mrkvička T., Roskovec T., Rost M.: A nonparametric graphical tests of significance in functional GLM. Methodology and Computing in Applied Probability 23:593–612(2021). https://doi.org/10.1007/s11009-019-09756-y,

Mrkvička T., Myllymäki M., Jílek M., et al: A one-way ANOVA test for functional data with graphical interpretation. Kybernetika 56(3):432–458 (2020). https://doi.org/10.14736/kyb-2020-3-0432,

Mrkvička T., Dvořák J., González JA., et al: Revisiting the random shift approach for testing in spatial statistics. Spatial Statistics 42:100,430 (2021). https://doi.org/10.1016/j.spasta.2020.100430,

Myllymäki M., Mrkvička T.: GET: Global envelopes in R. (2020). arXiv:191106583 [statME]
Figure C4  The mean FDR ($\pm 2 \cdot \sigma_{FDR}$ given by bars around dots) of the different methods for Model 8, 9 and 10 with Gaussian error and $m = 200$.

Figure C5  The mean power ($\pm 2 \cdot \sigma_{Power}$ given by bars around dots) of the four methods for Model 3 and 11 with Gaussian error and $m = 200$. 
Figure C6 The mean power ($\pm 2 \cdot \sigma_{\text{Power}}$ given by bars around dots) of the four methods for Model 5, 6 and 7 with Gaussian error and $m = 200$.

Figure C7 The mean power ($\pm 2 \cdot \sigma_{\text{Power}}$ given by bars around dots) of the four methods for Model 8, 9 and 10 with Gaussian error and $m = 200$.

Myllymäki M., Mrkvička T., Grabarnik P., et al: Global envelope tests for spatial processes. J R Statist Soc B 79:381–404 (2017). https://doi.org/10.1111/rssb.12172,

Nagy S., Gijbels I., Hlubinka D.: Depth-based recognition of shape outlying functions. Journal of Computational and Graphical Statistics 26(4):883–893 (2017). https://doi.org/10.1080/10618600.2017.1336445

Narisetty NN., Nair VJ.: Extremal depth for functional data and applications. Journal of the American Statistical Association 111(516):1705–1714 (2016).

Olsen NL., Pini A., Vantini S.: False discovery rate for functional data. TEST 30:784â€’809. (2021). https://doi.org/10.1007/s11749-020-00751-x

Pini A., Vantini S.: Interval-wise testing for functional data. Journal of Nonparametric Statistics
### Figure C8
The mean FDR ($\pm 2\cdot \sigma_{FDR}$ given by bars around dots) of the four methods for Model 3, 4 and 11 with Gaussian error, heavy tailed error ($t$) and bimodal error for $s = 5000$ and $m = 200$.

| Method | Gaussian | t | Bimodal |
|--------|----------|---|---------|
| ATSp   | ![Graph](image1) |  | ![Graph](image2) |
| ATS    | ![Graph](image3) |  | ![Graph](image4) |
| ATSE   | ![Graph](image5) |  | ![Graph](image6) |
| IATSE  | ![Graph](image7) |  | ![Graph](image8) |

### Figure C9
The mean FDR ($\pm 2\cdot \sigma_{FDR}$ given by bars around dots) of the four methods for Model 5, 6 and 7 with Gaussian error, heavy tailed error ($t$) and bimodal error for $s = 5000$ and $m = 200$.

| Method | Gaussian | t | Bimodal |
|--------|----------|---|---------|
| ATSp   | ![Graph](image9) |  | ![Graph](image10) |
| ATS    | ![Graph](image11) |  | ![Graph](image12) |
| ATSE   | ![Graph](image13) |  | ![Graph](image14) |
| IATSE  | ![Graph](image15) |  | ![Graph](image16) |

---

29(2):407–424 (2017). [https://doi.org/10.1080/10485252.2017.1306627](https://doi.org/10.1080/10485252.2017.1306627)

Romano JP., Shaikh AM., Wolf M.: Control of the false discovery rate under dependence using the bootstrap and subsampling. TEST 17(417):393–424 (2008).

Schwartzman A., Lin X.: The effect of correlation in false discovery rate estimation. Biometrika 98(1):199–214 (2011). [https://doi.org/10.1093/biomet/asq075](https://doi.org/10.1093/biomet/asq075)

Storey JD.: A direct approach to false discovery rates. Journal of the Royal Statistical Society: Series B (Statistical Methodology) 64(3):479–498 (2002). [https://doi.org/10.1111/1467-9868.00346](https://doi.org/10.1111/1467-9868.00346)

Storey JD., Tibshirani R.: Estimating false discovery rates under dependence, with applications to dna microarrays. Tech Rep 2001-28, Department
of Statistics, Stanford University (2001).

Storey JD., Tibshirani R.: Statistical significance for genomewide studies. Proceedings of the National Academy of Sciences 100(16):9440–9445 (2003). https://doi.org/10.1073/pnas.1530509100

Storey JD., Bass AJ., Dabney A., et al: qvalue: Q-value estimation for false discovery rate control.(2021). URL http://github.com/jdstorey/qvalue, R package version 2.26.0

Strimmer K.: A unified approach to false discovery rate estimation. BMC Bioinformatics 9(303) (2008).

Sun W., Cai TT.: Large-scale multiple testing under dependence. Journal of the Royal Statistical Society Series B (Statistical Methodology) 71(2):393–424 (2009). URL http://www.jstor.org/stable/40247580

Viladomat J., Mazumder R., McInturff A., et al: Assessing the significance of global and local correlations under spatial autocorrelation: A non-parametric approach. Biometrics 70(2):409–418 (2014).

Westfall PH., Young SS.: Resampling-Based Multiple Testing: Examples and Methods for p-Value Adjustment, 1st edn. John Wiley & Sons, Inc. (1993).

Xie Y., Pan W., Khodursky AB.: A note on using permutation-based false discovery rate estimates to compare different analysis methods for microarray data. Bioinformatics 21(23):4280–4288 (2005). https://doi.org/10.1093/bioinformatics/bti685

Xu M., Reiss P.: Distribution-free pointwise adjusted p-values for functional hypotheses. In: Aneiros G, Horová I., Hušková M., et al (eds) Handbook of Spatial Statistics. Functional and High-Dimensional Statistics and Related Fields. IWFSOS 2020. Contributions to Statistics, Springer, Cham, (2020). https://doi.org/10.1007/978-3-030-47756-1_32

Xu M., Reiss P.: b) pppvalue: Pointwise adjusted Permutation P-value (PPPvalue). R package version 0.01 (2020).

Yekutieli D., Benjamini Y.: Resampling-based false discovery rate controlling multiple test procedures for correlated test statistics. Journal of Statistical Planning and Inference 82(1):171–196 (1999). https://doi.org/10.1016/S0378-3758(99)00041-5