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# Tests multiples et bornes post hoc pour des données hétérogènes

## Multiple testing and post hoc bounds for heterogeneous data

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## Abstract

This manuscript presents my contributions in three areas of multiple testing where data heterogeneity can be exploited to better detect false null hypotheses or improve signal detection while controlling false positives:  $p$ -value weighting, discrete tests, and post hoc inference. First, a new class of data-driven weighting procedures, incorporating group structure and true null proportion estimators, is defined, and its False Discovery Rate (FDR) control is proven asymptotically. This procedure also achieves power optimality under some conditions on the proportion estimators. Secondly, new step-up and step-down procedures, tailored for discrete tests under independence, are designed to control the FDR for arbitrary  $p$ -value null marginals. Finally, new confidence bounds for post hoc inference (called post hoc bounds), tailored for the case where the signal is localized, are studied, and the associated optimal post hoc bounds are derived with a simple algorithm.

## Résumé

Ce manuscrit présente mes contributions dans trois domaines des tests multiples où l'hétérogénéité des données peut être exploitée pour mieux détecter le signal tout en contrôlant les faux positifs : pondération des  $p$ -valeurs, tests discrets, et inférence post hoc. Premièrement, une nouvelle classe de procédures avec pondération données-dépendante, avec une structure de groupe et des estimateurs de la proportion de vraies nulles, est définie, et contrôle le False Discovery Rate (FDR) asymptotiquement. Cette procédure atteint aussi l'optimalité en puissance sous certaines conditions sur les estimateurs. Deuxièmement, de nouvelles procédures step-up et step-down, adaptées aux tests discrets sous indépendance, sont conçues pour contrôler le FDR pour une distribution arbitraire des marginales des  $p$ -valeurs sous l'hypothèse nulle. Finalement, de nouvelles familles de référence pour l'inférence post hoc, adaptées pour le cas où le signal est localisé, sont étudiées, et on calcule les bornes post hoc associées avec un algorithme simple.



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# Résumé détaillé

Le domaine des tests multiples est un champ d'études très vaste qui possède de nombreuses applications dans des secteurs aussi variés que les études génomiques, l'imagerie médicale, l'astrophysique ou l'industrie. En particulier, dans les études d'association pangénomiques (GWAS), la nécessité de prendre en compte la multiplicité des tests surgit dès lors que des centaines de milliers de variants génétiques (SNPs) sont analysés simultanément, ce qui est très courant avec les technologies actuelles.

Une modélisation mathématique simple consiste à supposer que l'on observe une variable aléatoire  $X$  suivant une distribution inconnue  $P$  et en un jeu de  $m$  hypothèses  $H_{0,1}, \dots, H_{0,m}$  sur  $P$ , dites hypothèses nulles. Des  $p$ -valeurs  $p_1(X), \dots, p_m(X)$  sont calculées à partir de  $X$  et servent de statistiques de tests pour les hypothèses, qui sont soit acceptées, soit rejetées. Typiquement,  $p_i(X)$  représente la probabilité de réaliser une observation au moins aussi extrême que  $X$  si jamais  $H_{0,i}$  est vraie. Une faible  $p$ -valeur constitue donc un témoin en défaveur de  $H_{0,i}$ , et on aura tendance à rejeter les hypothèses avec des petites  $p$ -valeurs. Dans le cas d'une étude GWAS où l'on cherche des SNPs associés à un phénotype, l'hypothèse nulle  $H_{0,i}$  représentera la non-association du SNP  $i$  avec le phénotype. En d'autres termes, le signal que l'on cherche à détecter est constitué des hypothèses fausses. Naturellement, on souhaite rejeter un minimum d'hypothèses vraies (ce que l'on appelle un faux positif ou une erreur de type I) tout en rejetant beaucoup d'hypothèses fausses (les vrais positifs). Dans le cadre des tests multiples, de nombreux critères de contrôle de l'erreur de type I ont été proposés, les plus connus étant le Family-Wise Error Rate (FWER) qui est la probabilité qu'une procédure de tests multiples fasse au moins un faux positif, et le False Discovery Rate (FDR) qui est l'espérance du ratio entre le nombre de faux positifs et le nombre de rejets total. En notant  $\mathcal{H}_0$  l'ensemble des indices  $i$  tels que  $H_{0,i}$  est vraie et  $R$  l'ensemble des indices des hypothèses rejetées, on a donc :

$$\text{FWER}(R) = \mathbb{P}(|R \cap \mathcal{H}_0| > 0),$$

et

$$\text{FDR}(R) = \mathbb{E} \left[ \frac{|R \cap \mathcal{H}_0|}{\max(1, |R|)} \right].$$

Parmi les exemples de procédures classiques, on peut d'abord citer la procédure de Bonferroni ([Bonferroni, 1936](#))  $R_{\text{Bonf}} = \{i : p_i(X) \leq \frac{\alpha}{m}\}$ , qui contrôle le FWER au niveau  $\alpha$  sous n'importe quelle dépendance entre les  $p_i(X)$ . Pour le contrôle du FDR, la procédure classique est celle de Benjamini et Hochberg (BH, [Benjamini and Hochberg, 1995](#)) qui contrôle le FDR au niveau  $\alpha$  si les  $p$ -valeurs sont indépendantes ou, plus généralement, positivement dépendantes ([Benjamini and Yekutieli, 2001](#)). Elle est définie par  $R_{\text{BH}} = \left\{ i : p_i \leq \alpha \frac{\hat{k}_{\text{BH}}}{m} \right\}$ , où  $\hat{k}_{\text{BH}} = \max \left\{ 0 \leq k \leq m : p_{(k)}(X) \leq \alpha \frac{k}{m} \right\}$  et les  $p_{(k)}(X)$  sont les  $p$ -valeurs ordonnées. Par ailleurs, la puissance  $\text{Pow}(R)$  d'une procédure se définit par sa capacité à rejeter beaucoup de vrais positifs, donc de fausses hypothèses :  $\text{Pow}(R) = m^{-1} \mathbb{E} [|R \setminus \mathcal{H}_0|]$ .

À l'heure où l'on est capable d'extraire et de manipuler des jeux de données de plus en plus massifs et complexes, de nouveaux défis apparaissent. En premier lieu, les données actuelles présentent une forte hétérogénéité qu'il est possible d'exploiter pour développer des procédures plus puissantes. L'hétérogénéité peut se présenter sous différentes formes, elle peut être liée à une taille d'échantillon, comme dans les études GWAS où certains SNPs ont des fréquences alléliques bien plus faibles que d'autres, ou comme dans les études sociologiques où les résultats de lycées de différentes tailles sont comparés (voir [Cai and Sun, 2009](#) par exemple). L'hétérogénéité peut aussi être liée à une structure sous-jacente, comme lors d'études d'imagerie médicale où l'avant et l'arrière du cerveau se comportent différemment (voir encore [Cai and Sun, 2009](#)). Un second défi majeur est l'actuelle crise de la reproductibilité dans la recherche, qui part du constat que très peu de résultats scientifiques peuvent être reproduits par des pairs. Une des explications avancées est la pré-sélection de variables jugées plus significatives que d'autres avant d'appliquer la procédure statistique (qu'il s'agisse d'inférence ou de tests multiples), causant la perte des garanties statistiques classiques dans ce contexte. Le besoin de méthodes statistiques qui prennent en compte l'étape de sélection amène donc un nouveau domaine de recherche appelé inférence sélective ou inférence post hoc selon les auteurs.

Ce manuscrit de thèse présente mes trois principaux travaux de thèse, chacun étant motivé par une ou plusieurs des problématiques énoncées ci-dessus.

Le premier, présenté dans le Chapitre 2, consiste à donner des poids différents aux hypothèses testées, ce qui permet entre d'autres d'exprimer une hiérarchie ou une structure de groupe entre les hypothèses. L'idée remonte à [Holm \(1979\)](#), et [Genovese et al. \(2006\)](#)

ont formulé la procédure BH avec pondération, dite WBH : soit  $w = (w_1, \dots, w_m)$  un vecteur de poids positifs tels que  $\sum_{i=1}^m w_i = 1$ , la procédure WBH de poids  $w$  est définie par  $R_{WBH}(w) = \left\{ i : p'_i(X) \leq \alpha \frac{\hat{k}_{WBH}(w)}{m} \right\}$ , où  $\hat{k}_{WBH}(w) = \max \left\{ 0 \leq k \leq m : p'_{(k)}(X) \leq \alpha \frac{k}{m} \right\}$ , où  $p'_i(X) = p_i(X)/w_i$  est la  $p$ -valeur pondérée et les  $p'_{(k)}(X)$  sont les  $p$ -valeurs pondérées ordonnées. De très nombreux choix de pondération donnée-dépendante, calculée à partir de l'observation de  $X$ , ont été proposées ([Hu et al., 2010](#); [Zhao and Zhang, 2014](#); [Ignatiadis et al., 2016](#)), tandis que des procédures “oracle”, obtenues par la connaissance de paramètres inconnus en pratique, utilisent la pondération optimale au sens de la puissance ([Wasserman and Roeder, 2006](#); [Roquain and van de Wiel, 2009](#); [Dobriban et al., 2015](#)). Ma contribution est à la frontière des deux approches en obtenant des résultats d’optimalité pour une procédure données-dépendante dans un contexte où les hypothèses se trouvent dans  $G$  groupes fixés et connus à l'avance. Toutes les hypothèses dans un même groupe  $g$  se voient donc attribuer le même poids  $w_g$ . En utilisant la notion de multi-pondération MWBH de [Roquain and van de Wiel \(2009\)](#) où les poids sont des fonctions d'un niveau de rejet  $u$ , on propose les poids suivants qui maximisent le nombre de rejets à  $u$  fixé :

$$(w_g(u))_{1 \leq g \leq G} = \arg \max_{\substack{w_g \geq 0 \\ \sum_{g=1}^G \pi_g \hat{\pi}_{g,0} w_g = 1}} \sum_{g=1}^G |\{i \text{ dans le groupe } g : p_i(X) \leq \alpha w_g u\}|,$$

où  $\pi_g$  est la proportion d'hypothèses dans le groupe  $g$ , et  $\hat{\pi}_{g,0}$  est un sur-estimateur de la proportion  $\pi_{g,0}$  de vraies hypothèses dans le groupe  $g$ . C'est d'ailleurs l'existence de  $\hat{\pi}_{g,0}$  qui distingue ces poids de ceux de la procédure IHW de [Ignatiadis et al. \(2016\)](#), et qui permet de prendre en compte l'hétérogénéité des  $\pi_{g,0}$  en plus de l'hétérogénéité des distributions des  $p$ -valeurs dans chaque groupe. La nouvelle procédure, nommée Adaptive Data-Driven Optimal Weighting (ADDOW) applique la procédure de multi-pondération MWBH avec les poids ci-dessus. Le reste du Chapitre 2 consiste principalement à étudier les propriétés asymptotiques d'ADDOW quand le nombre de tests  $m$  tend vers l'infini et les estimateurs  $\hat{\pi}_{g,0}$  convergent en probabilité vers  $\bar{\pi}_{g,0} \geq \pi_{g,0}$ . On montre d'abord la convergence des poids ci-dessus vers des poids oracles asymptotiques qui correspondent aux poids de [Roquain and van de Wiel \(2009\)](#). Ensuite, on montre qu'ADDOW contrôle asymptotiquement le FDR au niveau  $\alpha$  (avec un résultat le plus précis possible, cf. Théorème 2.5.1). Les poids ci-dessus maximisant le nombre de rejets et non la puissance, il en est de même pour les poids oracles asymptotiques, et c'est donc par le biais d'une certaine condition sur  $\bar{\pi}_{g,0}$  et  $\pi_{g,0}$  que l'optimalité en puissance est obtenue (sur une certaine classe de pondérations, cf Théorème 2.5.2). Il est à noter que cette condition,

dite (ME), inclut les cas où les estimateurs sont constants, c'est-à-dire où  $\bar{\pi}_{g,0} = \pi_{g,0}$ . Vu qu'IHW est un cas particulier d'ADDOW, où  $\hat{\pi}_{g,0} = 1$ , des nouveaux résultats sur cette procédure, dont un d'optimalité, sont également obtenus (cf. Corollaire 2.5.1). Une variante stabilisatrice d'ADDOW est également introduite pour éviter le surapprentissage, il est montré qu'elle est asymptotiquement équivalente à ADDOW (cf. Théorème 2.5.3). Enfin, des simulations numériques illustrent le gain en puissance d'ADDOW dans plusieurs cas dont le cas consistant, ainsi que l'importance de la condition (ME).

Le deuxième travail, effectué en collaboration avec Sebastian Döhler et Etienne Roquain (Döhler et al., 2018), présenté dans le Chapitre 3, s'inscrit dans la thématique des multi-tests discrets ( $X$  prend ses valeurs dans un espace discret), où la super-uniformité des  $p$ -valeurs (au lieu de leur uniformité dans le cas continu) diminue la puissance des procédures classiques telles que Bonferroni ou BH. Remarquant que la distribution sous l'hypothèse nulle de  $p_i(X)$  est connue en général (on a accès à sa fonction de répartition  $F_i$ ), Heyse (2011) a proposé une procédure qui utilise la connaissance des  $F_i$  et leur hétérogénéité, c'est la procédure step-up  $R_{\mathbf{SU}}(\tau) = \{i : p_i(X) \leq \tau_{k_{\mathbf{SU}}}\}$ , où  $\hat{k}_{\mathbf{SU}} = \max \{0 \leq k \leq m : p_{(k)} \leq \tau_k\}$  et  $\tau_k$  est une suite de valeurs critiques définie par l'inversion de la fonctionnelle  $\bar{F}(\cdot) = m^{-1} \sum_{i=1}^m F_i(\cdot)$  aux points  $\alpha k/m$ . Il est à noter qu'utiliser  $\alpha k/m$  comme valeurs critiques nous ramène à la procédure BH, et que la procédure de Heyse revient à la procédure BH s'il n'y a pas d'hétérogénéité entre les  $F_i$  (cf. Lemme 3.3.1). La procédure de Heyse peut parfois se montrer anti-conservatrice et ne pas contrôler le FDR (cf. Appendice 3.B.1), d'où le besoin de modifier l'idée de Heyse pour assurer le contrôle du FDR. Nous présentons deux modifications de  $\bar{F}$ ,  $\bar{F}_{\mathbf{SU}}$  et  $\bar{F}_{\mathbf{SD}}$ , définies par

$$\bar{F}_{\mathbf{SU}}(t) = m^{-1} \sum_{i=1}^m \frac{F_i(t)}{1 - F_i(\tau_m)}, \quad t \in [0, 1],$$

et

$$\bar{F}_{\mathbf{SD}}(t) = m^{-1} \sum_{i=1}^m \frac{F_i(t)}{1 - F_i(t)}, \quad t \in [0, 1],$$

où  $\tau_m$  est issu de l'inversion de  $\bar{F}_{\mathbf{SD}}$  en  $\alpha$ . Nous introduisons une procédure step-up hétérogène HSU et son équivalent step-down HSD en utilisant des valeurs critiques  $\tau_k$  obtenues en inversant  $\bar{F}_{\mathbf{SU}}$  en  $\alpha k/m$ , où  $1 \leq k \leq m-1$ , pour HSU, et en inversant  $\bar{F}_{\mathbf{SD}}$  en  $\alpha k/m$ , où  $1 \leq k \leq m$ , pour HSD. Puis par analogie avec les procédures adaptatives de Blanchard and Roquain (2009) et Gavrilov et al. (2009), deux variantes adaptatives AHSU et AHSD sont présentées. Ces quatre procédures contrôlent le FDR au niveau  $\alpha$  comme montré dans le Théorème 3.4.1 qui donne de nouvelles bornes pour le FDR de procédures step-up et step-down dans le cas de  $p$ -valeurs indépendantes. Au-delà du

cadre discret, ces bornes, qui exploitent l'hétérogénéité des marginales des  $p$ -valeurs sous l'hypothèse nulle, permettent également de retrouver certains résultats de [Roquain and van de Wiel \(2009\)](#). Une application sur données réelles et des simulations numériques comparent les nouvelles procédures à plusieurs procédures de la littérature, calibrées ou non pour des tests discrets, et montrent l'amélioration de la puissance qu'il est possible d'obtenir. Les nouvelles procédures sont implémentées dans le package R [DiscreteFDR](#) disponible sur le CRAN. Le manuel du package se trouve dans l'Appendice C.

Dans le cadre des tests multiples, l'inférence post hoc consiste à se donner une borne sur le nombre de faux positifs sur n'importe quel ensemble d'hypothèses sélectionnées. Le but est donc de construire une fonction  $\hat{V}$ , appelée borne post hoc, qui associe à tout ensemble sélectionné  $S$  une borne supérieure sur le nombre de faux positifs  $|S \cap \mathcal{H}_0|$ . La garantie statistique doit valoir pour tout ensemble  $S$ , et prend donc la forme suivante :

$$\forall P \in \mathcal{P}, \mathbb{P}(\forall S \subset \mathbb{N}_m, |S \cap \mathcal{H}_0| \leq \hat{V}(S)) \geq 1 - \alpha.$$

Récemment, [Blanchard et al. \(2018b\)](#) ont introduit une méthodologie flexible pour calculer des bornes post hoc à partir d'une famille de référence  $\mathfrak{R} = ((R_k(X), \zeta_k(X))_{k \in \mathcal{K}}, R_k(X) \subset \mathbb{N}_m, \zeta_k(X) \in \mathbb{N}$ , qui contrôle un Joint Error Rate (JER), au sens suivant :

$$\forall P \in \mathcal{P}, \mathbb{P}(\forall k \in \mathcal{K}, |R_k \cap \mathcal{H}_0| \leq \zeta_k) \geq 1 - \alpha, \quad (0.0.1)$$

c'est-à-dire qu'on garantit un contrôle uniquement sur les membres de la famille de référence. On peut en déduire une borne post hoc sur tous les ensembles  $S$ , par exemple à l'aide de

$$V_{\mathfrak{R}}^*(S) = \max \{|S \cap A|, A \subset \mathbb{N}_m, \forall k \in \mathcal{K}, |R_k \cap A| \leq \zeta_k\},$$

ou

$$\bar{V}_{\mathfrak{R}}(S) = \min_{k \in \mathcal{K}} (\zeta_k + |S \setminus R_k|) \wedge |S|.$$

[Blanchard et al. \(2018b\)](#) donnent ensuite des méthodes pour construire des familles de référence où on impose  $\zeta_k = k - 1$ ,  $k \in \{1, \dots, K\}$ ,  $K \leq m$ , et où  $R_k$  est un ensemble aléatoire d'hypothèses destiné à garantir le contrôle du JER. Dans le Chapitre 4, un travail commun avec Etienne Roquain, Pierre Neuvial et Gilles Blanchard est présenté, dans la continuité de [Blanchard et al. \(2018b\)](#). Cette fois-ci, on fixe les ensembles  $R_k$  en avance et on cherche à estimer le nombre de faux positifs dans chacune avec une borne  $\zeta_k$ . Dans le cas de  $p$ -valeurs indépendantes, on propose une borne basée sur l'inégalité de Dvoretzky-Kiefer-Wolfowitz-Massart (DKWM) ([Dvoretzky et al., 1956; Massart, 1990](#)) qui est uniformément meilleure que celle de [Genovese and Wasserman \(2004\)](#). De plus, si

les ensembles  $R_k$  ont une structure dite de forêt, c'est-à-dire :

$$\forall k, k' \in \mathcal{K}, \quad R_k \cap R_{k'} \in \{R_k, R_{k'}, \emptyset\},$$

ce qui signifie que deux régions sont soit disjointes, soit imbriquées l'une dans l'autre, un algorithme simple, justifié par le Théorème 4.3.1, permet de calculer  $V_{\mathfrak{R}}^*(S)$  grâce à de nouvelles bornes d'interpolation, à savoir :

$$\tilde{V}_{\mathfrak{R}}^q(S) = \min_{Q \subset \mathcal{K}, |Q| \leq q} \left( \sum_{k \in Q} \zeta_k \wedge |S \cap R_k| + \left| S \setminus \bigcup_{k \in Q} R_k \right| \right), \quad 1 \leq q \leq K.$$

Le Théorème 4.3.1 permet aussi de retrouver le cas d'égalité entre  $V_{\mathfrak{R}}^*$  et  $\bar{V}_{\mathfrak{R}}$  (Blanchard et al., 2018b, Proposition 2.5). Quand le signal est groupé dans certaines des régions  $R_k$ , et que la structure de forêt est vérifiée, on s'attend à ce que les nouvelles bornes soient meilleures que les bornes de Blanchard et al. (2018b). Des simulations numériques confirment cette intuition tout en suggérant également une borne hybride qui combine les deux approches. Les nouvelles procédures ont été codées et ajoutées au package `sansSouci`, disponible sur [github](#), qui implémentait déjà les méthodes de Blanchard et al. (2018b). Des compléments mineurs (comme des contre-exemples sur les bornes d'interpolation) se trouvent dans l'Appendice B.

Après le Chapitre 4, une courte conclusion expose brièvement des idées de développements futurs sur les présents travaux.

Pour terminer, on trouvera dans l'Appendice A des notes techniques sur trois articles de la littérature comprenant des passages qui me semblaient incorrects, et dans l'Appendice D un article de génétique des populations co-écrit avec Sabin Lessard (Durand and Lessard, 2016) et dont nous avons effectué la révision pendant ma première année de thèse.

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# Chapter 1

## Introduction

### 1.1 Motivations

#### 1.1.1 Genome-Wide Association Studies

A large number of pathologies have been identified as having an origin at least partially genetic, like diabetes and many forms of cancer. Consequently, searching for the genomic variants that show correlation with these diseases has become an interesting field for the pharmaceutics industry, which is otherwise facing a downturn of its traditional methods and searches to address new challenges like targeted and personalized medicine (see e.g. [Maury, 2008](#), in French). Having a deeper comprehension of the relation between genomics and human health allows to make advances in both the development of personalized medicine and in the knowledge of diseases that remain mysterious and not well understood, like bipolar disorder (see e.g. [Kerner, 2014](#)).

Many genomic variants can be considered in practice, some of the most used are Single-Nucleotide Polymorphisms (SNPs), one SNP being a variation of one unique nucleotide in a given, known, position along a genetic sequence. Thus, in a SNP locus, two nucleotide bases among the four existing (A, T, C, G) can be found within a population. If the locus belongs to a gene, this leads to two versions of the gene, which we call alleles. For example, the human SNP rs12913832 is known to have two alleles, the first presenting the base A and associated with brown eyes, the second presenting the base G and associated with blue eyes (see e.g. [Visser et al., 2012](#)). SNPs are a target of choice for research because they explained the majority of the genetic variation of the human species. Namely, 90% of this variation is explained by the SNPs whose two alleles have a frequency of at least 1%, and there are 10 millions of such SNPs ([Gibbs et al., 2003](#)).

The search for statistical association between a SNP and a phenotype of interest can be conducted by performing a statistical test, that is a decision rule which will accept or reject a given hypothesis. This hypothesis, called the null hypothesis, corresponds roughly to a scientific guess that the practitioner wants to validate (or not) by evaluating how well it fits the data. In GWAS, it is typically an hypothesis of non-association between the SNP and the phenotype, which means that rejecting the null hypothesis is equivalent to detecting an association and thus to make a discovery. For a given SNP for which we denote its alleles A and a, three genotypes are possible: AA, Aa and aa (because we carry two chromosomes hence two versions of each gene). For a given disease, we can conduct a study on a cohort of people affected by the disease (the cases) and people unaffected (the controls), by retrieving their genotype in the SNP locus, and then constructing a contingency table as in table 1.1.  $O_{i,j}$  denotes the number of people observed in cell  $(i, j)$ ,  $O_{i,\cdot} = \sum_j O_{i,j}$ ,  $O_{\cdot,j} = \sum_i O_{i,j}$ , and  $N$  is the total number of individuals involved in the study.

Table 1.1 Contingency table in a case-control study.

	AA	Aa	aa	total
Cases	$O_{1,1}$	$O_{1,2}$	$O_{1,3}$	$O_{1,\cdot}$
Controls	$O_{2,1}$	$O_{2,2}$	$O_{2,3}$	$O_{2,\cdot}$
total	$O_{\cdot,1}$	$O_{\cdot,2}$	$O_{\cdot,3}$	$N$

If the null hypothesis is true, that is if there is no association, the probability  $p_{i,j}$  that an individual falls into cell  $(i, j)$  must be the product  $p_{i,\cdot} \times p_{\cdot,j}$  of the probability of falling into line  $i$  and the probability of falling into column  $j$ . So the quantity  $E_{i,j}$ , defined by

$$E_{i,j} = \frac{O_{i,\cdot} O_{\cdot,j}}{N},$$

must be close to  $O_{i,j}$ .  $E_{i,j}$  is roughly the expected count in cell  $(i, j)$  under the null. This in turn means that the statistic

$$\hat{S} = \sum_{\substack{1 \leq i \leq 2 \\ 1 \leq j \leq 3}} \frac{(O_{i,j} - E_{i,j})^2}{E_{i,j}}$$

must be small. Then a natural idea is to reject the null hypothesis if  $\hat{S}$  is above a certain threshold that we still have to choose.

First, it is well known that, asymptotically (in each  $O_{i,j}$ ), if the null hypothesis is true,  $\hat{S}$  follows a chi-squared ( $\chi^2$ ) distribution with two degrees of freedom, denoted  $\chi_2^2$ . From now we assume that  $\hat{S} \sim \chi_2^2$  (non asymptotically) to keep things simple. Note that this corresponds to the well known  $\chi^2$  test, and we describe it only for completeness and for illustration purpose.

Because quantities are random, we will always have a chance of falsely rejecting the null hypothesis, that is detecting an association between the disease and an irrelevant SNP. We call such wrong detection a false positive, or a type I error. Naturally, we want to avoid this phenomenon and choose the threshold in consequence. Let  $\alpha \in (0, 1)$  being the level of confidence we want to achieve, which means that we want the probability of making a false positive to be less than or equal to  $\alpha$ . The latter probability, for a threshold  $t$ , is the probability that  $\hat{S}$  is greater than or equal to  $t$ , if the null hypothesis is true, that is if  $\hat{S} \sim \chi_2^2$ , which can also be written as:

$$\mathbb{P}_{\hat{S} \sim \chi_2^2} (\hat{S} \geq t). \quad (1.1.1)$$

We also want a small threshold because we want to increase our chances to make a detection: we do not want to miss it if the null hypothesis is false, that would be committing a type II error. So the best threshold to choose is the smallest number such that (1.1.1) remains less than or equal to  $\alpha$ , that is the  $1 - \alpha$  quantile of the  $\chi_2^2$  distribution. There is a trade-off between type I error control and type II error control which is summarized in the choice of  $\alpha$ : we want it small to prevent type I errors, but an  $\alpha$  too small increases the chances for a type II error. For example, choosing  $\alpha = 0$  ensures that we won't detect a false positive, but in fact we won't detect anything at all, so we make for sure a type II error (if the null is false). In the literature, the default value for  $\alpha$  is 0.05.

An equivalent way to perform the test is to compute the  $p$ -value  $p$  from  $\hat{S}$  and reject the null if  $p \leq \alpha$ . The  $p$ -value is defined as the probability of making an observation at least as extreme as the one we have at hand if the null hypothesis was true. A small  $p$ -value hence provides evidence against the null hypothesis, as stated e.g. in the first principle of [Wasserstein and Lazar \(2016, Section 3\)](#). Let  $F$  be the cumulative distribution function (cdf) of a  $\chi_2^2$  distribution. Then  $p$  is defined as

$$p = 1 - F(\hat{S}) = \mathbb{P}_{\substack{S, \hat{S} \text{ indep.} \\ S \sim \chi_2^2}} (S \geq \hat{S} | \hat{S}), \quad (1.1.2)$$

it is a random variable and a function of  $\hat{S}$ .  $p$ -values are just another point of view on testing, equivalent to the previous one, but they provide an unified context, by being always expressed as probabilities and by being most often super-uniform or uniform under the null (more on that in Section 1.2.1). The equivalence is simple to demonstrate, the probability of making a false positive can be written this time as:

$$\begin{aligned}\mathbb{P}_{\hat{S} \sim \chi_2^2}(p \leq \alpha) &= \mathbb{P}_{\hat{S} \sim \chi_2^2}(1 - F(\hat{S}) \leq \alpha) \\ &= \mathbb{P}_{\hat{S} \sim \chi_2^2}(F^{-1}(1 - \alpha) \leq \hat{S}) \\ &= 1 - F(F^{-1}(1 - \alpha)) = \alpha.\end{aligned}$$

Notice that  $F^{-1}(1 - \alpha)$  is the  $1 - \alpha$  quantile of the  $\chi_2^2$  distribution, hence it is the threshold chosen in previous paragraph and the equivalence is demonstred.

While previous paragraphs cover the basics of simple testing, in modern days, the enhancement of the genotyping technology, via DNA microarrays or high-throughput sequencing, allows a cheap and fast genotyping of  $10^5$ – $10^6$  SNP loci simultaneously, and pave the way of Genome-Wide Association Studies (GWAS), where we search for the association between a large number of SNPs and a trait such as a disease. GWAS have proven to be popular and to discover thousands of SNP-trait associations for recent years (MacArthur et al., 2016). GWAS imply running multiple tests on the same data set, ignoring this multiplicity can dramatically increase the number of false positives, as we show now.

Assume that we have at hand  $m$  independent observations where, for each  $k \in \{1, \dots, m\}$ ,  $X_k$  follows a standard normal distribution  $\mathcal{N}(\mu_k, 1)$ ,  $\mu_k \geq 0$ . We are testing for each  $k$  the null hypothesis “ $\mu_k = 0$ ” versus its alternative “ $\mu_k > 0$ ”. Let  $\Phi$  be the cdf of the  $\mathcal{N}(0, 1)$  distribution, and  $p_k = 1 - \Phi(X_k)$  the  $p$ -value associated to the  $k$ -th test. Assume that all null hypotheses are true, hence all  $p_k$ 's have uniform distribution over  $[0, 1]$ . The probability of making at least one false positive, also called the Family-Wise Error Rate (FWER), is then:

$$\begin{aligned}\text{FWER} &= \mathbb{P}(\exists k : p_k \leq \alpha) \\ &= 1 - \mathbb{P}(\forall k : p_k > \alpha) \\ &= 1 - \prod_{k=1}^m \mathbb{P}(p_k > \alpha) \text{ by independence} \\ &= 1 - (1 - \alpha)^m.\end{aligned}\tag{1.1.3}$$

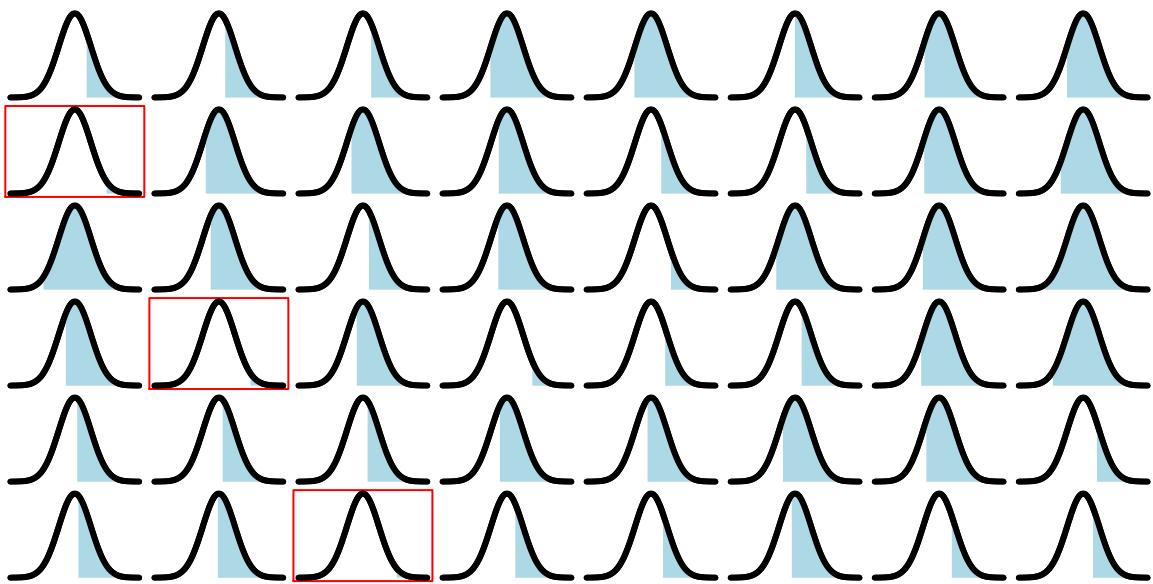


Fig. 1.1 48 observations under the null hypothesis and associated false positives for  $\alpha = 0.05$ .

Hence, the more tests we perform, the closer the FWER is to 1. We can also observe the increasing number of false positives via simple numerical experiments. Figures 1.1 and 1.2 represent the above situation described above with  $m = 48$  and  $m = 192$ , respectively. Each cell of each figure represents one observation  $X_k$  placed on the  $X$ -axis, the curve being the graph of the density function  $\phi$  associated to  $\Phi$ , and the area in blue being the associated  $p$ -value. False positives, i.e.  $p$ -values less than or equal to  $\alpha = 0.05$ , are framed in red. The increasing number of false positives appears clearly, the simple testing method fails to provide a correct type I error control and threatens to provide a large number of spurious detections, which is not desirable in exploratory research like GWAS. This indicates that using uncorrected single testing methods is not suitable anymore and appropriate modifications, or corrections, should be designed.

For less than a century, methods have been developed to guarantee a control on a given criterion. First, control of the FWER has been searched, with, for example, the notorious Bonferroni method (Bonferroni, 1936), which simply consists in replacing  $\alpha$  by  $\frac{\alpha}{m}$ . We could also replace  $\alpha$  by  $1 - (1 - \alpha)^{\frac{1}{m}}$ ; equation (1.1.3) ensures that both corrections provide  $\text{FWER} \leq \alpha$  if all nulls are true, hence  $\text{FWER} \leq \alpha$  no matter which nulls are true or false, because the “full null” situation is the worst case. The FWER control can be too restrictive for exploratory research, hence another criterion, less stringent, has been proposed and studied for the last twenty years. The False Discovery Rate (FDR) is defined as the expected value of the False Discovery Proportion (FDP), itself defined as

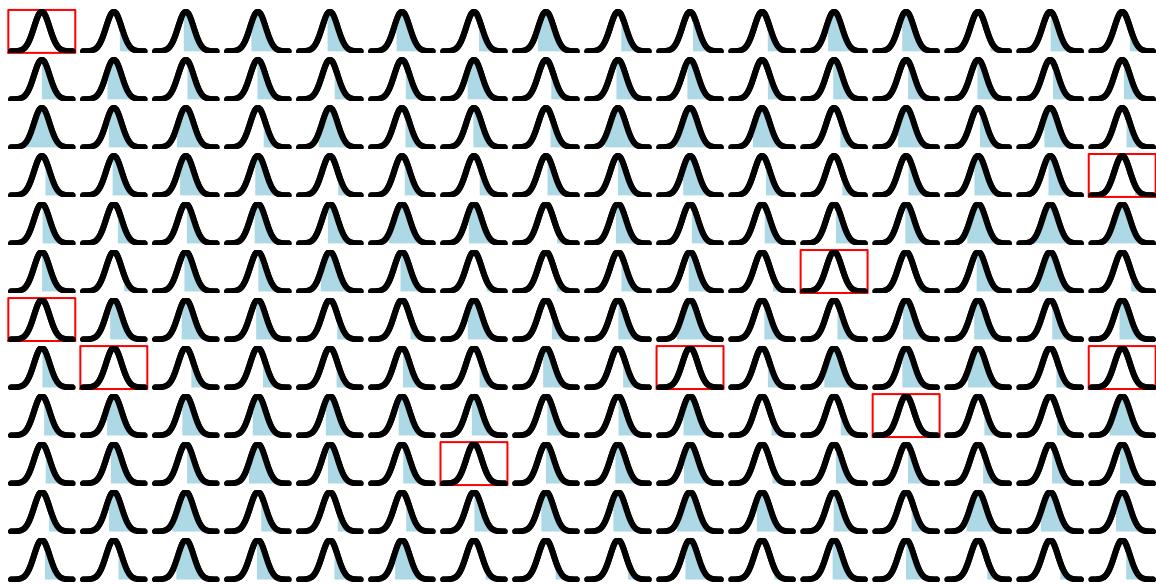


Fig. 1.2 192 observations under the null hypothesis and associated false positives for  $\alpha = 0.05$ .

the ratio of the number of false positives to the total number of rejections, if any, or 0 (see Equation (1.2.6)). It has been presented in a seminal paper by Yoav Benjamini and Yosef Hochberg (1995), along with a procedure able to control it in the independent case, the so-called Benjamini-Hochberg (BH) procedure. The FDR has been quickly adopted by the scientific community, so that Benjamini and Hochberg's paper has now more than 46 000 citations on Google Scholar. More details and more formalization on these error criterions and procedures are provided in Section 1.2.2.

### 1.1.2 Challenges and outline

Modern applications and technologies present some new challenges. On the one hand, classical methods can suffer of some conservativeness, while on the other hand, the data can present some structure or heterogeneity that may exploitable to gain power, that is, ability to detect false nulls. For example in GWAS, a natural structure is the clustering of SNPs into chromosomes, see Section 1.1.4 for further examples. Another situation where classical methods lose power is when the  $p$ -values have a discrete distribution (see Section 1.2.4), which is typically the case in GWAS if we do not make any asymptotic approximation for the  $\chi^2$  test. The first challenge is then to provide new methods being able to take into account the heterogeneity or the discreteness of the  $p$ -values.

A second important challenge is the so-called replication crisis (or reproducibility crisis) happening currently in many scientific fields, such as psychology and medicine, coming

from the fact that scientists fail to reproduce results of past experiments ([Ioannidis, 2005](#); [Prinz et al., 2011](#); [Earp and Trafimow, 2015](#); [Baker, 2016](#)). This has sometimes resulted in a confidence crisis against the testing framework and the use of  $p$ -values ([Trafimow and Marks, 2015](#)). Many explanations have been advanced to explain the replication crisis. The first one is a misinterpretation of the meaning of  $p$ -values ([Wasserstein and Lazar, 2016](#), Principles 2-3), but the main one is that researchers often manipulate their data to obtain more significant results. These manipulations, conscious or not, impact various scientific communities, and are often driven by the need of producing a large number of publications in the competitive modern academic world ([National Academies of Sciences, Engineering, and Medicine, 2016](#)). One typical manipulation is to remove some variables from the study following an arbitrary selection process (see [Ioannidis, 2005](#) and [Wasserstein and Lazar, 2016](#), Principle 4). In our GWAS example, it could be for example removing SNPs with a  $p$ -value exceeding 0.5, because that would be a strong indication that those SNPs show no association with the trait. This practice, called data snooping,  $p$ -hacking, or significance chasing, has the downside that statistical methods not accounting for the selection step lose their statistical guarantees, hence producing results that may sound promising but are likely to be too optimistic, and not reproducible. To illustrate this, we can think of a toy example presented by [Taylor and Tibshirani \(2015\)](#): during a study, a  $z$ -score of 2.5 seems relevant, because the probability that  $|Z|$ ,  $Z$  following a standard normal distribution, exceeds 2.5 is  $\approx 0.012$  (that is, the  $p$ -value is  $\approx 0.012$ ). Now, assume that the score comes from a screening where scores with absolute value less or equal than 2 have been discarded. In this case, the  $p$ -value should be computed conditional to the event “ $|z| > 2$ ”, which ultimately gives a result of  $\approx 0.27$  and does not seem that much relevant anymore. The need to properly take into consideration the selection step is consequently an actual and major concern.

The rest of this introduction is organized as follows: Section [1.1.3](#) briefly reviews other application domains of multiple testing, beyond GWAS, and Section [1.1.4](#) gives many examples of heterogeneity among the data. Section [1.2](#) first formalizes mathematically the multiple testing framework, then reviews some recent works aiming at adapting to the heterogeneity of the data by weighting the  $p$ -values (Section [1.2.3](#)), or at using the discreteness of the data (Section [1.2.4](#)). Section [1.3](#) reviews works in the selective inference area, which aims to provide valid statistical guarantees on procedures that are applied after a selection step. Finally, Section [1.4](#) succinctly presents my contributions to these fields, which are the subject of the next chapters.

### 1.1.3 Other applications of multiple testing

Besides GWAS, another common application in pharmaceutics and medicine of multiple testing is the analysis of gene expression ([Dudoit et al., 2002](#)), with a setting close to the case-control study of GWAS. Gene expression levels are evaluated thanks to measurements of protein level or RNA (a transcription of the DNA that is then translated into proteins) level. The expression level of many genes can be compared at the same time, for example between two different phenotypes, which naturally asks for a multiple testing procedure to account for multiplicity. Another possibility is to search for co-expression of two genes in a given phenotype by testing each pair of gene which greatly increases the multiplicity of the study. Many genetic applications of multiple testing, notably in gene expression, are found in the book of [Dudoit and van der Laan \(2008\)](#).

Multiple tests also occur in the analysis of data coming from functional magnetic resonance imaging (fMRI). Assume that we want to discover which regions of the brain are involved in a given task, like picture recognition. During a study we can then perform an fMRI on subjects performing the task and retrieve a 3D mapping of their brain during the task. On each voxel (a 3D pixel) a measure is associated and a test is performed to detect an association with the task. The brain mapping can also be considered as continuous sets (instead of being discretized in voxels) and some continuous definitions of the FDR have been proposed to accommodate such formalization ([Pacifico et al., 2004](#); [Blanchard et al., 2014](#)). More applications of multiple testing in medical imaging can be found in ([Worsley et al., 1992](#); [Forman et al., 1995](#); [Kriegeskorte and Goebel, 2001](#); [Genovese et al., 2002](#); [Viswanathan et al., 2012](#)). Finally note that the book of [Dickhaus \(2014\)](#) deals with various kinds of biological applications including the ones described above (GWAS, gene expression, fMRI).

Multiple testing procedures and FDR control in particular are not only restricted to biological applications. In astrophysics, for instance, one approach is to test each pixel of astronomical images to separate noise from true signal. Other astrophysical applications are found in [Miller et al. \(2001\)](#) and the following literature ([Hopkins et al., 2002](#); [Pires et al., 2006](#); [Starck et al., 2006](#)), for example the observation of the cosmic microwave background, or dark matter detection by gravitational lens. Applications in economics can be found in [Romano et al. \(2008, 2010\)](#), for instance testing the efficiency of many risky hedge funds against a non risky one used as a reference. Finally, in many industries, the search for anomalies (or outliers) involves multiple tests and an adequate correction ([Archimbaud et al., 2016](#), and references therein).

### 1.1.4 Heterogeneous data

As said above, contemporary data sets are massive, complex, and heterogeneous. Several types of heterogeneity can be exploited by the statistician to incorporate previous knowledge on the data and improve procedures, whereas not taking into account the heterogeneity can lead to a reduction of power ([Efron, 2008b](#)).

A first example of such data comes from an analysis led in Californian high-schools ([Rogosa, 2005](#)). The Adequate Yearly Progress (AYP) study compares mathematics examination results between socioeconomically advantaged (SEA) and socioeconomically disadvantaged (SED) students from 7867 schools. Each school is tested, to find if there is a significant difference in the results of the two groups of students, by computing a  $z$ -score for each school. [Cai and Sun \(2009\)](#) point that the previous analyses conducted on this data set, by computing an empirical density under the null hypothesis ([Efron, 2007, 2008a](#)), do not take into consideration that the schools have different sizes (in terms of number of students). As a result, most detections are coming from large schools which are favored because the sample size available to make detections is larger. Then [Cai and Sun](#) propose to separate the schools into three groups (large, medium, and small) and computed for each group the empirical density of the  $z$ -score under the null hypothesis. They find three significantly different distributions, the one for the large group having much heavier tails than the other. After applying a procedure that takes into account these three groups and their different distribution under the null, they make more detections inside the medium and small groups. The AYP study is an example of heterogeneity due to sample size, that also shows up in GWAS when SNPs have very different allelic frequencies ([Sun et al., 2006; Dalmasso et al., 2008](#)).

Another type of heterogeneity comes from the intrinsic structure of the data. An example of spatial structure in the data comes from a well-known data set ([Schwartzman et al., 2005](#)), also mentioned by [Efron \(2008b\)](#) and [Cai and Sun \(2009\)](#). It is an fMRI study aiming at finding brain regions differently activated between six dyslexic children and six healthy children. A total of 15443 voxels have been analyzed, and once more an empirical density computation shows an important difference between the voxels at the frontside and those at the backside of the brain. This suggests to group the hypotheses into two categories and to take this structure into account when applying a multiple testing procedure.

Another heterogeneity coming from a hierarchical structure comes from the so-called biological pathways, most often encountered in genomic or proteomic studies. Namely, some components of the study are constituted into networks where some act on others, as repressors or activators, like in the simple example of the lactose operon

where a gene named lacI codes for a repressor of three other genes: lacZ, lacY and lacA ([Jacob and Monod, 1961](#)). Many databases index the known biological pathways, see [Wikipedia \(2017\)](#) for a list of some of them. See also the Gene Ontology project ([The Gene Ontology Consortium, 2000](#)) which tries to create a unified ontology, and can be used to retrieve pathways by identifying genes involved in the same biological process.

Finally there are heterogeneities coming from the design of the experiment itself. Imagine a GWAS study testing the association of  $m$  SNPs with  $K$  different phenotypes, instead of only one. Then  $K \times m$  tests are to be conducted, but with an intuitive clustering of the hypotheses into  $K$  groups of size  $m$ . [Sun et al. \(2006\)](#) provide an example of such study where 1500 SNPs are tested with 5 different health complications linked to type 1 diabetes ([Boright et al., 2005](#)). Also, many genetic models can be tested for a single SNP, for example the additive, recessive and dominant models can each be tested in the same study, leading to a structure of three groups of  $m$  hypotheses each. When searching for association between pairs of SNPs and a trait, the number of models is even higher, some of them being detailed in [Emily \(2012\)](#).

## 1.2 Multiple testing and short state of the art

Sections [1.2.1](#) and [1.2.2](#) give an introduction to classical theory of multiple testing. They can be skipped by readers familiar with multiple testing.

### 1.2.1 Formal framework

We observe a random variable  $X$ , drawn from a probability space  $(\Omega, \mathfrak{A}, \mathbb{P})$ , valued in a measurable space  $(\Xi, \mathfrak{X})$  and which follows a distribution  $P$ , where  $P$  is unknown but lies in a known collection of distributions  $\mathcal{P}$ . In all generality, we do not search to exactly identify  $P$  but to check whether  $P$  belongs or not to some subsets  $H_{0,i}$  of  $\mathcal{P}$ , for  $i \in \mathbb{N}_m$  ( $\mathbb{N}_m$  is defined as  $\{1, \dots, m\}$ ). Those subsets are the null hypotheses we want to test. We say that  $H_{0,i}$  is true if  $P \in H_{0,i}$ , otherwise  $H_{0,i}$  is false and  $P \in H_{1,i}$ , where  $H_{1,i} = H_{0,i}^c$  is the alternative hypothesis of  $H_{0,i}$ . Let  $\mathcal{H}_0(P)$  be the set of indices  $i \in \mathbb{N}_m$  such that  $H_{0,i}$  is true and  $\mathcal{H}_1(P) = \mathcal{H}_0(P)^c$  be the set of false null indices; let  $m_0(P) = |\mathcal{H}_0(P)|$  and  $m_1(P) = |\mathcal{H}_1(P)|$ . In particular, we have

$$\mathcal{H}_0(P) = \{i \in \mathbb{N}_m : P \in H_{0,i}\}.$$

In general we search for the indices that belong to  $\mathcal{H}_1(P)$ , so a multiple testing procedure is a measurable function  $R$  of  $X$  which takes its values in the subsets of  $\mathbb{N}_m$ :

$$R : \begin{cases} \Xi & \longrightarrow \mathcal{P}(\mathbb{N}_m) \\ x & \longmapsto R(x), \end{cases}$$

where  $R(X)$  is a set of indices that our procedure declares as false null hypotheses. In other words, we reject the null hypothesis for these indices and  $R(X)$  is the rejection set of the procedure. The procedure is often based on a vector of  $p$ -values  $p(X) = (p_1(X), \dots, p_m(X))$ , where  $p_i(X)$  serves to test  $H_{0,i}$ . So a multiple testing procedure can also be defined as:

$$R : \begin{cases} [0, 1]^m & \longrightarrow \mathcal{P}(\mathbb{N}_m) \\ (p_1, \dots, p_m) & \longmapsto R(p_1, \dots, p_m). \end{cases}$$

In all generality, the  $p$ -value  $p_i(X)$  represents the largest probability that a random variable  $Y$  defined on the same probabilistic space, under the null hypothesis  $H_{0,i}$ , and independent from  $X$ , realizes an observation at least as extreme as  $X$ . This can be written

$$p_i(X) = \sup_{P' \in H_{0,i}} \mathbb{P}_{Y \sim P'}(E(Y, X) | X),$$

where  $E(Y, X)$  is a measurable event which represents the notion that “ $Y$  is as extreme as  $X$ ”. To this end, we often use a test statistic  $S_i$  and let  $E(Y, X)$  be the event “ $S_i(Y) \geq S_i(X)$ ”, which leads to the common way of defining a  $p$ -value:

$$p_i(X) = \sup_{P' \in H_{0,i}} T_{i,P'}(S_i(X)), \quad (1.2.1)$$

where

$$T_{i,P'}(s) = \mathbb{P}_{Y \sim P'}(S_i(Y) \geq s), \quad (1.2.2)$$

which is in line with the definitions of  $p$ -values based on test statistics of [Roquain \(2011\)](#) and [Giraud \(2014\)](#). Those  $p$ -values enjoy an important property often required in the multiple testing framework.

**Proposition 1.2.1** (see [Roquain, 2011](#), Proposition A.1 or [Giraud, 2014](#), Proposition 8.1 for a proof). *A  $p$ -value defined with (1.2.1) and (1.2.2) is super-uniform under the null. That is, if  $P \in H_{0,i}$ , then:*

$$\forall u \in [0, 1], \mathbb{P}(p_i(X) \leq u) \leq u. \quad (1.2.3)$$

*Remark 1.2.1.* In many contexts,  $\Xi = \mathbb{R}^m$  and  $H_{0,i}$  is only an hypothesis on the distribution  $P_i \in \mathcal{P}_i$  of  $X_i$ . In this case,  $H_{0,i}$  (which is formally a subset of  $\mathcal{P}$ ) can be identified to a subset of  $\mathcal{P}_i$  and  $S_i(X)$  (thus  $p_i(X)$ ) is often taken as a function of  $X_i$  instead of  $X$ . If  $H_{0,i}$ , as a subset of  $\mathcal{P}_i$ , is a singleton, and if  $S_i(X)$  has continuous distribution under the null, then  $p_i(X)$  is uniform under the null, which strengthens the result of Proposition 1.2.1 (see e.g. Roquain, 2011, Proposition A.1).

*Example 1.2.1* (Gaussian one-sided setting). We observe a Gaussian vector  $X \in \mathbb{R}^m$  distributed according to  $\mathcal{N}(\mu, \Sigma)$ ,  $\mu \in \mathbb{R}^m$ ,  $\Sigma \in \mathbb{R}^{m \times m}$ , such that  $\text{Var}(X_i) = 1$  for each  $i \in \mathbb{N}_m$ . For each  $i$ , we test  $H_{0,i}$ : “ $\mu_i \leq 0$ ” against  $H_{1,i}$ : “ $\mu_i > 0$ ”. Hence, the collection of distributions and the null hypotheses are:

$$\begin{aligned}\mathcal{P} &= \{\mathcal{N}(\mu, \Sigma) : \forall j \in \mathbb{N}_m, \Sigma_{jj} = 1\}, \\ \forall i \in \mathbb{N}_m, \quad H_{0,i} &= \{\mathcal{N}(\mu, \Sigma) : \mu_i \leq 0, \forall j \in \mathbb{N}_m, \Sigma_{jj} = 1\}.\end{aligned}$$

*p*-values can be computed from the test statistic  $S_i(X) = X_i$ , which leads to  $p_i(X) = \bar{\Phi}(X_i)$ , where  $\Phi$  is the cdf of  $\mathcal{N}(0, 1)$  distribution and  $\bar{\Phi}(\cdot) = 1 - \Phi(\cdot)$ .

*Example 1.2.2* (Gaussian one-sided setting, nonnegative). Additionally, if we assume that  $\mu_i$  is always nonnegative,  $H_{0,i}$  becomes “ $\mu_i = 0$ ”, and we have:

$$\begin{aligned}\mathcal{P} &= \{\mathcal{N}(\mu, \Sigma) : \forall j \in \mathbb{N}_m, \mu_j \geq 0, \Sigma_{jj} = 1\}, \\ \forall i \in \mathbb{N}_m, \quad H_{0,i} &= \{\mathcal{N}(\mu, \Sigma) : \mu_i = 0, \forall j \in \mathbb{N}_m \setminus \{i\}, \mu_j \geq 0, \forall j \in \mathbb{N}_m, \Sigma_{jj} = 1\}.\end{aligned}$$

Furthermore, contrary to previous example, we are fully in the context of Remark 1.2.1, because  $H_{0,i}$ , viewed as a subset of  $\mathcal{P}_i = \{\mathcal{N}(\mu_i, 1) : \mu_i \geq 0\}$ , is the singleton  $\{\mathcal{N}(0, 1)\}$ . Hence, if  $P \in H_{0,i}$ ,  $p_i(X)$  has a uniform distribution.

*Example 1.2.3* (Gaussian two-sided setting). As in Example 1.2.1, except that for each  $i$ , we test  $H_{0,i}$ : “ $\mu_i = 0$ ” against  $H_{1,i}$ : “ $\mu_i \neq 0$ ”. Hence we have:

$$\begin{aligned}\mathcal{P} &= \{\mathcal{N}(\mu, \Sigma) : \forall j \in \mathbb{N}_m, \Sigma_{jj} = 1\}, \\ \forall i \in \mathbb{N}_m, \quad H_{0,i} &= \{\mathcal{N}(\mu, \Sigma) : \mu_i = 0, \forall j \in \mathbb{N}_m, \Sigma_{jj} = 1\}.\end{aligned}$$

*p*-values can be computed from the test statistic  $S_i(X) = |X_i|$ , which leads to  $p_i(X) = 2\bar{\Phi}(|X_i|)$ . If  $P \in H_{0,i}$ ,  $p_i(X)$  has a uniform distribution by Remark 1.2.1.

### 1.2.2 Error criteria and classical procedures

From now on, we drop the dependence in  $X$  or in  $P$  in the notation when there is no ambiguity. As previously announced, it is desirable for a procedure to make as few false positives as possible, where  $i$  is a false positive if it is a true null ( $i \in \mathcal{H}_0$ ) but it has been detected by the procedure ( $i \in R$ ). To be able to propose some guarantees on the number of type I errors, suitable error criterions must be defined, along with procedures able to control these criterions at a desired level  $\alpha$ . Denote by  $V(R)$  the number of false positives made by a procedure  $R$ , that is,  $V(R) = |\mathcal{H}_0 \cap R|$ . The first criterion that we may be interested to control is the Family-Wise Error Rate (FWER), which is simply the probability to make at least one false positive:

$$\text{FWER}(R) = \mathbb{P}(V(R) > 0). \quad (1.2.4)$$

Searching to control the FWER means that no false positive can be tolerated in the study, because making a false positive is considered as too dangerous or costly.

One of the simplest methods to control the FWER at level  $\alpha$  is the Bonferroni correction (Bonferroni, 1936; Dunn, 1961). It simply consists in rejecting  $p$ -values less than or equal to  $\alpha/m$ , that is  $R_{\text{Bonf}} = \{i : p_i \leq \frac{\alpha}{m}\}$ .

**Proposition 1.2.2.** *If the  $p$ -values are super-uniform under the null (see (1.2.3)), then:*

$$\begin{aligned} \forall P \in \mathcal{P}, \text{FWER}(R_{\text{Bonf}}) &\leq \alpha \frac{m_0}{m} \\ &\leq \alpha. \end{aligned} \quad (1.2.5)$$

*Proof.* Let  $P \in \mathcal{P}$  and  $X \sim P$ .

$$\begin{aligned} \text{FWER}(R_{\text{Bonf}}) &= \mathbb{P}(V(R) > 0) \\ &= \mathbb{P}\left(\exists i \in \mathcal{H}_0, p_i \leq \frac{\alpha}{m}\right) \\ &\leq \sum_{i \in \mathcal{H}_0} \mathbb{P}\left(p_i \leq \frac{\alpha}{m}\right) \\ &\leq \sum_{i \in \mathcal{H}_0} \frac{\alpha}{m} = \alpha \frac{m_0}{m}. \end{aligned} \quad \square$$

Equation (1.2.5) shows that the FWER is in fact controlled at level  $\alpha m_0/m$  instead of  $\alpha$ , which is smaller as soon as there are false nulls. This means that the control of the Bonferroni correction may be too conservative. For example, if we knew  $m_0$ , we could reject  $p$ -values at level  $\alpha/m_0$  instead of  $\alpha/m$ , which could enable more detections while

maintaining the control at level  $\alpha$ . Hence, a number of works aim at approaching the threshold  $\alpha/m_0$  either directly (by plugging an estimator of  $\pi_0 = m_0/m$ , see e.g. [Storey, 2002](#) or [Finner and Gontscharuk, 2009](#)) or indirectly (by step-wise algorithms).

One classical way of doing so is the Holm-Bonferroni (HB) procedure ([Holm, 1979](#)), which is a step-down procedure that can be sequentially defined as the following: order the  $p$ -values  $p_{(1)} \leq \dots \leq p_{(m)}$ . We start with a rejection level of  $\alpha/m$ . If  $p_{(1)} > \alpha/m$ , we stop the procedure. If  $p_{(1)} \leq \alpha/m$ , then we reject the hypothesis corresponding to  $p_{(1)}$  and, by assuming it was a false null, we assume that  $m_0 \leq m - 1$  and we update the rejection level to  $\alpha/(m - 1)$ . We check if  $p_{(2)} \leq \alpha/(m - 1)$ , and so on. By denoting  $p_{(0)} = 0$ , this can be written as:

$$R_{\text{HB}} = \left\{ i : p_i \leq \frac{\alpha}{m - \hat{k}_{\text{HB}} + 1} \right\},$$

where

$$\hat{k}_{\text{HB}} = \max \left\{ 0 \leq k \leq m : \forall k' \leq k, p_{(k')} \leq \frac{\alpha}{m - k' + 1} \right\}.$$

It is a step-down procedure in the following sense.

**Definition 1.2.1.** Given a nondecreasing sequence  $\tau = (\tau_1, \dots, \tau_m)$ , the respective step-up and step-down procedures associated to  $\tau$  are:

$$\begin{aligned} R_{\text{SU}}(\tau) &= \left\{ i : p_i \leq \tau_{\hat{k}_{\text{SU}}} \right\}, \\ R_{\text{SD}}(\tau) &= \left\{ i : p_i \leq \tau_{\hat{k}_{\text{SD}}} \right\}, \end{aligned}$$

where

$$\begin{aligned} \hat{k}_{\text{SU}} &= \max \left\{ 0 \leq k \leq m : p_{(k)} \leq \tau_k \right\}, \\ \hat{k}_{\text{SD}} &= \max \left\{ 0 \leq k \leq m : \forall k' \leq k, p_{(k')} \leq \tau_{k'} \right\}. \end{aligned}$$

The HB procedure is then the step-down procedure with critical values  $\tau_k = \frac{\alpha}{m - k + 1}$ . Note that the Bonferroni procedure is both a step-up and a step-down procedure with critical values  $\tau_k = \frac{\alpha}{m}$ .

*Remark 1.2.2.* It is easy to check that  $|R_{\text{SU}}(\tau)| = \hat{k}_{\text{SU}}$  and  $|R_{\text{SD}}(\tau)| = \hat{k}_{\text{SD}}$ .

The HB procedure controls the FWER at level  $\alpha$  as shown in the following result.

**Proposition 1.2.3.** *If the  $p$ -values are super-uniform under the null (see (1.2.3)), then:*

$$\forall P \in \mathcal{P}, \text{FWER}(R_{\text{HB}}) \leq \alpha.$$

*Proof.* Let  $P \in \mathcal{P}$  and  $X \sim P$ . Assume that the event “ $\{i : p_i \leq \frac{\alpha}{m_0}\} \cap \mathcal{H}_0 = \emptyset$ ” holds, which happens with probability at least  $1 - \alpha$ , as we already discussed. Assume that

$k_{\text{HB}} \geq 1$ ; if not,  $V(R_{\text{HB}}) = 0$ . We know that  $p_{(k)} \leq \frac{\alpha}{m-k+1}$  for all  $k \leq \hat{k}_{\text{HB}}$ . We use a recursion on  $k \in \{1, \dots, \hat{k}_{\text{HB}}\}$  to show that  $m_0 \leq m - k + 1$ . It is trivial for  $k = 1$ , and if it is true for  $k < \hat{k}_{\text{HB}}$ , then for all  $k' \leq k$  we have:

$$p_{(k')} \leq p_{(k)} \leq \frac{\alpha}{m - k + 1} \leq \frac{\alpha}{m_0},$$

hence at least  $k$  hypotheses are false, and  $m_0 \leq m - k$ , which ends the recursion. Finally,  $R_{\text{HB}} \subset \{i : p_i \leq \frac{\alpha}{m_0}\} \subset \mathcal{H}_1$ , which concludes the proof.  $\square$

As the philosophy of FWER control is to avoid any false positive, it may not be suitable to exploratory research, where a small number of false positives may be acceptable, provided that the procedure discovers many true positives. This can be interpreted as the necessity of having a small ratio between false positives and total number of detections, leading to the False Discovery Proportion (FDP) and its expected value, the False Discovery Rate (FDR), in [Benjamini and Hochberg \(1995\)](#):

$$\text{FDP}(R) = \frac{V(R)}{|R| \vee 1}, \quad (1.2.6)$$

$$\text{FDR}(R) = \mathbb{E} [\text{FDP}(R)]. \quad (1.2.7)$$

Thereby, controlling the FDR or the FDP means controlling the proportion of false positives among detections. This is desirable, because making 20 false positives can be acceptable if 500 null hypotheses are rejected: we are still discovering 480 true positives. Moreover, it is easy to show that the FDR is less conservative than the FWER:

$$\text{FDR} = \mathbb{E} \left[ \frac{V(R)}{|R| \vee 1} \right] \leq \mathbb{E} [\mathbf{1}_{V(R)>0}] = \mathbb{P}(V(R) > 0) = \text{FWER}.$$

The inequality above becomes an equality if all hypotheses are true, which shows a kind of adaptivity to the data, where the FDR automatically becomes more restrictive without false nulls. Controlling the FDR hence allows to increase the number of detections, at the expense of more false positives, but in a controlled proportion.

[Benjamini and Hochberg \(1995\)](#) also introduced a procedure controlling the FDR at level  $\alpha$  if the  $p$ -values are independent. Namely, the Benjamini-Hochberg (BH) procedure is the step-up procedure with critical values  $\tau_k = \alpha \frac{k}{m}$ :

$$R_{\text{BH}} = \left\{ i : p_i \leq \alpha \frac{\hat{k}_{\text{BH}}}{m} \right\},$$

where

$$\hat{k}_{\text{BH}} = \max \left\{ 0 \leq k \leq m : p_{(k)} \leq \alpha \frac{k}{m} \right\}.$$

The BH procedure can be thought as a trade-off between the uncorrected procedure and the Bonferroni procedure because it rejects  $p$ -values at threshold  $\alpha \hat{k}_{\text{BH}}/m$ , which lies between  $\alpha/m$  and  $\alpha$ . It also adapts to the signal because the smallest the  $p$ -values, the higher  $\hat{k}_{\text{BH}}$ , as illustrated in Figure 1.3. The only difference between the two graphs is the proportion  $\pi_0$  of true nulls. For  $\pi_0 = 0.5$  (on left hand),  $\hat{k}_{\text{BH}} = 23$ , whereas for  $\pi_0 = 0.8$  (on right hand),  $\hat{k}_{\text{BH}} = 8$ . So BH tends to behave more like the uncorrected procedure, or like the Bonferroni procedure, as the proportion of signal fluctuates. Another illustration of this phenomenon is given with Figures 1.4 and 1.5, representing two Manhattan plots, where the  $p$ -values are plotted after taking their negative logarithm, so that the smallest ones are the highest on the Y-axis. In Figure 1.4, where  $\pi_0 = 0.5$ , BH makes many more rejections than Bonferroni, whereas in Figure 1.5, where  $\pi_0 = 0.99$ , BH makes only one more rejection than Bonferroni.

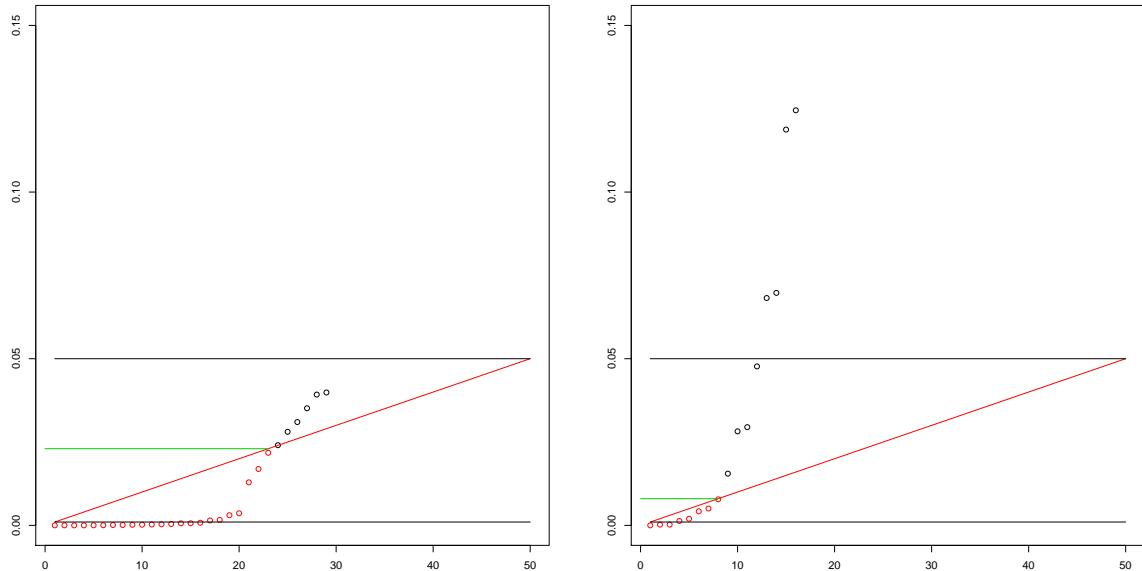


Fig. 1.3 Ordered  $p$ -values of  $m = 50$  Gaussian one-sided tests where 25 (left) or 40 (right) hypotheses are true. Only  $p$ -values smallest than  $3\alpha$  are displayed, and the ones rejected by BH are in red. Black horizontal lines represent the thresholds  $\alpha$  and  $\frac{\alpha}{m}$ , showing which  $p$ -values are rejected by the uncorrected and the Bonferroni procedures. The green horizontal is the threshold  $\alpha \frac{\hat{k}_{\text{BH}}}{m}$ . The red line is the function  $k \mapsto \alpha \frac{k}{m}$ .

As previously announced, we have the following result.

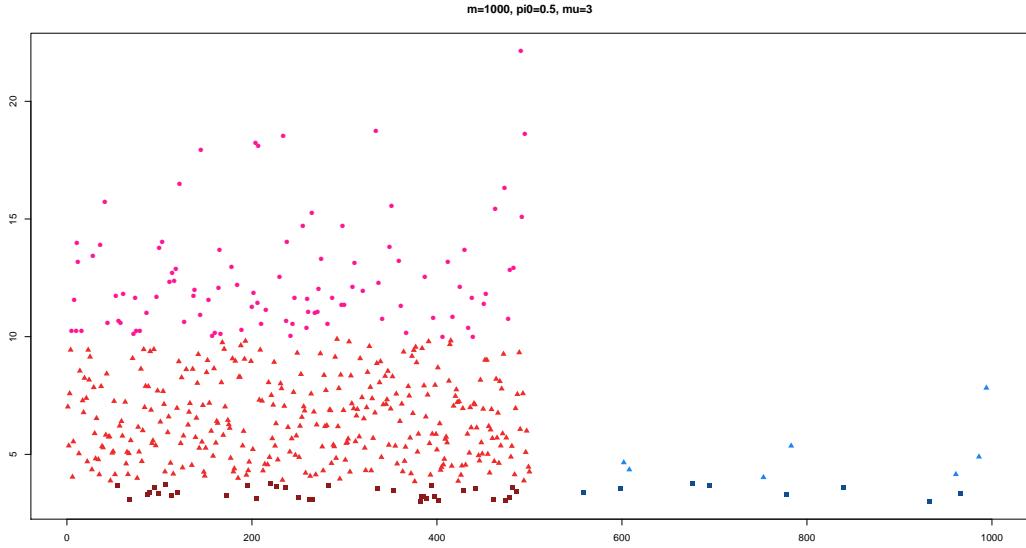


Fig. 1.4 Plot of the  $-\log$  of the rejected  $p$ -values of 1000 Gaussian one-sided tests with 500 true nulls. True positives are in warm colors (and all on the left for the sake of simplicity): deep red squares for hypotheses only rejected by the uncorrected procedure, orange triangles for hypotheses rejected by BH but not by Bonferroni, and pink rounds for hypotheses rejected by the three procedures. False positives are in cool colors following the same pattern (and all on the right), with deep blue squares for hypotheses only rejected by the uncorrected procedure and light blue triangles for hypotheses rejected by BH but not by Bonferroni.

**Proposition 1.2.4.** *If the  $p$ -values  $p_i$ , for  $i \in \mathcal{H}_0$ , are super-uniform (see (1.2.3)) and mutually independent, and if the family  $(p_i)_{i \in \mathcal{H}_0}$  is independent of  $(p_i)_{i \in \mathcal{H}_1}$ , then:*

$$\begin{aligned} \forall P \in \mathcal{P}, \text{FDR}(R_{\text{BH}}) &\leq \alpha \frac{m_0}{m} \\ &\leq \alpha. \end{aligned} \tag{1.2.8}$$

Moreover, the inequality in (1.2.8) becomes an equality if the  $p$ -values are uniform under the null.

Before proving it, we need two lemmas which describe the behavior of step-up procedures when we pull out a  $p$ -value.

**Lemma 1.2.1.** *Let  $p_{(1)} \leq \dots \leq p_{(m)}$  be the ordered  $p$ -values, with the convention  $p_{(0)} = 0$ . Let  $\tau$  be a nondecreasing sequence of  $m$  critical values and  $\hat{k}$  the number of rejections of the associated step-up procedure. Let  $i \in \{1, \dots, m\}$ . Consider the step-up procedure with critical values  $\tau^{-i} = (\tau_1^{-i}, \dots, \tau_{m-1}^{-i}) = (\tau_2, \dots, \tau_m)$  applied to all  $p$ -values except  $p_i$ . Let*

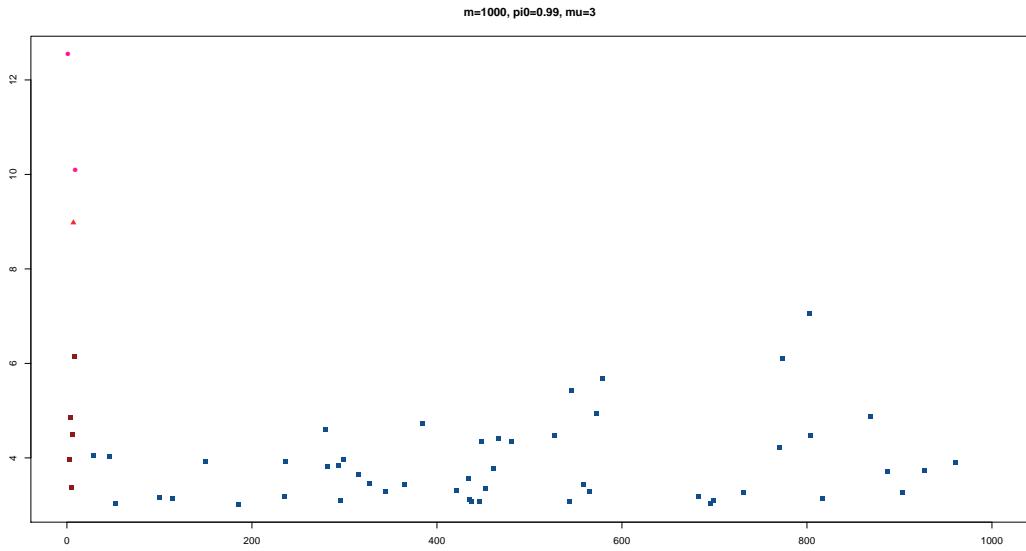


Fig. 1.5 Plot of the  $-\log$  of the rejected  $p$ -values of 1000 Gaussian one-sided tests with 990 true nulls. The caption of Figure 1.4 applies also here.

$p_{(1)}^{-i} \leq \dots \leq p_{(m-1)}^{-i}$  be the ordered  $p$ -values of this procedure, with the convention  $p_{(0)}^{-i} = 0$ , and let  $\hat{k}^{-i} = \max \{k : p_{(k)}^{-i} \leq \tau_k^{-i}\}$  be the number of rejections of this procedure. Then  $\hat{k}^{-i} \geq \hat{k} - 1$  and the three following assertions are equivalent:

- (i)  $p_i \leq \tau_{\hat{k}}$ .
- (ii)  $p_i \leq \tau_{\hat{k}^{-i}+1}$ .
- (iii)  $\hat{k}^{-i} = \hat{k} - 1$ .

*Proof.* Assume  $\hat{k} \geq 2$ , otherwise  $\hat{k}^{-i} \geq \hat{k} - 1$  is trivial. Note that  $p_{(\hat{k}-1)}^{-i}$  is always equal to  $p_{(\hat{k})}$  or  $p_{(\hat{k})}$ , so  $p_{(\hat{k}-1)}^{-i} \leq \tau_{\hat{k}} = \tau_{\hat{k}-1}^{-i}$  and  $\hat{k}^{-i} \geq \hat{k} - 1$ , by definition of  $\hat{k}^{-i}$ . Now we show the equivalence by showing three implications.

**(i) $\Rightarrow$ (ii)** If  $p_i \leq \tau_{\hat{k}}$  then obviously  $p_i \leq \tau_{\hat{k}^{-i}+1}$  because  $\tau$  is nondecreasing and  $\hat{k} \leq \hat{k}^{-i} + 1$ .

**(ii) $\Rightarrow$ (iii)** If  $p_i \leq \tau_{\hat{k}^{-i}+1}$ , notice that we also have  $p_{(1)}^{-i}, \dots, p_{(\hat{k}-i)}^{-i} \leq \tau_{\hat{k}^{-i}}^{-i} = \tau_{\hat{k}^{-i}+1}$ . Hence at least  $\hat{k}^{-i} + 1$   $p$ -values are  $\leq \tau_{\hat{k}^{-i}+1}$ , so  $p_{(\hat{k}-i+1)} \leq \tau_{\hat{k}^{-i}+1}$  and  $\hat{k} \geq \hat{k}^{-i} + 1$  by definition of  $\hat{k}$ .

**(iii) $\Rightarrow$ (i)** Assume that  $p_i > \tau_{\hat{k}}$ . Then  $p_{(\hat{k})}^{-i} = p_{(\hat{k})} \leq \tau_{\hat{k}} = \tau_{\hat{k}-1}^{-i} \leq \tau_{\hat{k}}^{-i}$  and  $\hat{k}^{-i} \geq \hat{k}$ . Hence  $\hat{k}^{-i} = \hat{k} - 1$  implies that  $p_i \leq \tau_{\hat{k}}$ .  $\square$

**Lemma 1.2.2.** *With the same notation as in Lemma 1.2.1, let  $k \in \{1, \dots, m\}$ . We have the following equality between events :*

$$\{p_i \leq \tau_{\hat{k}}, \hat{k} = k\} = \{p_i \leq \tau_k, \hat{k}^{-i} = k - 1\}.$$

*Proof.* We realize the following chain of equivalences thanks to Lemma 1.2.1:

$$\begin{aligned} p_i \leq \tau_{\hat{k}}, \hat{k} = k &\iff p_i \leq \tau_{\hat{k}}, \hat{k}^{-i} = \hat{k} - 1, \hat{k} = k && \text{because (i) $\Rightarrow$ (iii)} \\ &\iff p_i \leq \tau_{\hat{k}}, \hat{k}^{-i} = k - 1 && \text{because (i) $\Rightarrow$ (iii)} \\ &\iff p_i \leq \tau_{\hat{k}-i+1}, \hat{k}^{-i} = k - 1 && \text{because (i) $\Leftrightarrow$ (ii)} \\ &\iff p_i \leq \tau_k, \hat{k}^{-i} = k - 1. \end{aligned}$$

$\square$

*Proof of Proposition 1.2.4.* Let  $P \in \mathcal{P}$  and  $X \sim P$ . Recall that  $\hat{k}_{\text{BH}}$  is exactly the number of rejections  $|R_{\text{BH}}|$  of the BH procedure (see Remark 1.2.2). For all  $i \in \mathcal{H}_0$ , let  $\hat{k}_{\text{BH}}^{-i}$  be the number of rejections of the step-up procedure with critical values  $(\alpha \frac{2}{m}, \alpha \frac{3}{m}, \dots, \alpha)$  applied to all  $p$ -values except  $p_i$ . Then,

$$\begin{aligned} \text{FDR}(R_{\text{BH}}) &= \mathbb{E} \left[ \frac{\sum_{i \in \mathcal{H}_0} \mathbf{1}_{\{p_i \leq \alpha \hat{k}_{\text{BH}} / m\}}}{\hat{k}_{\text{BH}} \vee 1} \right] \\ &= \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \frac{1}{k} \mathbb{P} \left( p_i \leq \alpha \frac{\hat{k}_{\text{BH}}}{m}, \hat{k}_{\text{BH}} = k \right), \end{aligned}$$

where  $\mathbb{P} \left( p_i \leq \alpha \frac{\hat{k}_{\text{BH}}}{m}, \hat{k}_{\text{BH}} = k \right) = \mathbb{P} \left( p_i \leq \alpha \frac{k}{m}, \hat{k}_{\text{BH}}^{-i} = k - 1 \right)$  by Lemma 1.2.2. This last probability is equal to  $\mathbb{P} \left( p_i \leq \alpha \frac{k}{m} \right) \mathbb{P} \left( \hat{k}_{\text{BH}}^{-i} = k - 1 \right)$  by independence of  $p_i$  and  $\hat{k}_{\text{BH}}^{-i}$ . Moreover, by super-uniformity under  $H_{0,i}$ ,

$$\mathbb{P} \left( p_i \leq \alpha \frac{k}{m} \right) \leq \alpha \frac{k}{m}. \quad (1.2.9)$$

Finally,

$$\text{FDR}(R_{\text{BH}}) \leq \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \frac{1}{k} \alpha \frac{k}{m} \mathbb{P}(\hat{k}_{\text{BH}}^{-i} = k - 1) = \frac{\alpha}{m} \sum_{i \in \mathcal{H}_0} \sum_{k=1}^m \mathbb{P}(\hat{k}_{\text{BH}}^{-i} = k - 1) = \alpha \frac{m_0}{m}.$$

Moreover, if  $p$ -values are uniform under the null, the inequality in (1.2.9) becomes an equality.  $\square$

[Benjamini and Yekutieli \(2001\)](#) also showed that BH controls the FDR at level  $\alpha$  for a more general dependence pattern, called the Positive Regression Dependence on a Subset (PRDS). The authors also present the so-called Benjamini-Yekutieli (BY) procedure which controls the FDR under any dependence, at the cost of being more conservative. The BY procedure is the step-up procedure with critical values  $\tau_k = \alpha k / (m H_m)$  where  $H_m = \sum_{i=1}^m i^{-1}$ . See e.g. [Giraud \(2014, Chapter 8\)](#) for simple proofs of these two results. Many other procedures have been described in the literature, for example [Benjamini and Liu \(1999\)](#) (BL) introduced the step-down procedure with critical values  $\tau_k = 1 - (1 - \min(1, \alpha m / (m - k + 1)))^{1/(m-k+1)}$  and showed that BL controls the FDR at level  $\alpha$  when the  $p$ -values are independent. [Sarkar \(2002\)](#) strengthened this result by extending it to MTP<sub>2</sub> dependency (a setting more general than PRDS, see e.g. [Benjamini and Yekutieli, 2001](#)), while also producing results on the FDR of step-up-down procedures (a class of procedures more general than step-up and step-down).

Finally, note that many other type I error criteria have been designed over time, along with procedures to control them. We can cite for instance:

- the  $k$ -FWER, where  $k\text{-FWER}(R) = \mathbb{P}(V(R) \geq k)$  (hence the FWER is also the 1-FWER), which is discussed for example in [Lehmann and Romano \(2005\); Romano et al. \(2007\); Roquain \(2011\)](#),
- the positive FDR (pFDR), where  $\text{pFDR}(R) = \mathbb{E}[\text{FDP}(R) | |R| > 0]$  ([Storey et al., 2003](#)),
- the marginal FDR (mFDR), defined as  $\text{mFDR}(R) = \mathbb{E}[V(R)] / \mathbb{E}[|R|]$  (see e.g. [Cai and Sun, 2009](#)), related to the Bayesian FDR ([Efron and Tibshirani, 2002](#)),
- the FDP which can be directly controlled instead of the FDR, in the form of  $\mathbb{P}(\text{FDP}(R) \leq \alpha) \geq 1 - \zeta$  for some  $\zeta \in (0, 1)$  (see e.g. [Genovese and Wasserman, 2004; Lehmann and Romano, 2005; Delattre and Roquain, 2015](#)).

### 1.2.3 Weighting

One way to deal with the heterogeneity of the data is to incorporate a vector of weights into the procedure. Weights naturally induce an order of importance among the nulls and allow to incorporate known information that can be relevant to the study, as the minor allele frequency (MAF) in GWAS. See more examples in [Ignatiadis et al. \(2016, Table 1\)](#). Let us assume that some weight  $w_i \geq 0$  is given for each null  $H_{0,i}$ . While they can have a general form, they often rely on some underlying structure either continuous (e.g.  $w_i = f(i/m)$  for some smooth  $f$ ) or clustered (that is, if hypotheses can be grouped into  $G$  groups  $\mathcal{G}_1, \dots, \mathcal{G}_G$ , then  $w_i = w_{i'}$  when  $i, i' \in \mathcal{G}_g$ ).

To our knowledge, the first idea of adding weights can be found in the original paper introducing the HB method ([Holm, 1979](#)), where a variant of HB using weights is also presented. This variant weighs each  $p$ -value, by replacing  $p_i$  by  $p_i/w_i$  with  $w_i$  a positive constant such that  $\sum_{i=1}^m w_i = m$ . Then the weighted HB (WHB) procedure controls the FWER at level  $\alpha$ . Holm suggests to calibrate the weights with independent statistics (using the data would lead to some overfitting). [Benjamini and Hochberg \(1997\)](#) later developed a slight modification of WHB which was then applied to GWAS by [Dalmasso et al. \(2008\)](#), where the weight of SNP  $i$  is chosen according to its MAF  $f_i$ :  $w_i = m f_i^{-1} / \sum_{j=1}^m f_j^{-1}$ .

Instead of weighting the  $p$ -values, [Benjamini and Hochberg \(1997\)](#) also introduced a way to weigh the type-I error criterion leading to the weighted FDR, defined as:

$$\text{FDR}(R, (w_i)_{1 \leq i \leq m}) = \mathbb{E} \left[ \frac{\sum_{i \in R} w_i V(\{i\})}{(\sum_{i \in R} w_i) \vee 1} \right].$$

It is straightforward to check that when all weights are equal to one, the wFDR is the FDR. The two approaches can be combined as in [Blanchard and Roquain \(2008\)](#) where both the  $p$ -values and the criterion (through a finite positive measure  $\Lambda$ ) are weighted. [Ramdas et al. \(2017\)](#) also used an unified setting and clearly interpreted weighting the  $p$ -values as incorporating prior information on which hypotheses are more likely to be true (“prior weights”), while weighting the criterion quantifies the price to pay when wrongly rejecting each null (“penalization weights”).

The weighted BH procedure (WBH) has been introduced by [Genovese et al. \(2006\)](#) as a procedure which controls the FDR by applying the BH procedure to the weighted  $p$ -values  $p_i/w_i$ . Control is achieved in finite sample and asymptotically for independent  $p$ -values, and random weights that are independent from the  $p$ -values. [Roeder et al. \(2006\)](#) applied WBH in a GWAS context, by assigning larger weights to SNPs in regions under

a linkage peak (that is regions of the genome where alleles of SNPs are not independently distributed).

[Hu et al. \(2010\)](#) designed weights in a context where  $p$ -values are grouped, for which two  $p$ -values under the alternative that are in the same group  $\mathcal{G}_g$  share the same distribution  $F_g$ . Those weights incorporate an estimator  $\hat{\pi}_{g,0}$  of  $\pi_{g,0}$ , the proportion of true nulls in group  $\mathcal{G}_g$ , for example the [Storey et al. \(2004\)](#) estimator. For  $i \in \mathcal{G}_g$ ,  $w_i$  is taken equal to  $w_i = (1 - \hat{\pi}_{g,0}) / ((1 - \hat{\pi}_0) \hat{\pi}_{g,0})$ , where  $\hat{\pi}_0 = \sum_{g=1}^G \pi_g \hat{\pi}_{g,0}$  and  $\pi_g$  is the proportion of hypotheses in group  $\mathcal{G}_g$ . Asymptotic FDR control and power improvement over BH are achieved if  $\hat{\pi}_{g,0}$  is a consistent estimator of  $\pi_{g,0}$ . [Zhao and Zhang \(2014\)](#) designed two procedures using weights computed in the following fashion. First, two WBH procedures are performed, the first with weights all equal to  $1/\hat{\pi}_0$ , the second with the weights of [Hu et al. \(2010\)](#). The largest of the two rejection thresholds is kept and weights that maximize the number of rejections are computed (at this threshold). Asymptotic FDR control is achieved if  $\hat{\pi}_{g,0}$  is consistent, and [Zhao and Zhang \(2014\)](#) procedures also have a higher asymptotic power than the two aforementioned WBH procedures.

A natural issue in weighting is the design of optimal weights, in the sense of achieving maximal power in some sense. First works ([Wasserman and Roeder, 2006](#); [Roeder and Wasserman, 2009](#)) in this direction are focused on a Gaussian one-sided setting (see Example 1.2.1) for FWER control. A weighted Bonferroni procedure is used with oracle optimal weights, given by the following closed formula:

$$w_i = \frac{m}{\alpha} \bar{\Phi} \left( \frac{\mu_i}{2} + \frac{c}{\mu_i} \right) \mathbb{1}_{\{\mu_i > 0\}},$$

where  $c$  is such that  $\sum_{i=1}^m w_i = m$ . Estimating  $\mu_i$  is then proposed, leading to data-driven weights. A recent related work is the paper of [Dobriban et al. \(2015\)](#), where there is a known Gaussian prior  $\mu_i \sim \mathcal{N}(\tilde{\mu}_i, \sigma_i^2)$ . [Roquain and van de Wiel \(2009\)](#) introduced the multi weighted BH (MWBH) where weights are a function of a rejection proportion  $u$ , and derived the optimal weight functions for FDR control, by assuming that the alternative cdf are known. For example, in the Gaussian one-sided problem, the weight function is

$$w_i(u) = \frac{1}{\alpha u} \bar{\Phi} \left( \frac{\mu_i}{2} + \frac{c(u)}{\mu_i} \right) \mathbb{1}_{\{\mu_i > 0\}},$$

where  $c(u)$  is such that  $\sum_{i=1}^m w_i(u) = 1$ . We can notice the analogy with [Wasserman and Roeder \(2006\)](#) weights, the difference being that the  $\alpha/m$  rejection level of the weighted Bonferroni is replaced by  $\alpha u$ . Finite sample results on FDR and power are obtained, and

asymptotic FDR control and optimality are proven. Oracle weights are of limited interest in practice because they assume the knowledge of some parameters that are unknown in practice. In the same group context as [Hu et al. \(2010\)](#), a recent work of [Ignatiadis et al. \(2016\)](#) presents a procedure which is equivalent to a MWBH where data-driven weight functions maximizing the number of rejection for each  $u$ . With  $w_g$  being the weight given to all  $p_i$  such that  $i \in \mathcal{G}_g$ , we have:

$$(w_g(u))_{1 \leq g \leq G} = \arg \max_{\substack{w_g \geq 0 \\ \sum_{g=1}^G \pi_g w_g = 1}} \sum_{g=1}^G |\{i \in \mathcal{G}_g : p_i \leq \alpha w_g u\}|. \quad (1.2.10)$$

Asymptotic FDR control is provided but there are no power considerations. My contribution in Chapter 2 aims to fill the gap between [Roquain and van de Wiel \(2009\)](#) and [Ignatiadis et al. \(2016\)](#).

### 1.2.4 Discrete tests

As we have seen in Remark 1.2.1, when the test statistic is continuous, the corresponding  $p$ -value has a uniform distribution under the null, and classical methods are precisely calibrated with respect to this uniform distribution (see Proposition 1.2.4 and its equality case). However,  $p$ -values are only super-uniform in general, and when they are built upon a discrete statistic, their distribution can be really far from uniform, hence classical methods like BH become overly conservative. For BH, the difference lies in equation (1.2.9). As an example, assume  $X = (X_i)_{1 \leq i \leq m}$  where the  $X_i$  are independent integer variables following an hypergeometric distribution under the null. Assume all nulls are true and that the parameters of the distribution are 30, 30 and 10, which means that the distribution of  $X_i$  can be realized as the number of white balls drawn without replacement when drawing 10 balls from an urn with 30 white balls and 30 black balls. The cdf of the corresponding  $p$ -value distribution (assuming that the test statistic  $S_i$  is the identity) is plotted in Figure 1.6. We clearly see how small the cdf can be compared to the identity function (which is the cdf of a uniform). The FDR (computed with  $10^4$  replications) of the BH procedure applied to both uniform  $p$ -values and  $p$ -values drawn from  $X$  is displayed in Figure 1.7, for different values of  $m$  and for  $\alpha = 0.1$ . As the FDR of BH with uniform  $p$ -values is equal to  $\alpha$ , which is in line with Proposition 1.2.4, the FDR of BH with discrete  $p$ -values is much lower which indicates an excess of conservativeness.

One idea to reduce this conservativeness, developed in [Tarone \(1990\)](#) (and hinted in [Mantel, 1980](#)), lies in the fact that the smallest value of the support of a  $p$ -value under the null may exceed  $\alpha$ . Hence this  $p$ -value may not be counted when applying

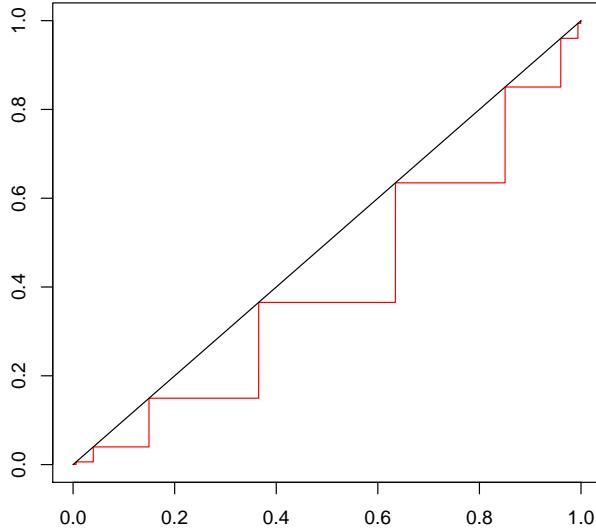


Fig. 1.6 Cdf of uniform (in black) and of discrete (in red)  $p$ -value distribution. The discrete distribution comes from a test statistic following an hypergeometric distribution of parameters 30, 30 and 10.

a Bonferroni-like correction, dividing  $\alpha$  by a number smaller than  $m$ , thus increasing power. To formalize this idea, for each  $i \in \{1, \dots, m\}$ , let  $\bar{S}_i$  be the support of its discrete distribution under the null, and let  $\bar{s}_i = \min \bar{S}_i$ . Let  $m(1)$  be the number of elements  $i$  such that  $\bar{s}_i \leq \alpha$ :

$$m(1) = |\{i : \bar{s}_i \leq \alpha\}|.$$

Then the procedure  $R_{m(1)} = \{i : p_i \leq \alpha/m(1)\}$  rejecting  $p$ -values below the threshold  $\alpha/m(1)$  is a valid FWER-controlling procedure at level  $\alpha$  (this is proven below). This means that hypotheses  $i$  such that  $\bar{s}_i > \alpha$  are not relevant when applying the Bonferroni correction, since they cannot be rejected in any case if they are true. But we can go further, since there may exist some  $i$  such that  $\bar{s}_i \leq \alpha$  but  $m(1)\bar{s}_i > \alpha$ . Such an  $i$  is also irrelevant since it cannot be rejected by  $R_{m(1)}$  if it is a true null. Hence there is a sequential refinement that can be written like this: for each  $k \geq 1$ , let

$$m(k) = \left| \left\{ i : \bar{s}_i \leq \frac{\alpha}{k} \right\} \right|.$$

Let  $K = \min\{k \geq 1 : m(k) \leq k\}$ . It is well defined because  $m(k) \leq m(1)$  for all  $k \geq 1$  thus  $m(m(1)) \leq m(1)$ . Then the Tarone-Bonferroni (TB) procedure  $R_K = \{i : p_i \leq \alpha/K\}$

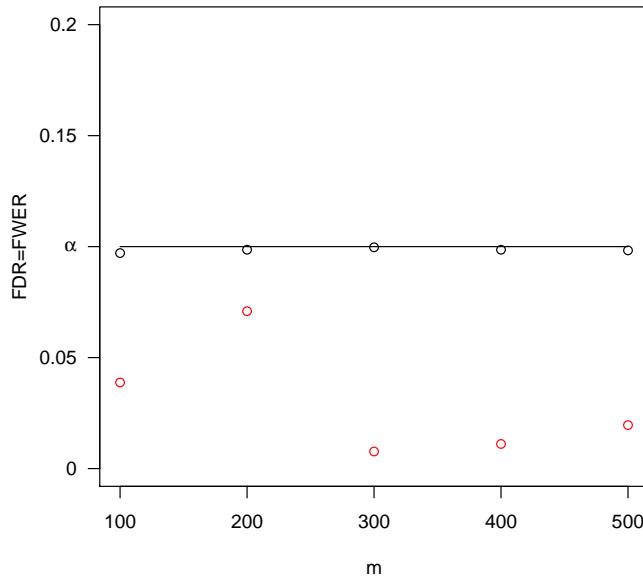


Fig. 1.7 FDR of BH procedure applied to independent  $p$ -values following a continuous (in black) or discrete (in red) distribution, for  $m \in \{100, 200, 300, 400, 500\}$  and  $\alpha = 0.1$ .

is a valid FWER-controlling procedure at level  $\alpha$ , more powerful than  $R_{m(1)}$ , the latter being itself more powerful than  $R_{\text{Bonf}}$ .

**Proposition 1.2.5.** *For each  $k \leq 1$  such that  $m(k) \leq k$ , the procedure  $R_k = \{i : p_i \leq \alpha/k\}$  controls the FWER at level  $\alpha$ :*

$$\forall P \in \mathcal{P}, \text{FWER}(R_k) \leq \alpha.$$

In particular,  $R_{m(1)}$  and  $R_K$  control the FWER at level  $\alpha$ .

*Proof.* First note that  $\bar{s}_i$  and  $m(k)$  are deterministic for all  $i$  and  $k$ , and so is  $K$ . Let  $P \in \mathcal{P}$ ,  $X \sim P$  and  $k$  such that  $m(k) \leq k$ . Then,

$$\begin{aligned} \text{FWER}(R_k) &= \mathbb{P}\left(\exists i \in \mathcal{H}_0 : p_i \leq \frac{\alpha}{k}\right) \\ &\leq \sum_{\substack{i \in \mathcal{H}_0 \\ \bar{s}_i \leq \alpha/k}} \mathbb{P}\left(p_i \leq \frac{\alpha}{k}\right) \\ &\leq \sum_{\substack{i : \bar{s}_i \leq \alpha/k}} \mathbb{P}\left(p_i \leq \frac{\alpha}{k}\right) \\ &\leq \left|\left\{i : \bar{s}_i \leq \frac{\alpha}{k}\right\}\right| \times \frac{\alpha}{k} = \alpha \frac{m(k)}{k} \leq \alpha. \end{aligned} \quad \square$$

Note that  $\bar{S}_i = [0, 1]$ ,  $\bar{s}_i = 0$  and  $m(k) = m$  for all  $k$  if the  $p$ -values are uniform under the null, hence the TB procedure reduces to the Bonferroni procedure with no power improvement. [Tarone \(1990\)](#) suggested that the TB procedure can be further improved, based on the following remark: for  $i$  such that  $\bar{s}_i \leq \alpha/K$ , let  $\eta_i$  be the largest element of  $\bar{S}_i$  which is less than or equal to  $\alpha/K$ . Then:

$$\forall P \in \mathcal{P}, \text{FWER}(R_k) \leq \sum_{\bar{s}_i \leq \alpha/K} \eta_i,$$

because  $\mathbb{P}(p_i \leq \frac{\alpha}{K}) = \mathbb{P}(p_i \leq \eta_i) \leq \eta_i$  (with equality most often, see Equation 3.2.3). Hence, if  $\sum_{\bar{s}_i \leq \alpha/K} \eta_i < \alpha$  (which is likely to happen), some refinement may be conducted. [Gilbert \(2005\)](#) suggested to simply search for the largest  $\alpha^* \geq \alpha$  such that  $\sum_{\bar{s}_i \leq \alpha^*/K^*} \eta_i^* \leq \alpha$ , where  $\eta_i^*$  is the largest element of  $\bar{S}_i$  which is less than or equal to  $\alpha^*/K^*$ ,  $K^*$  being the largest  $k \geq 1$  such that  $m^*(k) \leq k$ , and  $m^*(k) = |\{i : \bar{s}_i \leq \alpha^*/k\}|$ . The TB procedure run at level  $\alpha^*$  then controls the FWER at level  $\alpha$  (note that  $\alpha^*$  is deterministic). Then [Gilbert \(2005\)](#) also proposed modified BH and BY procedures (see Section 1.2.2) by simply replacing  $m$  by  $m(K)$ . That is, the Tarone-BH (TBH) procedure is the step-up procedure with critical values  $\tau_k = \alpha k / m(K)$ , and the Tarone-BY (TBY) procedure is the step-up procedure with critical values  $\tau_k = \alpha k / (m(K) H_{m(K)})$ . FDR control at level  $\alpha$  is achieved when the  $p$ -values are PRDS for TBH, and under any dependence for TBY. Furthermore, the same kind of improvement as for TB can be applied to TBH by deriving an appropriate  $\alpha^*$ .

Another direction to account for the discreteness of the  $p$ -values is to deflate them in an appropriate fashion. Assume that  $S_i$  is the identity and that  $H_{0,i}$  can be identified to a singleton of  $\mathcal{P}_i$  as in Remark 1.2.1. Then, with a slight notation abuse, the  $p$ -value  $p_i(X) = p_i(X_i)$  is a function of  $X_i$  via the functional  $p_i : x \mapsto \mathbb{P}_{Y \sim H_{0,i}}(Y \geq x)$ . The idea is

to replace the  $p$ -value  $p_i(X_i)$  by the randomized  $p$ -value  $\tilde{p}_i(X_i, U_i)$  where  $U = (U_1, \dots, U_m)$  is a vector of i.i.d. uniform variables which is independent from  $X$ , and

$$\tilde{p}_i : (x, u) \mapsto p_{i-}(x) + u(p_i(x) - p_{i-}(x)), \quad (1.2.11)$$

with  $p_{i-} : x \mapsto \mathbb{P}_{Y \sim H_{0,i}}(Y > x)$ . Randomized  $p$ -values are described in [D. R. Cox \(1974, Section 4.5\)](#) (while the idea of randomization can be traced back to [Cohen, 1958](#)). Note that  $\tilde{p}_i(X_i, U_i) \leq p_i(X_i)$  almost surely. The most interesting property of the randomized  $p$ -value is that they are uniform under the null.

**Lemma 1.2.3.** *Assume  $X_i \sim H_{0,i}$  and that the support of  $X_i$  is discrete. Then  $\tilde{p}_i(X_i, U_i) \sim \mathcal{U}([0, 1])$ .*

*Proof.* Obviously,  $\mathbb{P}(\tilde{p}_i(X_i, U_i) \leq 1) = 1$ . Let  $u \in [0, 1]$ . Let  $\text{supp}(X_i)$  be the discrete support of the distribution of  $X_i$ . Then,

$$\begin{aligned} \mathbb{P}(\tilde{p}_i(X_i, U_i) \leq u) &= \mathbb{E}[\mathbb{P}(\tilde{p}_i(X_i, U_i) \leq u | X_i)] \\ &= \mathbb{E}[\mathbb{P}(p_{i-}(X_i) + U_i(p_i(X_i) - p_{i-}(X_i)) \leq u | X_i)] \\ &= \mathbb{E}\left[\mathbb{1}_{\{p_{i-}(X_i) \leq u < p_i(X_i)\}} \frac{u - p_{i-}(X_i)}{p_i(X_i) - p_{i-}(X_i)}\right] + \mathbb{E}\left[\mathbb{1}_{\{p_i(X_i) \leq u\}}\right] \\ &= \sum_{x \in \text{supp}(X_i)} \mathbb{1}_{\{p_{i-}(x) \leq u < p_i(x)\}} (u - p_{i-}(x)) + \mathbb{P}(p_i(X_i) \leq u), \end{aligned}$$

because  $p_i(x) - p_{i-}(x) = \mathbb{P}_{Y \sim H_{0,i}}(Y = x)$  and  $X_i \sim H_{0,i}$ . Let  $\bar{x}$  the only element of  $\text{supp}(X_i)$  such that  $p_{i-}(\bar{x}) \leq u < p_i(\bar{x})$ . Note that  $X_i \leq \bar{x}$  implies  $p_i(X_i) \geq p_i(\bar{x}) > u$  because  $p_i(\cdot)$  is nonincreasing. Furthermore,  $X_i > \bar{x}$  implies  $p_i(X_i) < p_i(\bar{x})$  because  $p_i(\cdot)$  is decreasing on  $\text{supp}(X_i)$ . This in turn implies that  $p_i(X_i) \leq p_{i-}(\bar{x}) \leq u$ . Hence  $p_i(X_i) \leq u$  if and only if  $X_i > \bar{x}$  and we can conclude:

$$\begin{aligned} \mathbb{P}(\tilde{p}_i(X_i, U_i) \leq u) &= u - p_{i-}(\bar{x}) + \mathbb{P}(X_i > \bar{x}) \\ &= u - p_{i-}(\bar{x}) + p_{i-}(\bar{x}) = u. \end{aligned}$$

because  $X_i \sim H_{0,i}$ . □

This allows to use classical procedures like Bonferroni and BH with randomized  $p$ -value without loss of power due to discreteness (the FDR/FWER control holding unconditionally on the  $U$ ). However, they are often criticized because they lead to a random output which cannot be easily interpreted by the practitioner. To circumvent this interpretation caveat, [Kulinskaya and Lewin \(2009\)](#) defines variants of Bonferroni

and BH procedures, called “fuzzy”, which exploit that the difference  $p_i(X_i) - p_{i-}(X_i)$  is positive in the case of discrete tests, without drawing  $\tilde{p}_i(X_i, U_i)$ . The concept of “fuzziness” or “abstract randomization” appears in [Geyer and Meeden \(2005\)](#) and consists in accepting some hypotheses, rejecting others, and allowing some hypotheses for which we do not take an immediate decision, only reporting a probability of rejection. As noted by [Habiger \(2015\)](#), it is like computing randomized  $p$ -values without actually generating  $U$ , which Habiger calls abstract randomized  $p$ -values. As an example, let us take the fuzzy Bonferroni procedure of [Kulinskaya and Lewin \(2009\)](#). Each hypothesis such that  $p_{i-} \geq \alpha/m$  is accepted and each hypothesis such that  $p_i \leq \alpha/m$  is rejected, but the case of hypotheses such that  $p_{i-} < \alpha/m < p_i$  remains fuzzy and only the probability of rejection, namely

$$\tau_{\text{Bonf}}(X_i) = \frac{\alpha/m - p_{i-}}{p_i - p_{i-}},$$

is reported. We clearly see that  $U_i$  did not need to be generated for non fuzzy  $i$  since the decision of accepting or rejecting  $H_{0,i}$  can be made without it. The fuzzy Bonferroni procedure becomes the randomized Bonferroni procedure if, additionally, we generate  $U_i$  for each fuzzy  $i$  and reject or accept  $H_{0,i}$  based on  $U_i \leq \tau_{\text{Bonf}}(X_i)$  or  $U_i > \tau_{\text{Bonf}}(X_i)$ .

Another variant of the usage of the  $\tilde{p}_i(\cdot, \cdot)$  function is to define the mid  $p$ -values  $\tilde{p}_i(X_i, 1/2)$  (see e.g. [Agresti, 2002](#), Note 1.5, which also criticizes randomized  $p$ -values). Simulation studies conducted by [Ahmed et al. \(2010\)](#) suggested that using mid  $p$ -values instead of  $p$ -values in the discrete case can lead to more detections in an FDR control framework for pharmacovigilance data. [Heller and Gur \(2011\)](#) showed that the FDR of the BH procedure used with mid  $p$ -values (midBH) is closer to  $\alpha m_0/m$  than the FDR of BH. However, midBH can be anticonservative, as the FDR of midBH can be  $> \alpha$ , although [Heller and Gur \(2011\)](#) also showed that the FDR of midBH is  $\leq 2\alpha$ . [Habiger \(2015\)](#) provides an unified framework to compare mid, randomized, and abstract randomized  $p$ -values.

Step-up and step-down procedures with critical values accounting for discreteness have also been studied. For example, [Heller and Gur \(2011\)](#) presented the discrete Benjamini-Liu (DBL) procedure, proved that it has more power than BL and that its FDR is controlled if the  $p$ -values are independent. The DBL procedure is the step-down procedure with critical values  $\tau_k$  defined recursively by  $\tau_0 = 0$  and, for  $1 \leq k \leq m$ ,

$$\tau_k = \max \left( \tau_{k-1}, \max \left\{ z \leq 1 : \frac{m-k+1}{m} \left( 1 - \prod_{j=k}^m (1 - F_{(j)}(z)) \right) \leq \alpha \right\} \right),$$

where  $F_i$  is the cdf of  $p_i$  under the null, and the notation  $(j)$  indicates the index of the  $j$ -th largest  $p$ -value, making the critical values random. It is simple to see that this is the discrete equivalent of BL, because if the  $p$ -values are uniform under the null then the above  $\tau_k$  becomes the critical values of BL. [Heyse \(2011\)](#) proposed a step-up procedure where the critical values are computed after having been transformed by the functional  $\bar{F}(\cdot) = m^{-1} \sum_{i=1}^m F_i(\cdot)$ . Note that both DBL and Heyse assume that the distributions under the null are known, which is usually the case with discrete tests. Let  $\mathcal{A} = \bigcup_{i=1}^m \mathcal{A}_i$  where  $\mathcal{A}_i$  is the discrete support of  $p_i$  (under both the null and the alternative). The critical values of the Heyse procedure are then:

$$\tau_k = \max\{t \in \mathcal{A} : \bar{F}(t) \leq \alpha k/m\}.$$

This corresponds to a pseudo-inversion of  $\bar{F}$  at each point  $\alpha k/m$ . The key idea is that  $\bar{F}(t) \leq t$  so the  $\tau_k$  are larger than  $\alpha k/m$  which yields more rejections than with the BH procedure. However we usually have that  $F_i(t) = t$  for  $t \in \mathcal{A}_i$ , hence, if the  $F_i$  are all equal, Heyse procedure is equivalent to BH (see [Heller and Gur, 2011](#), Proposition 2.3 or Lemma 3.3.1). However, if the  $F_i$  are heterogeneous,  $\bar{F}$  can be much smaller than the identity function and yield critical values strictly better than BH (see the figures of Chapter 3 for more details). Hence, combining discreteness and heterogeneity is a key to improve power. Nevertheless, the Heyse procedure may be anticonservative, as shown in [Heller and Gur \(2011\)](#), [Döhler \(2016, Appendix\)](#), or Appendix 3.B.1. We show that Heyse's idea may still be exploited to design step-up and step-down procedures which control the FDR and improve power when the tests are discrete with heterogeneous null distribution in Chapter 3.

## 1.3 Selective inference

Selective inference, or post hoc inference, is the area of statistics that aims at studying the detrimental effects of data snooping (see Section 1.1.2) by providing a valid statistical inference after one or several selection steps. To set these ideas on a common example, we can adopt a linear regression framework where an observation variable  $Y \in \mathbb{R}^n$  follows a Gaussian distribution  $\mathcal{N}(\mu, \sigma^2 I_n)$  and  $\mu$  is modeled as a linear function of a design matrix  $X \in \mathbb{R}^{n \times m}$ , hence we try to infer the linear coefficients  $\beta = (\beta_1, \dots, \beta_m)$ . In modern applications,  $m$  is typically larger  $n$ , while we assume that only few columns of  $X$  have a an effect, that is few linear coefficients are non zero. In this situation, a selection step is often conducted to reduce the number of coefficients, for example with

the lasso (Tibshirani, 1996). Formally, this selection step, also called “screening”, consists in computing a subset  $\widehat{M}$  of  $\mathbb{N}_m$ , also called a “model”. Classic statistical inference is then conducted to  $X_{\widehat{M}}$  and  $\beta_{\widehat{M}}$  (that is, only the columns of  $X$  and the coefficients of  $\beta$  that are indexed by an element of  $\widehat{M}$ ) instead of the whole  $X$  and  $\beta$ . Classic statistical methods lose their guarantees in this setting by not taking into the selection step which is often random and based on the data (meaning that, in the end, the data is used twice).

A first approach to selective inference is the simultaneous inference, in the sense that a guarantee is offered on all possible models  $M$  among a collection of models, simultaneously, which in turns implies a guarantee for the selected model  $\widehat{M}$ . This method can be traced back to Scheffé (1953) where a constant  $K_{\text{Sch}}$  is defined such that

$$\mathbb{P} \left( \sup_{x \in \text{span}(X)} |t_x| \leq K_{\text{Sch}} \right) \geq 1 - \alpha,$$

where

$$t_x = \frac{(Y - \mu)^T x}{\hat{\sigma} \|x\|}$$

follows a  $t$ -distribution and  $\hat{\sigma}$  is an appropriate estimator of  $\sigma$ . The sup in the equation above induces the simultaneous nature of  $K_{\text{Sch}}$  and allows to build confidence intervals at level  $(1 - \alpha)$  for any coefficient  $\beta_{j \cdot M}$ . Here  $j \in M$  and  $\beta_{j \cdot M}$  is the  $j$ -th coefficient of  $\beta_M = \mathbb{E} [\hat{\beta}_M]$ , where  $\hat{\beta}_M$  is the Ordinary Least Square (OLS) estimator of the regression of  $Y$  onto  $X_M$ , for any  $M \subset \mathbb{N}_m$ .

This first work has recently been refined by Berk et al. (2013), who noticed that the sup does not have to be over all  $\text{span}(X)$ . Only the elements  $x$  of the form  $X_{j \cdot M}$ ,  $M \subset \mathbb{N}_m$ ,  $j \in M$  can be considered, where  $X_{j \cdot M}$  is the residual vector of the orthogonal projection of the column  $X_j$  on the other columns of  $X_M$ . This results in a new constant  $K_{\text{PoSI}}$  which is smaller than  $K_{\text{Sch}}$  hence less conservative. The computation of  $K_{\text{PoSI}}$  is, however, a difficult computational problem. The  $K_{\text{PoSI}}$  constant is the subject of many recent works, see e.g. Bachoc et al. (2014, 2016, 2018).

Another direction for making selective inference comes from the natural idea of splitting the data  $Y = (Y_1, Y_2)$ , one half ( $Y_1$ ) of the data being used to select the model, and the other half ( $Y_2$ ) to infer the parameters, leading to the so-called data-splitting. This way, each data is used only once, which avoids the spurious conclusions that may result from using the same data many times. Data-splitting (also called sample-splitting) is the source of many studies and investigations, see e.g. Cox (1975); Picard and Berk (1990); Bühlmann and Mandozzi (2014); Dezeure et al. (2015). However, data-splitting

is generally undesirable (especially for testing) since it reduces by nature the sample and thus also the signal detection ability (see below for more details).

In line with the FDR definition, [Benjamini and Yekutieli \(2005\)](#) defined the False Coverage Rate (FCR) as an analogous type-I error criterion for confidence intervals constructed after selection of a given set of parameters:

$$\text{FCR} = \mathbb{E} \left[ \frac{|\{j \in \hat{M} : \beta_{j,\hat{M}} \notin C_{j,\hat{M}}\}|}{|\hat{M}| \vee 1} \right],$$

where  $C_{j,\hat{M}}$  is the confidence interval constructed for  $\beta_{j,\hat{M}}$ . [Benjamini and Yekutieli \(2005\)](#) provided a procedure to construct adjusted confidence intervals after selection which controls the FCR under an independence or PRDS assumption. This work has later been extended in [Benjamini and Bogomolov \(2014\)](#) where families of parameters, not individual parameters, are selected. In this paper, several error measures are explored, not only the FCR. A selection-adjusted procedure analogous to the one of [Benjamini and Yekutieli \(2005\)](#) is then presented.

Another series of works, reviewed by [Taylor and Tibshirani \(2015\)](#), focus on conditioning on the selection event, that is conditioning on the event  $\{\hat{M} = M\}$  or  $\{\hat{M} \in \mathbb{M}\}$  for a collection  $\mathbb{M}$  of models, to derive valid inference. Because this type of inference is not simultaneous over all  $M$  but conditional on only some  $M$ , this approach is expected to be less conservative than the simultaneous one of [Berk et al. \(2013\)](#). In [Lee et al. \(2016\)](#), exact inference conditional to  $\hat{M}$ , where  $\hat{M}$  is selected by the lasso, for a fixed penalization coefficient  $\lambda$ , is performed. First, the event  $\{\hat{M} = M\}$  is rewritten as an affine condition, which can be geometrically interpreted as a union of polyhedra. Then the exact distribution of the observations restricted to such polyhedra is shown to be a truncated Gaussian (assuming a gaussian model), which yields confidence intervals that are, as expected, tighter than in [Berk et al. \(2013\)](#). In [Tibshirani et al. \(2016\)](#), exact inference conditional is performed conditional to a subset selected at a given step of a sequential regression procedure like forward stepwise selection, least angle regression, or lasso (hence with a moving  $\lambda$ ), using the same geometrical tools and truncated Gaussian results as [Lee et al. \(2016\)](#). In [Fithian et al. \(2017\)](#), a more general point of view on inference conditional to a selected subset, or a selection variable, is developed, for exponential families, hence addressing more distribution families than just the Gaussian case. The main goal is to control the selective type I error with the theory of [Lehmann and Scheffé \(1955\)](#), and the former can be linked to pFCR (described as the pFDR but for the FCR) and FWER control. Some Monte Carlo sampling methods may be required to compute the conditional distributions. Additionally, the authors explain that conditioning on an

overly finer selection variable (in the sense that its associated filtration is finer) can lead to a waste of information in the inference step (see their Section 2.5). They illustrate this phenomenon with data-splitting, where  $Y_1$  is used to make the selection and  $Y_2$  to make the inference. From a conditional point of view, this means that the selection variable is  $Y_1$ , and that all information contained in  $Y_1$  is discarded for the inference step. However, usually the selection depends only on a given event  $A$ , so one could use only  $\mathbb{1}_A(Y_1)$  as the selection variable, instead of  $Y_1$ . The filtration associated to  $\mathbb{1}_A(Y_1)$  is coarser hence discards less information. Nonetheless, conditioning on a finer selection variable may be useful to avoid some computation issues. Next, in Choi et al. (2017), exact tests and confidence intervals for inferring the rank of a matrix in a PCA context are designed. The statistic used is inspired from the Kac-Rice test (Taylor et al., 2016) and is conditional to the selection of the first principal components, in a way similar to Tibshirani et al. (2016) for sequential regression procedures. The authors also underline the trade-off between detection power and computation capacity when choosing the conditioning event. Finally, Taylor and Tibshirani (2018) present procedures that extend Lee et al. (2016) to generalized linear model setting for  $\ell_1$  penalizations, but without formal proofs.

Now, let us formalize the above idea in a multiple testing context (see the setting in Section 1.2.1). A natural reinterpretation of simultaneous selective inference is that we may want to ensure a guarantee (in term of number of false positives) on any selected subset  $\hat{S}$  of hypotheses, by having a guarantee uniform over all possible subsets  $S$ . That is, we want to have a function  $\hat{V}$  that takes a subset  $S$  as input and return an upper-bound of  $V(S) = |S \cap \mathcal{H}_0|$ . The statistical guarantee then takes the following form:

$$\forall P \in \mathcal{P}, \mathbb{P}(\forall S \subset \mathbb{N}_m, V(S) \leq \hat{V}(S)) \geq 1 - \alpha, \quad (1.3.1)$$

for a given  $\alpha \in (0, 1)$ . Note that by dividing both terms of the inequality inside the probability by  $|S| \vee 1$ , the guarantee can be written in terms of FDP. Depending on the author,  $\hat{V}$  is called a confidence envelope or a post hoc bound. Early works focus on sets  $S$  that are selected after rejecting  $p$ -values that are smaller than a certain threshold, that is  $S$  is on the form  $\{i : p_i(X) \leq t\}$ ,  $t \in [0, 1]$  (Genovese and Wasserman, 2004; Meinshausen, 2006). More recent works deal with arbitrary  $S$ . A first series of works compute post hoc bounds from FWER control over a family of intersection hypotheses (Genovese and Wasserman, 2006; Goeman and Solari, 2011; Meijer et al., 2015), while Blanchard et al. (2018b) introduced a new methodology to derive post hoc bounds from a family  $\mathfrak{R} = ((R_k(X), \zeta_k(X))_{k \in \mathcal{K}}, R_k(X) \subset \mathbb{N}_m, \zeta_k(X) \in \mathbb{N}$ , which controls a Joint

Error Rate (JER). Namely,  $\mathfrak{R}$  controls the JER at level  $\alpha$  if

$$\forall P \in \mathcal{P}, \mathbb{P}(\forall k \in \mathcal{K}, V(R_k) \leq \zeta_k) \geq 1 - \alpha, \quad (1.3.2)$$

the main difference with (1.3.1) being that the control is not achieved for all  $S$  but only the  $R_k$ ,  $k \in \mathcal{K}$ , where the cardinal of  $\mathcal{K}$  is typically much smaller than the total number of subsets of  $\mathbb{N}_m$ . The JER control (1.3.2) allows to build post hoc bounds such as

$$V_{\mathfrak{R}}^*(S) = \max \{ |S \cap A|, A \subset \mathbb{N}_m, \forall k \in \mathcal{K}, |R_k \cap A| \leq \zeta_k \},$$

and

$$\bar{V}_{\mathfrak{R}}(S) = \min_{k \in \mathcal{K}} (\zeta_k + |S \setminus R_k|) \wedge |S|.$$

While  $V_{\mathfrak{R}}^*(S) \leq \bar{V}_{\mathfrak{R}}(S)$  without equality in general, equality can be achieved when the subset  $R_k$  are nested. The authors then introduce several methods to build  $R_k$  when  $\zeta_k = k - 1$ ,  $k \in \{1, \dots, K\}$ ,  $K \leq m$ . In this case, JER control can be interpreted as “joint  $k$ -FWER control”. Interestingly, the inversion method of [Genovese and Wasserman \(2006\)](#), the closed testing method of [Goeman and Solari \(2011\)](#) and the JER method of [Blanchard et al. \(2018b\)](#) can all be seen as particular cases one of each other. For example, the procedure of [Goeman and Solari \(2011\)](#) is based on closed testing (introduced by [Marcus et al., 1976](#)), returns a set of subsets that can be labeled  $R_k$  and that achieves JER control if we take  $\zeta_k = |R_k| - 1$ ; their derived bound is then exactly  $V_{\mathfrak{R}}^*(S)$ . See the supplement of [Blanchard et al. \(2018b, Section S-1\)](#) for a detailed comparison between all these approaches. However, the JER methodology has the advantage to infer a bound from a reference family, which is very convenient. Hence, our contribution of Chapter 4 will rely on this flexible JER approach.

## 1.4 Main contributions

The remaining of this manuscript presents the different works I did during the three years of my PhD preparation. This consists mainly in three chapters, each one dedicated to an area discussed above (weighting in Section 1.2.3, discrete tests in Section 1.2.4, and selective inference in Section 1.3). Those works have been supported by CNRS (PEPS FaSciDo), ANR-16-CE40-0019 (SansSouci project) and ANR-17-CE40-0001 (Basics project). While we tried to keep the notation as coherent as possible across the manuscript, note that some slight local variations may exist.

Chapter 2 presents a work available from arXiv and currently in revision (Durand, 2017), where an optimal data-driven weighting is presented, combining ideas from Roquain and van de Wiel (2009) and Zhao and Zhang (2014) to propose a generalization of the IHW procedure (Ignatiadis et al., 2016). The aforementioned works all present a gap of some sort, and we aim at filling these gaps while providing a unified approach. Zhao and Zhang (2014) choose a somewhat arbitrary threshold, while Ignatiadis et al. (2016) do not incorporate the heterogeneity of the  $\pi_{g,0}$  which can lead to a substantial loss of power (see Figure 2.6). Furthermore, these two works do not address power optimality in the sense defined by Roquain and van de Wiel (2009). Hence the need of our unified approach, named ADDOW (Adaptive Data Driven Optimal Weighting). Namely, in a setting where the null hypotheses are structured in known groups, a data-driven weight function is defined as

$$(w_g(u))_{1 \leq g \leq G} = \arg \max_{\substack{w_g \geq 0 \\ \sum_{g=1}^G \pi_g \hat{\pi}_{g,0} w_g = 1}} \sum_{g=1}^G |\{i \in \mathcal{G}_g : p_i \leq \alpha w_g u\}|, \quad (1.4.1)$$

the difference between (1.2.10) and (1.4.1) being the addition of an estimator  $\hat{\pi}_{g,0}$  of  $\pi_{g,0}$ . ADDOW is the associated multi weighted BH procedure, and is then studied asymptotically, that is when  $m$  tends to infinity, assuming that  $\hat{\pi}_{g,0}$  converges in probability to some over-estimated value  $\bar{\pi}_{g,0} \geq \pi_{g,0}$  and that the  $p$ -values are weakly dependent (Storey et al., 2004). First, we prove the convergence of the data-driven weights to some oracle asymptotic weights, similar to the weights of Roquain and van de Wiel (2009). Then, we show the asymptotic FDR control at level  $\alpha$  (with some refinements, see Theorem 2.5.1). Note that the oracle asymptotic weights maximize the number of rejections (because the data-driven do so), but not necessarily the power, that is, the number of correct rejections (i.e. the number of true positives). By studying a condition on  $\bar{\pi}_{g,0}$  and  $\pi_{g,0}$  under which maximizing the power or the number of rejections is equivalent, the optimal asymptotic power of ADDOW is derived (see Theorem 2.5.2). This condition, called (ME), notably includes the case where  $\hat{\pi}_{g,0}$  is consistent, that is  $\bar{\pi}_{g,0} = \pi_{g,0}$ . When  $\bar{\pi}_{g,0} \neq \pi_{g,0}$ , however, our optimality result is restricted to a weighting class depending on  $\bar{\pi}_{g,0}$ . As IHW is a particular case of ADDOW where  $\hat{\pi}_{g,0} = 1$ , and because condition (ME) can be achieved in that setting, some results on the FDR and power of IHW are derived (see Corollary 2.5.1). Simulation studies showing the power improvement of ADDOW over existing procedures are provided.

Chapter 3 presents a published work (Döhler et al., 2018). This is a joint work with Sebastian Döhler and Etienne Roquain. The point is to iterate from the Heyse procedure

to provide new step-up and step-down procedures following Heyse's idea of using the heterogeneity and discreteness of the cdf  $F_i$ , but with proven FDR control. Recall that the critical values of the Heyse procedure are computed from the inversion of  $\bar{F}$  at values  $\alpha k/m$ ,  $1 \leq k \leq m$ . First, two modifications of  $\bar{F}$  are defined, namely  $\bar{F}_{\text{SU}}$  and  $\bar{F}_{\text{SD}}$ , defined by

$$\bar{F}_{\text{SU}}(t) = m^{-1} \sum_{i=1}^m \frac{F_i(t)}{1 - F_i(\tau_m)}, \quad t \in [0, 1],$$

and

$$\bar{F}_{\text{SD}}(t) = m^{-1} \sum_{i=1}^m \frac{F_i(t)}{1 - F_i(t)}, \quad t \in [0, 1],$$

where  $\tau_m = \max\{t \in \mathcal{A} : \bar{F}_{\text{SD}}(t) \leq \alpha\}$ . The Heterogenous Step-Up (HSU) is the step-up with critical values  $\tau_k$  where  $\tau_k$  is obtained by the inversion of  $\bar{F}_{\text{SU}}$  at values  $\alpha k/m$ ,  $1 \leq k \leq m-1$ . The Heterogenous Step-Down (HSD) is the step-down with critical values  $\tau_k$  where  $\tau_k$  is obtained by the inversion of  $\bar{F}_{\text{SD}}$  at values  $\alpha k/m$ ,  $1 \leq k \leq m$ . Then, by analogy with the adaptive procedures of [Blanchard and Roquain \(2009\)](#) and [Gavrilov et al. \(2009\)](#), two adaptive versions are introduced, called AHSU and AHSD, respectively. We show that the four new procedures control the FDR under independence of the  $p$ -values. This is a direct consequence of Theorem 3.4.1 which provides new bounds for the FDR of step-up or step-down procedures. The latter has the important specificity of being valid for any sequence of critical values  $\tau$  and for any  $p$ -value null distributions (even not super-uniform). Interestingly, these bounds have applications beyond the discrete setting, and allow to recover some weighting results of [Roquain and van de Wiel \(2009\)](#). Real data applications and simulation studies compare our new procedures with many procedures of the literature calibrated for continuous or discrete tests, and show the power improvement that can be obtained in various contexts. The new procedures are implemented in the R package `DiscreteFDR` available from CRAN ([Durand and Junge, 2018](#)). The manual of the package is provided in Appendix C.

Chapter 4 presents a joint work with Etienne Roquain, Pierre Neuvial, and Gilles Blanchard, available from arXiv ([Durand et al., 2018](#)). In the JER framework described in Section 1.3, we investigate new reference families and associated post hoc bounds by reversing the paradigm of [Blanchard et al. \(2018b\)](#). In the latter, the upper bounds  $\zeta_k$  were deterministic and fixed in advance ( $\zeta_k = k-1$ ), and the regions  $R_k$  were random and computed accordingly. Instead, in Chapter 4, the regions  $R_k$  are deterministic and given in advance, and we upper bound the number of false positives in each region with a random confidence bound  $\zeta_k$ . By assuming the independence of the  $p$ -values, we deduce  $\zeta_k$  from the Dvoretzky-Kiefer-Wolfowitz-Massart (DKWM) inequality ([Dvoretzky et al.,](#)

1956; Massart, 1990). The latter is proven to be uniformly better than the confidence bound of Genovese and Wasserman (2004). Furthermore, if the regions  $R_k$  follow the Forest structure defined by

$$\forall k, k' \in \mathcal{K}, \quad R_k \cap R_{k'} \in \{R_k, R_{k'}, \emptyset\},$$

that is, two regions are either disjoint or nested, we provide a simple algorithm to compute  $V_{\mathfrak{R}}^*(S)$ , based on new interpolation bounds (see Equations (4.2.5) and (4.2.6) and Theorem 4.3.1 for details). Theorem 4.3.1 also recovers the nested case of Blanchard et al. (2018b, Proposition 2.5). It should be noted that the computation  $V_{\mathfrak{R}}^*(S)$  is difficult in general (Blanchard et al., 2018b, Proposition 2.3). When the signal is locally structured, that is the elements of  $\mathcal{H}_1$  are grouped inside some regions  $R_k$ , and the regions follow the aforementioned Forest structure, our new derived post hoc bounds are expected to perform better than the usual Simes bound of Goeman and Solari (2011). Some numerical experiments support this claim while also suggesting the use of an hybrid bound combining the two approaches. I implemented the new procedures in R functions which were added to the existing `sansSouci` package (Blanchard et al., 2018a), available from [github](#), which already implemented the methods of Blanchard et al. (2018b). Let us note that some complements for this work (including alternative procedures or counterexamples), that were discarded from the arXiv version, can be found in Appendix B.

Finally, a short conclusion briefly exposing possible further developments of these works is provided after Chapter 4.

## 1.5 Additional contributions

During these three years, I have also written technical comments on three papers. These notes fix some errors that I have identified in these papers, which are key bibliographic references for my thesis. They can be found in Appendix A. I have been part of the writing of a published paper (Chatelain et al., 2018) based on a previous work I made as an intern in bioinformatics at Sanofi. Finally, with Sabin Lessard, we finished the revision of our common paper, now published (Durand and Lessard, 2016), which was written after a previous work I made as an intern in population genetics at Centre de Recherches Mathématiques (Montréal). The latter is attached in Appendix D and has been supported by NSERC of Canada, Grant no 8833.

# Chapter 2

## Adaptive $p$ -value weighting with power optimality

This chapter corresponds to a paper currently in revision for *Electronic Journal of Statistics*. This is an updated version of the arXiv preprint ([Durand, 2017](#)), which incorporates improved assumptions (condition (ME)) and additional simulations.

**Abstract** Weighting the  $p$ -values is a well-established strategy that improves the power of multiple testing procedures while dealing with heterogeneous data. However, how to achieve this task in an optimal way is rarely considered in the literature. This paper contributes to fill the gap in the case of group-structured null hypotheses, by introducing a new class of procedures named ADDOW (for Adaptive Data Driven Optimal Weighting) that adapts both to the alternative distribution and to the proportion of true null hypotheses. We prove the asymptotical FDR control and power optimality among all weighted procedures of ADDOW, which shows that it dominates all existing procedures in that framework. Some numerical experiments show that the proposed method preserves its optimal properties in the finite sample setting when the number of tests is moderately large.

### 2.1 Introduction

Recent high-throughput technologies bring to the statistical community new type of data being increasingly large, heterogeneous and complex. Addressing significance in such context is particularly challenging because of the number of questions that could naturally come up. A popular statistical method is to adjust for multiplicity by controlling the False Discovery Rate (FDR), which is defined as the expected proportion of errors

among the items declared as significant. Once the amount of possible false discoveries is controlled, the question of increasing the power, that is the amount of true discoveries, arises naturally. In the literature, it is well-known that the power can be increased by clustering the null hypotheses into homogeneous groups. The latter can be derived in several ways:

- sample size: a first example is the well-studied data set of the Adequate Yearly Progress (AYP) study ([Rogosa, 2005](#)), which compares the results in mathematics tests between socioeconomically advantaged and disadvantaged students in Californian high school. As studied by [Cai and Sun \(2009\)](#), ignoring the sizes of the schools tends to favor large schools among the detections, simply because large schools have more students and not because the effect is stronger. By grouping the schools in small, medium, and large schools, more rejections are allowed among the small schools, which increases the overall detection capability. This phenomenon also appears in more large-scale studies, as in GWAS (Genome-Wide Association Studies) by grouping hypotheses according to allelic frequencies, ([Sun et al., 2006](#)) or in microarrays experiments by grouping the genes according to the DNA copy number status ([Roquain and van de Wiel, 2009](#)). Common practice is generally used to build the groups from this type of covariate.
- spatial structure: some data sets naturally involve a spatial (or temporal) structure into groups. A typical example is neuroimaging: in [Schwartzman et al. \(2005\)](#), a study compares diffusion tensor imaging brain scans on 15443 voxels of 6 normal and 6 dyslexic children. By estimating the densities under the null of the voxels of the front and back halves of the brain, some authors highlight a noteworthy difference which suggests that analysing the data by making two groups of hypotheses seems more appropriate, see [Efron \(2008b\)](#) and [Cai and Sun \(2009\)](#).
- hierarchical relation: groups can be derived from previous knowledge on hierarchical structure, like pathways for genetic studies, based for example on known ontologies (see e.g. [The Gene Ontology Consortium \(2000\)](#)). Similarly, in clinical trials, the tests are usually grouped in primary and secondary endpoints, see [Dmitrienko et al. \(2003\)](#).

In these examples, while ignoring the group structure can lead to overly conservative procedures, this knowledge can easily be incorporated by using weights. This method can be traced back to [Holm \(1979\)](#) who presented a sequentially rejective Bonferroni procedure that controls the Family-Wise Error Rate (FWER) and added weights to the

*p*-values. Weights can also be added to the type-I error criterion instead of the *p*-values, as presented in Benjamini and Hochberg (1997) with the so-called weighted FDR. Blanchard and Roquain (2008) generalized the two approaches by weighting the *p*-values and the criterion, with a finite positive measure to weigh the criterion (see also Ramdas et al. (2017) for recent further generalizations). Genovese et al. (2006) introduced the *p*-value weighted BH procedure (WBH) which has been extensively used afterwards with different choices for the weights. Roeder et al. (2006); Roeder and Wasserman (2009) have built the weights upon genomic linkage, to favor regions of the genome with strong linkage. Hu et al. (2010) calibrated the weights by estimating the proportion of true nulls inside each group (procedure named HZZ here). Zhao and Zhang (2014) went one step further by improving HZZ and BH with weights that maximize the number of rejections at a threshold computed from HZZ and BH. They proposed two procedures Pro1 and Pro2 shown to control the FDR asymptotically and to have a better power than BH and HZZ.

However, the problem of finding optimal weights (in the sense of achieving maximal averaged number of rejected false nulls) has been only scarcely considered in the literature. For FWER control and Gaussian test statistics, Wasserman and Roeder (2006) designed oracle and data-driven optimal weights, while Dobriban et al. (2015) considered a Gaussian prior on the signal. For FDR control, Roquain and van de Wiel (2009) and Habiger (2014) designed oracle optimal weights by using the knowledge of the distribution under the alternative of the hypotheses. Unfortunately, this knowledge is not reachable in practice. This leads to the natural idea of estimating the oracle optimal weights by maximizing the number of rejections. This idea has been followed by Ignatiadis et al. (2016) with a procedure called IHW. While they proved that IHW controls asymptotically the FDR, its power properties have not been considered. In particular, it is unclear whether maximizing the overall number of rejections is appropriate in order to maximize power.

In this paper, we present a general solution to the problem of optimal data-driven weighting of BH procedure in the case of grouped null hypotheses. The new class of procedures is called ADDOW (for Adaptive Data-Driven Optimal Weighting). It relies on the computation of weights that maximize the number of detections at any rejection threshold, combined with the application of a step-up procedure with those weights. This is similar to IHW, however, by taking a larger weight space thanks to the use of estimators of true null proportion in each group, we allow for larger weights, hence more detections. With mild assumptions, we show that ADDOW asymptotically controls the FDR and has optimal power among all weighted step-up procedures. Interestingly, our study shows that the heterogeneity with respect to the proportion of true nulls should be

taken into account in order to attain optimality. This fact seems to have been ignored so far: for instance we show that IHW has optimality properties when the true nulls are evenly distributed across groups but we also show that its performance can quickly deteriorate otherwise with a numerical counterexample.

In Section 2.2, we present the mathematical model and assumptions. In Section 2.3, we define what is a weighting step-up procedure. In Section 2.4, we introduce ADDOW along with a stabilized version, designed to deal with the overfitting problem due to weak signal. Section 2.5 provides our main theoretical results. Our numerical simulations are presented in Section 2.6, while we conclude in Section 2.7 with a discussion. The proofs of the two main theorems are given in Section 2.8 and more technical results are deferred to appendix. Let us underline that an effort has been made to make the proofs as short and concise as possible, while keeping them as clear as possible.

In all the paper, the probabilistic space is denoted  $(\Omega, \mathcal{A}, \mathbb{P})$ . The notations  $\xrightarrow{a.s.}$  and  $\xrightarrow{\mathbb{P}}$  stand for the convergence almost surely and in probability.

## 2.2 Setting

### 2.2.1 Model

We consider the following stylized grouped  $p$ -value modeling: let  $G \geq 2$  be the number of groups. In each group  $g \in \{1, \dots, G\}$ , let  $(H_{g,1}, H_{g,2}, \dots)$  be some binary variables corresponding to the null hypotheses to be tested in this group, with  $H_{g,i} = 0$  if it is true and  $= 1$  otherwise. Consider in addition  $(p_{g,1}, p_{g,2}, \dots)$  some random variables in  $[0, 1]$  where each  $p_{g,i}$  corresponds to the  $p$ -value testing  $H_{g,i}$ .

We make the following marginal distributional assumptions for  $p_{g,i}$ .

**Assumption 2.2.1.** If  $H_{g,i} = 0$ ,  $p_{g,i}$  follows a uniform distribution on  $[0, 1]$ .

We denote by  $U : x \mapsto \mathbf{1}_{\{x>0\}} \times \min(x, 1)$  its cumulative distribution function (c.d.f.).

**Assumption 2.2.2.** If  $H_{g,i} = 1$ ,  $p_{g,i}$  follows a common distribution corresponding to c.d.f.  $F_g$ , which is strictly concave on  $[0, 1]$ .

In particular, note that the  $p$ -values are assumed to have the same alternative distribution within each group. Note that the concavity assumption is mild (and imply continuity on  $\mathbb{R}$  as proven in Lemma 2.A.1 for the sake of completeness). Furthermore, by concavity,  $x \mapsto \frac{F_g(x) - F_g(0)}{x - 0}$  has a right limit in 0 that we denote by  $f_g(0^+) \in [0, \infty]$ , and  $x \mapsto \frac{F_g(x) - F_g(1)}{x - 1}$  has a left limit in 1 that we denote by  $f_g(1^-) \in [0, \infty]$ .

Above, we considered an infinite set of hypotheses/ $p$ -values because our study will be asymptotic in the number of tests  $m$ . At step  $m$ , we observe the  $p$ -values  $p_{g,i}$ ,  $g \leq G$ ,  $i \leq m_g$  where the  $m_g$  are non-decreasing integer sequences depending on  $m$  and such that  $\sum_{g=1}^G m_g = m$ . Let us emphasize that  $G$  is kept fixed throughout the paper. Note also  $m_{g,1} = \sum_{i=1}^{m_g} H_{g,i}$  the number of false nulls and  $m_{g,0} = m_g - m_{g,1}$  the number of true nulls in group  $g$ .

**Assumption 2.2.3.** There exists  $\pi_g > 0$  and  $\pi_{g,0} > 0$  such that for all  $g$ ,  $m_g/m \rightarrow \pi_g$  and  $m_{g,0}/m_g \rightarrow \pi_{g,0}$  when  $m \rightarrow \infty$ . Additionally, for each  $g$ ,  $\pi_{g,1} = 1 - \pi_{g,0} > 0$ .

The above assumption means that, asymptotically, no group, and no proportion of signal or sparsity, is vanishing. We denote  $\pi_0 = \sum_g \pi_g \pi_{g,0}$  the mean of the  $\pi_{g,0}$ 's and denote the particular case where the nulls are evenly distributed in each group by (ED):

$$\pi_{g,0} = \pi_0, \quad 1 \leq g \leq G. \quad (\text{ED})$$

Let us finally specify assumptions on the joint distribution of the  $p$ -values.

**Assumption 2.2.4.** The  $p$ -values are weakly dependent within each group:

$$\frac{1}{m_{g,0}} \sum_{i=1}^{m_g} \mathbf{1}_{\{p_{g,i} \leq t, H_{g,i}=0\}} \xrightarrow{a.s.} U(t), \quad t \geq 0, \quad (2.2.1)$$

and

$$\frac{1}{m_{g,1}} \sum_{i=1}^{m_g} \mathbf{1}_{\{p_{g,i} \leq t, H_{g,i}=1\}} \xrightarrow{a.s.} F_g(t), \quad t \geq 0. \quad (2.2.2)$$

This assumption is mild and classical, see [Storey et al. \(2004\)](#). Note that weak dependence is trivially achieved if the  $p$ -values are independent. Note also that no assumption on the  $p$ -value dependence across groups is made.

## 2.2.2 $\pi_{g,0}$ estimation

**Assumption 2.2.5.** For each  $g$ , we have at hand an (over-)estimator  $\hat{\pi}_{g,0} \in (0, 1]$  of  $m_{g,0}/m_g$  such that  $\hat{\pi}_{g,0} \xrightarrow{\mathbb{P}} \bar{\pi}_{g,0}$  for some  $\bar{\pi}_{g,0} \geq \pi_{g,0}$ .

Let also  $\bar{\pi}_0 = \sum_g \pi_g \bar{\pi}_{g,0}$ . In the model of Section 2.2.1, this assumption can be fulfilled by using the estimators introduced in [Storey et al. \(2004\)](#):

$$\hat{\pi}_{g,0}(\lambda) = \frac{1 - \frac{1}{m_g} \sum_{i=1}^{m_g} \mathbf{1}_{\{p_{g,i} \leq \lambda\}} + \frac{1}{m}}{1 - \lambda}, \quad (2.2.3)$$

for a given parameter  $\lambda \in (0, 1)$  let arbitrary (the  $\frac{1}{m}$  is here just to ensure  $\hat{\pi}_{g,0}(\lambda) > 0$ ). It is easy to deduce from (2.2.1) and (2.2.2) that  $\frac{1}{m_g} \sum_{i=1}^{m_g} \mathbb{1}_{\{p_{g,i} \leq \lambda\}} \xrightarrow{a.s.} \pi_{g,0}\lambda + \pi_{g,1}F_g(\lambda)$ , which fulfills our condition:

$$\hat{\pi}_{g,0}(\lambda) \xrightarrow{a.s.} \pi_{g,0} + \pi_{g,1} \frac{1 - F_g(\lambda)}{1 - \lambda} \geq \pi_{g,0}.$$

While  $(\bar{\pi}_{g,0})_g$  is let arbitrary in our setting, some particular cases will be of interest in the sequel. First is the Evenly Estimation case (EE) one where

$$\bar{\pi}_{g,0} = \bar{\pi}_0, \quad 1 \leq g \leq G. \quad (\text{EE})$$

In that case, our estimators all share the same limit, and doing so they do not take in account the heterogeneity with respect to the proportion of true nulls. Case (EE) is relevant when the proportion of true nulls is homogeneous across groups, that is, when (ED) holds. A particular subcase of (EE) is the Non Estimation case (NE) where:

$$\hat{\pi}_{g,0} = 1 \text{ which implies } \bar{\pi}_{g,0} = 1, \quad 1 \leq g \leq G. \quad (\text{NE})$$

Case (NE) is basically the case where no estimation is intended, and the estimators are simply taken equal to 1.

Let us also introduce the Consistent Estimation case (CE) for which the estimators  $\hat{\pi}_{g,0}$  are assumed to be all consistent:

$$\bar{\pi}_{g,0} = \pi_{g,0}, \quad 1 \leq g \leq G. \quad (\text{CE})$$

While this corresponds to a favorable situation, this assumption can be met in classical situations, where  $f_g(1^-) = 0$  and  $\lambda = \lambda_m$  tends to 1 slowly enough in definition (2.2.3), see Lemma 2.A.2 in Section 2.8.3. The condition  $f_g(1^-) = 0$  is called “purity” in the literature. It has been introduced in Genovese and Wasserman (2004) and then deeply studied, along with the convergence of Storey estimators, in Neuvial (2013).

Finally, the main case of interest is the Multiplicative Estimation case (ME) defined as the following:

$$\exists C \geq 1, \quad \bar{\pi}_{g,0} = C\pi_{g,0}, \quad 1 \leq g \leq G. \quad (\text{ME})$$

Note that the constant  $C$  above cannot depend on  $g$ . Interestingly, the (ME) case covers the (CE) case (in this respect,  $C = 1$ ) and also the case where (ED) and (EE) both hold (in this respect,  $C = \frac{\bar{\pi}_0}{\pi_0}$ ). So the (ME) case can be viewed as a generalization of previous cases.

### 2.2.3 Criticality

Depending on the choice of  $\alpha$ , multiple testing procedures may make no rejection at all when  $m$  tends to  $\infty$ . This case is not interesting and we should focus on the other case. To this end, [Chi \(2007\)](#) introduced the notion of criticality: they defined some critical alpha level, denoted  $\alpha^*$ , for which BH procedure has no asymptotic power if  $\alpha < \alpha^*$ . [Neuvial \(2013\)](#) generalized this notion for any multiple testing procedure (see Section 2.5 therein) and also established a link between criticality and purity.

In Section 2.8.3, Definition 2.A.1, we define  $\alpha^*$  in our heterogeneous setting and will focus in our results on the supercritical case.

**Assumption 2.2.6.** The target level  $\alpha$  lies in  $(\alpha^*, 1)$ .

Lemma 2.A.3 states that  $\alpha^* < 1$  so such an  $\alpha$  always exists. While the formal definition of  $\alpha^*$  is reported to the appendix for the sake of clarity, let us emphasize that it depends on the parameters of the model, that are  $(F_g)_g$ ,  $(\pi_g)_g$  and  $(\pi_{g,0})_g$ , and on the parameters of the chosen estimators, that are  $(\bar{\pi}_{g,0})_g$ .

### 2.2.4 Leading example

While our framework allows a general choice for  $F_g$ , a canonical example that we have in mind is the Gaussian one-sided framework where the test statistic in group  $g$  follows  $\mathcal{N}(0, 1)$  under the null, while they follow  $\mathcal{N}(\mu_g, 1)$  under the alternative, for  $G$  unknown parameters  $\mu_g > 0$ .

Classically, this corresponds to consider  $p$ -values uniform under the null with alternative c.d.f. given by

$$F_g(\cdot) = \bar{\Phi}\left(\bar{\Phi}^{-1}(\cdot) - \mu_g\right),$$

with derivative

$$f_g(\cdot) = \exp\left(\mu_g\left(\bar{\Phi}^{-1}(\cdot) - \frac{\mu_g}{2}\right)\right),$$

where we denoted  $\bar{\Phi}(z) = \mathbb{P}(Z \geq z)$  for  $Z \sim \mathcal{N}(0, 1)$ . Hence  $F_g$  is strictly concave and this framework fulfills the assumptions of Section 2.2.1.

Furthermore we easily check that  $f_g(0^+) = \infty$ , so  $\alpha^* = 0$  (see Definition 2.A.1) and  $f_g(1^-) = 0$  which means that this framework is supercritical with purity and then can achieve consistent estimation ([CE](#)).

### 2.2.5 Criterion

The set of indices corresponding to true nulls is denoted by  $\mathcal{H}_0$ , that is  $(g, i) \in \mathcal{H}_0$  if and only if  $H_{g,i} = 0$ , and we also denote  $\mathcal{H}_1 = \mathcal{H}_0^c$ .

In this paper, we define a multiple testing procedure  $R$  as a set of indices that are rejected:  $p_{g,i}$  is rejected if and only if  $(g, i) \in R$ . The False Discovery Proportion (FDP) of  $R$ , denoted by  $\text{FDP}(R)$ , is defined as the number of false discoveries divided by the number of rejections if there are any, and 0 otherwise:

$$\text{FDP}(R) = \frac{|R \cap \mathcal{H}_0|}{|R| \vee 1}.$$

We denote  $\text{FDR}(R) = \mathbb{E}[\text{FDP}(R)]$  the FDR of  $R$ . Its power, denoted  $\text{Pow}(R)$ , is defined as the mean number of true positives divided by  $m$ :

$$\text{Pow}(R) = m^{-1} \mathbb{E}[|R \cap \mathcal{H}_1|].$$

Note that our power definition is slightly different than the usual one for which the number of true discoveries is divided by  $m_1 = \sum_g m_{g,1}$  instead of  $m$ . This simplifies our expressions (see Section 2.8.1) and does not have any repercussion because the two definitions differ only by a multiplicative factor converging to  $1 - \pi_0 \in (0, 1)$  when  $m \rightarrow \infty$ .

## 2.3 Weighting

### 2.3.1 Weighting the BH procedure

Say we want to control the FDR at level  $\alpha$ . Assume that the  $p$ -values are arranged in increasing order  $p_{(1)} \leq \dots \leq p_{(m)}$  with  $p_{(0)} = 0$ , the classic BH procedure consists in rejecting all  $p_{g,i} \leq \alpha \frac{\hat{k}}{m}$  where  $\hat{k} = \max \{k \geq 0 : p_{(k)} \leq \alpha \frac{k}{m}\}$ .

Take a nondecreasing function  $h$  defined on  $[0, 1]$  such that  $h(0) = 0$  and  $h(1) \leq 1$ , we denote  $\mathcal{I}(h) = \sup \{u \in [0, 1] : h(u) \geq u\}$ . Some properties of the functional  $\mathcal{I}(\cdot)$  are gathered in Lemma 2.A.4, in particular  $h(\mathcal{I}(h)) = \mathcal{I}(h)$ . We now reformulate BH with the use of  $\mathcal{I}(\cdot)$ , because it is more convenient when dealing with asymptotics. Doing so, we follow the formalism notably used in [Roquain and van de Wiel \(2009\)](#) and [Neuvial \(2013\)](#). Define the empirical function

$$\widehat{G} : u \mapsto m^{-1} \sum_{g=1}^G \sum_{i=1}^{m_g} \mathbf{1}_{\{p_{g,i} \leq \alpha u\}},$$

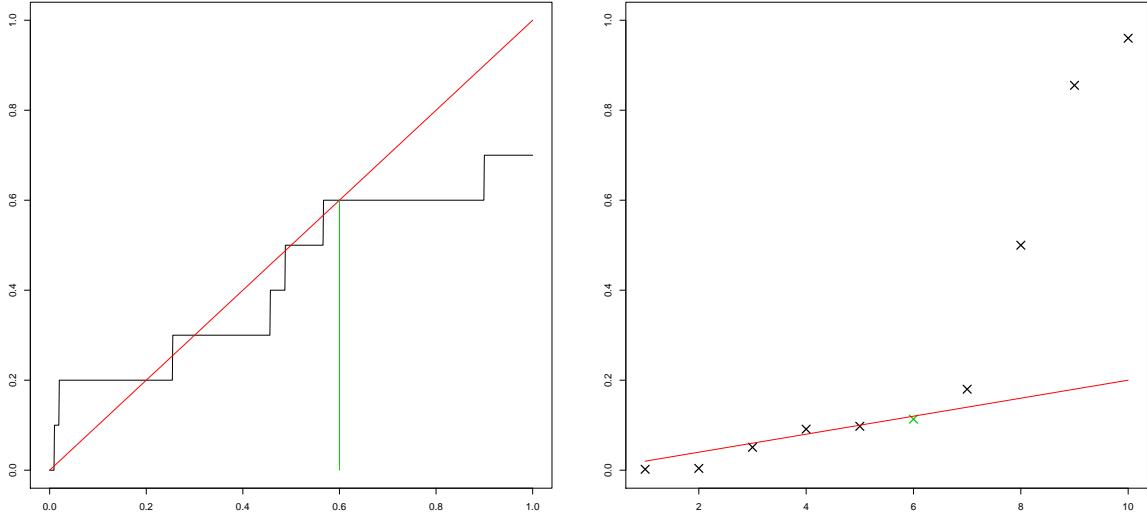


Fig. 2.1 The BH procedure applied to a set of 10  $p$ -values. Right plot: the  $p$ -values and the function  $k \mapsto \alpha k / m$ . Left plot: identity function and  $\hat{G}$ . Each plot shows that 6  $p$ -values are rejected.

then  $\hat{k} = m \times \mathcal{I}(\hat{G})$ . This is a particular case of Lemma 2.A.5. Note that  $\hat{G}(u)$  is simply the number of  $p$ -values that are less than or equal to  $\alpha u$ , divided by  $m$ .

The graphical representation of the two points of view for BH is depicted in Figure 2.1 with  $m = 10$ . The  $p$ -values are plotted on the right part of the figure along with the function  $k \mapsto \alpha k / m$  and we see that the last  $p$ -value under the line is the sixth one. On the left, the function  $\hat{G}$  corresponding to these  $p$ -values is displayed alongside the identity function, with the last crossing point being located between the sixth and seventh jumps, thus  $\mathcal{I}(\hat{G}) = 6/m$  and 6  $p$ -values are rejected.

The weighted BH (WBH) with weight vector  $w \in \mathbb{R}_+^G$  is defined by computing

$$\hat{G}_w : u \mapsto m^{-1} \sum_{g=1}^G \sum_{i=1}^{m_g} \mathbf{1}_{\{p_{g,i} \leq \alpha u w_g\}}$$

and rejecting all  $p_{g,i} \leq \alpha \mathcal{I}(G_w) w_g$ . We denote it  $\text{WBH}(w)$ . Note that  $w$  is authorized to be random, hence it can be computed from the  $p$ -values. In particular,  $\text{BH} = \text{WBH}(\mathbf{1})$  where  $\mathbf{1} = (1, \dots, 1) \in \mathbb{R}_+^G$ .

Following Roquain and van de Wiel (2009), to deal with optimal weighting, we need to further generalize WBH into a multi-weighted BH (MWBH) procedure by introducing a

weight function  $W : [0, 1] \rightarrow \mathbb{R}_+^G$ , which can be random, such that the following function:

$$\hat{G}_W : u \mapsto m^{-1} \sum_{g=1}^G \sum_{i=1}^{m_g} \mathbf{1}_{\{p_{g,i} \leq \alpha u W_g(u)\}}, \quad (2.3.1)$$

is nondecreasing. The resulting procedure rejects all the  $p$ -values such that  $p_{g,i} \leq \alpha \hat{u}_W W_g(\hat{u}_W)$  and is denoted MWBH( $W$ ) where, for the rest of the paper, we denote

$$\hat{u}_W = \mathcal{I}(\hat{G}_W), \quad (2.3.2)$$

and name it the step-up threshold. One different weight vector  $W(u)$  is associated to each  $u$ , hence the “multi”-weighting. Note that the class of MWBH procedures is a straightforward generalization of the class of WBH procedures because for any weight vector  $w$ ,  $w$  can be seen as a constant weight function  $u \mapsto w$  and  $\hat{G}_w$  is nondecreasing.

Note that, there is a simple way to compute  $\hat{u}_W$ . For each  $r$  between 1 and  $m$  denote the  $W(r/m)$ -weighted  $p$ -values  $p_{g,i}^{[r]} = p_{g,i}/W_g(r/m)$  (with the convention  $p_{g,i}/0 = \infty$ ), order them  $p_{(1)}^{[r]} \leq \dots \leq p_{(m)}^{[r]}$  and note  $p_{(0)}^{[r]} = 0$ . Then  $\hat{u}_W = m^{-1} \max \{r \geq 0 : p_{(r)}^{[r]} \leq \alpha \frac{r}{m}\}$  (this is Lemma 2.A.5).

As in previous works (see e.g. Genovese et al., 2006 or Zhao and Zhang, 2014), in order to achieve a valid FDR control, these procedures should be used with weights that satisfy some specific constraints. The following weight spaces will be used in the following of the paper:

$$\hat{K} = \left\{ w \in \mathbb{R}_+^G : \sum_g \frac{m_g}{m} \hat{\pi}_{g,0} w_g \leq 1 \right\}, \quad (2.3.3)$$

$$\hat{K}_{\text{NE}} = \left\{ w \in \mathbb{R}_+^G : \sum_g \frac{m_g}{m} w_g \leq 1 \right\}. \quad (2.3.4)$$

Note that  $\hat{K}$  may appear unusual because it depends on the estimators  $\hat{\pi}_{g,0}$ , however it is completely known and usable in practice. Some intuition about the choice of  $\hat{K}$  is given in next section. Note also that  $\hat{K} = \hat{K}_{\text{NE}}$  in the (NE) case.

Finally, for a weight function  $W$  and a rejection threshold  $u \in [0, 1]$ , we denote by  $R_{u,W}$  the double indexed procedure rejecting the  $p$ -values less than or equal to  $\alpha u W_g(u)$ , that is  $R_{u,W} = \{(g, i) : p_{g,i} \leq \alpha u W_g(u)\}$ . By (2.3.1), note that  $\hat{G}_W(u) = m^{-1} |R_{u,W}|$  (which means that  $\hat{G}_W(u)$  is the number of rejections of  $R_{u,W}$ , divided by  $m$ ) and that MWBH( $W$ ) can also be written as  $R_{\hat{u}_W, W}$ .

### 2.3.2 Choosing the weights

Take  $W$  and  $u$ , and let  $P_W^{(m)}(u) = \text{Pow}(R_{u,W})$ . We have

$$\begin{aligned} P_W^{(m)}(u) &= m^{-1} \mathbb{E} \left[ \sum_{g=1}^G \sum_{i=1}^{m_g} \mathbf{1}_{\{p_{g,i} \leq \alpha u W_g(u), H_{g,i}=1\}} \right] \\ &= \sum_{g=1}^G \frac{m_{g,1}}{m} F_g(\alpha u W_g(u)). \end{aligned}$$

Note that these relations are valid only if  $W$  and  $u$  are deterministic. In particular, they are not valid when used a posteriori with a data-driven weighting and  $u = \hat{u}_W$ .

In Roquain and van de Wiel (2009), the authors define the oracle optimal weight function  $W_{or}^*$  as:

$$W_{or}^*(u) = \arg \max_{w \in \hat{K}_{\text{NE}}} P_w^{(m)}(u). \quad (2.3.5)$$

Note that they defined  $W_{or}^*$  only in case (NE), but their definition easily extends to the general case as above, by replacing  $\hat{K}_{\text{NE}}$  by  $\hat{K}$ . They proved the existence and uniqueness of  $W_{or}^*$  when both (ED) and (NE) hold and that, asymptotically, MWBH( $W_{or}^*$ ) controls the FDR at level  $\pi_0 \alpha$  and has a better power than every MWBH( $w^{(m)}$ ) for  $w^{(m)} \in \hat{K}_{\text{NE}}$  some deterministic weight vectors satisfying a convergence criterion.

However, computing  $W_{or}^*$  requires the knowledge of the  $F_g$ , not available in practice, so the idea is to estimate  $W_{or}^*$  with a data driven weight function  $\widehat{W}^*$  and then apply MWBH with this random weight function. For this, consider the functional defined by, for any (deterministic) weight function  $W$  and  $u \in [0, 1]$ :

$$\begin{aligned} G_W^{(m)}(u) &= \mathbb{E} [\widehat{G}_W(u)] = \sum_{g=1}^G \left( \frac{m_{g,0}}{m} U(\alpha u W_g(u)) + \frac{m_{g,1}}{m} F_g(\alpha u W_g(u)) \right) \\ &= P_W^{(m)}(u) + \sum_{g=1}^G \frac{m_{g,0}}{m} U(\alpha u W_g(u)). \end{aligned} \quad (2.3.6)$$

$G_W^{(m)}(u)$  is the mean ratio of rejections for the procedure rejecting each  $p_{g,i} \leq \alpha u W_g(u)$ .  $P_W^{(m)}(u)$  is the rescaled mean of the number of true positives (i.e. the power) of this procedure while the other term in (2.3.6) is the rescaled mean of the number of its false positives.

Heuristically, maximizing  $G_W^{(m)}(u)$  should be close to maximizing  $P_W^{(m)}(u)$ : consider weight functions  $W$  such that  $\sum_g \frac{m_{g,0}}{m} W_g(u) = 1$  and then replace  $U(x)$  by  $x$  for all  $x \in \mathbb{R}_+$  (whereas  $U(x) = x$  only holds for  $x \leq 1$ ), then the right term of (2.3.6) becomes  $\alpha u \sum_g \frac{m_{g,0}}{m} W_g(u) = \alpha u$  and it does not depend on the weights. So  $P_W^{(m)}(u)$  is the only

term depending on  $W$  in (2.3.6) and maximizing  $P_W^{(m)}(u)$  or  $G_W^{(m)}(u)$  is the same. Now, we can evaluate the constraint on  $W$  by estimating  $\frac{m_{g,0}}{m} = \frac{m_g}{m} \frac{m_{g,0}}{m_g}$  by  $\frac{m_g}{m} \hat{\pi}_{g,0}$  (which leads to the weight space  $\hat{K}$  defined in equation (2.3.3)), and  $G_w^{(m)}(u)$  can be easily estimated by the (unbiased) estimator  $\hat{G}_w(u)$ . As a result, maximizing the latter in  $w$  should lead to good weights, not too far from  $W_{or}^*(u)$ .

Zhao and Zhang (2014) followed this heuristic by applying a two-stage approach to derive two procedures, named Pro1 and Pro2. Precisely, in the first stage they use the weight vectors  $\hat{w}^{(1)} = (\frac{1}{\hat{\pi}_0}, \dots, \frac{1}{\hat{\pi}_0})$ , where  $\hat{\pi}_0 = \sum_g \frac{m_g}{m} \hat{\pi}_{g,0}$ , and  $\hat{w}^{(2)}$  defined by  $\hat{w}_g^{(2)} = \frac{\hat{\pi}_{g,1}}{\hat{\pi}_{g,0}(1-\hat{\pi}_0)}$ , where  $\hat{\pi}_{g,1} = 1 - \hat{\pi}_{g,0}$ , and let  $\hat{u}_M = \max(\hat{u}_{\hat{w}^{(1)}}, \hat{u}_{\hat{w}^{(2)}})$ . In the second stage, they maximize  $\hat{G}_w(\hat{u}_M)$  over  $\hat{K}$ , which gives rise to the weight vector  $\hat{W}^*(\hat{u}_M)$  according to our notation. Then they define their procedures as the following:

$$\text{Pro 1} = R_{\hat{u}_M, \hat{W}^*(\hat{u}_M)},$$

and

$$\text{Pro 2} = \text{WBH}\left(\hat{W}^*(\hat{u}_M)\right).$$

Pro 2 comes from an additional step-up step compared to Pro 1, hence its rejection threshold,  $\hat{u}_{\hat{W}^*(\hat{u}_M)}$ , is larger than  $\hat{u}_M$  and allows for more detections. The caveat of this approach is that the initial thresholding, that is the definition of  $\hat{u}_M$ , seems somewhat arbitrary, which will result in sub-optimal procedures, see Corollary 2.5.3. As a side remark,  $\hat{w}^{(1)}$  and  $\hat{w}^{(2)}$  are involved in other procedures of the literature. The HZZ procedure of Hu et al. (2010) is  $\text{WBH}(\hat{w}^{(2)})$ , and  $\text{WBH}(\hat{w}^{(1)})$  is the classical Adaptive BH procedure (see e.g. Lemma 2 of Storey et al. (2004)) denoted here as ABH.

Ignatiadis et al. (2016) actually used the above heuristic with multi-weighting (while their formulation differs from ours) which consists in maximizing  $\hat{G}_w(u)$  in  $w$  for each  $u$ . However, their choice of the weight space is only suitable for the case (NE) and can make the heuristic break down, because in general the right term in (2.3.6) can still depend on  $w$ , see remark 2.3.1 below. In the next section, we take the best of the two approaches to attain power optimality with data-driven weighting. Let us already mention that the crucial point is Lemma 2.B.3, that fully justifies the heuristic, but only in case (ME). When (ME) does not hold, we must take care that the heuristic can fail for the same reason that it can fail with IHW. Thereby, in general, more detections do not necessarily imply more power.

*Remark 2.3.1.* In particular, we can compute numerical counterexamples where BH has larger asymptotic power than IHW. For example, if we break (ED) by taking a small  $\pi_{1,0}$  (almost pure signal) and a large  $\pi_{2,0}$  (sparse signal), along with a small group and a large

one ( $\pi_1$  much smaller than  $\pi_2$ ) and strong signal in both groups, we can achieve a larger power with BH than with IHW. Our interpretation is that, in that case, IHW slightly favors group 2 because of its size, whereas the oracle optimal favors group 1 thanks to the knowledge of the true parameters. BH, by weighting uniformly, does not favor any group, which allows its power to end up between the power of the oracle and the power of IHW. This example is studied in Section 2.6.3 and illustrated in Figure 2.6.

## 2.4 New procedures

### 2.4.1 ADDOW definition

We exploit the previous intuition and propose to estimate the oracle optimal weights  $W_{or}^*$  by maximizing in  $w \in \hat{K}$  the empirical counterpart to  $G_w^{(m)}(u)$ , that is  $\hat{G}_w(u)$ .

**Definition 2.4.1.** We call an adaptive data-driven optimal weight function a random function  $\hat{W}^* : [0, 1] \rightarrow \hat{K}$  such that for all  $u \in [0, 1]$ :

$$\hat{G}_{\hat{W}^*}(u) = \max_{w \in \hat{K}} \hat{G}_w(u).$$

Such maximum is guaranteed to exist because  $\{\hat{G}_w(u), w \in \hat{K}\}$  is a finite set. Indeed, it is a subset of  $\left\{\frac{k}{m}, k \in \llbracket 0, m \rrbracket\right\}$ . However, for a given  $u$ ,  $\hat{W}^*(u)$  may not be uniquely defined, hence there is no unique optimal weight function  $\hat{W}^*$  in general. So, in all the following, we fix a certain  $\hat{W}^*$ , and our results do not depend on the choice of  $\hat{W}^*$ . An important fact is that  $\hat{G}_{\hat{W}^*}$  is nondecreasing (see Lemma 2.A.6) so  $\hat{u}_{\hat{W}^*}$  exists and the corresponding MWBH procedure is well-defined:

**Definition 2.4.2.** The ADDOW procedure is the MWBH procedure using  $\hat{W}^*$  as the weight function, that is, ADDOW = MWBH  $(\hat{W}^*)$ .

One shall note that ADDOW is in fact a class of procedures depending on the estimators  $\hat{\pi}_{g,0}$  through  $\hat{K}$ . Its rationale is similar to IHW in that we intend to maximize the number of rejections, but incorporating the estimators  $\hat{\pi}_{g,0}$  allows for larger weights and more detections. Finally, note that, in the (NE) case, ADDOW reduces to IHW.

*Remark 2.4.1.* It turns out that ADDOW is equal to a certain WBH procedure. It comes from part 2 of the proof of Theorem 2.5.2 and Remark 2.8.2. Moreover, to every MWBH procedure, corresponds a WBH procedure with power higher or equal. This fact does not limit the interest of the MWBH class, because computing the dominating

WBH procedure of a given MWBH( $\widehat{W}$ ) procedure requires the knowledge of the step-up threshold  $\widehat{u}_{\widehat{W}}$  which is known by actually computing MWBH( $\widehat{W}$ ).

### 2.4.2 Stabilization for weak signal

Since ADDOW uses the data both through the  $p$ -values and the weights, this will result in a slight increase of the FDR, as we will see in the simulations (Section 2.6.2). This effect is close in spirit to the well known overfitting phenomenon. In our setting where the signal is strong enough, this drawback is proved to vanish when  $m$  is large enough, see the simulations and Theorem 2.5.1. However, the latter is not true for weak signal: if the data are close to be random noise, making the weight optimization leads ADDOW to assign its weighting budget at random, and giving large weights to the wrong groups increases the FDP. To circumvent this concern, we propose to stabilize ADDOW by using a pre-testing phase close in spirit to the Kolmogorov-Smirnov (KS) test ([Kolmogorov, 1933](#)) to determine whether the signal is weak or not and then to apply ADDOW only if the signal is large enough (and just apply BH otherwise).

Formally, we reject the hypothesis that the signal is weak if  $Z_m > q_{\beta,m}$ , where

$$Z_m = \sqrt{m} \sup_{w \in \hat{K}_{\text{NE}}} \sup_{u \in [0,1]} (\widehat{G}_w(u) - \alpha u),$$

and  $q_{\beta,m}$  is the  $(1 - \beta)$ -quantile of the distribution of  $Z_{0m}$ , where  $Z_{0m}$  is defined as

$$Z_{0m} = \sqrt{m} \sup_{u \in [0,1]} \left( m^{-1} \sum_{g=1}^G \sum_{i=1}^{m_g} \mathbb{1}_{\{U_{g,i} \leq \alpha u \widetilde{W}_g^*(u)\}} - \alpha u \right), \quad (2.4.1)$$

where the  $U_{g,i}$  are uniform variables over  $[0, 1]$  with, for all  $g$ ,  $U_{g,1}, \dots, U_{g,m_g}$  independent, and

$$\widetilde{W}^*(u) \in \arg \max_{w \in \hat{K}_{\text{NE}}} m^{-1} \sum_{g=1}^G \sum_{i=1}^{m_g} \mathbb{1}_{\{U_{g,i} \leq \alpha u w_g\}}.$$

$Z_{0m}$  is similar to  $Z_m$  but with two fundamental differences: for  $Z_{0m}$  the  $p$ -values are assumed to be all uniforms (this is the so-called full null model) and they are independent inside each group (instead of weakly dependent). We denote the test rejecting the weak signal scenario by  $\phi_\beta = \mathbb{1}_{\{Z_m > q_{\beta,m}\}}$ . This gives us a stabilization procedure depending on  $\beta$  that we call sADDOW $_\beta$ :

$$\text{sADDOW}_\beta = \begin{cases} \text{ADDOW} & \text{if } \phi_\beta = 1 \\ \text{BH} & \text{if } \phi_\beta = 0 \end{cases} \quad (2.4.2)$$

We expect that in the weak signal case, the stabilized procedures have better control of the FDR than ADDOW, because in that case, without estimating  $\pi_{g,0}$  and if the  $p$ -values are all independent, the distribution of  $Z_m$  is close to the distribution of  $Z_{0m}$ , and we have the following approximation:

$$\begin{aligned}\text{FDR}(\text{sADDOW}_\beta) &= \mathbb{E}[\phi_\beta \text{FDP}(\text{ADDOW}) + (1 - \phi_\beta) \text{FDP}(\text{BH})] \\ &\leq \mathbb{E}[\phi_\beta + \text{FDP}(\text{BH})] \\ &\leq \mathbb{P}(Z_m > q_{\beta,m}) + \text{FDR}(\text{BH}) \\ &\lesssim \mathbb{P}(Z_{0m} > q_{\beta,m}) + \frac{m_0}{m}\alpha \\ &\leq \beta + \frac{m_0}{m}\alpha,\end{aligned}$$

where  $\mathbb{P}(Z_{0m} > q_{\beta,m}) \leq \beta$  by definition of  $q_{\beta,m}$  and  $m_0 = \sum_g m_{g,0}$  is the number of true nulls. If  $\beta$  is chosen small the control at level  $\alpha$  should be achieved. This heuristic will be supported by the simulations in Section 2.6.2.

## 2.5 Results

### 2.5.1 Main results

Now we present the two main Theorems of this paper. The two are asymptotical and justify the use of ADDOW when  $m$  is large. The first is the control of the FDR at level at most  $\alpha$ . The second shows that ADDOW has maximum power over all MWBH procedures in the (ME) case. The two are proven in Section 2.8.

**Theorem 2.5.1.** *Let us assume that Assumptions 2.2.1 to 2.2.6 are fulfilled. We have*

$$\lim_{m \rightarrow \infty} \text{FDR}(\text{ADDOW}) \leq \alpha. \quad (2.5.1)$$

If  $\alpha \leq \bar{\pi}_0$ , we have a more accurate result: if (ME) holds,

$$\lim_{m \rightarrow \infty} \text{FDR}(\text{ADDOW}) = \frac{\alpha}{C}. \quad (2.5.2)$$

*Remark 2.5.1.* Equation (2.5.2) means that in the (CE) case (where  $C = 1$ ), exact asymptotic control is achieved.

**Theorem 2.5.2.** *Let us assume that Assumptions 2.2.1 to 2.2.6 are fulfilled, with the additional assumption that (ME) holds. For any sequence of random weight functions*

$(\widehat{W})_{m \geq 1}$ , such that  $\widehat{W} : [0, 1] \rightarrow \hat{K}$  and  $\widehat{G}_{\widehat{W}}$  is nondecreasing, we have

$$\lim_{m \rightarrow \infty} \text{Pow}(\text{ADDOW}) \geq \limsup_{m \rightarrow \infty} \text{Pow}(\text{MWBH}(\widehat{W})).$$

### 2.5.2 Relation to IHW

Recall that IHW is ADDOW in the (NE) case, that (NE) is a subcase of (EE), and that when both (EE) and (ED) hold then (ME) is achieved. Hence, as a byproduct, we deduce from Theorems 2.5.1 and 2.5.2 the following result on IHW.

**Corollary 2.5.1.** *Let us assume that Assumptions 2.2.1 to 2.2.6 are fulfilled, with the additional assumption that (ED) holds. Then*

$$\lim_{m \rightarrow \infty} \text{FDR}(\text{IHW}) = \pi_0 \alpha,$$

and for any sequence of random weight functions  $(\widehat{W})_{m \geq 1}$  such that  $\widehat{W} : [0, 1] \rightarrow \hat{K}_{\text{NE}}$  and  $\widehat{G}_{\widehat{W}}$  is nondecreasing, we have

$$\lim_{m \rightarrow \infty} \text{Pow}(\text{IHW}) \geq \limsup_{m \rightarrow \infty} \text{Pow}(\text{MWBH}(\widehat{W})).$$

While equation (2.5.1) of Theorem 2.5.1 covers Theorem 4 of the supplementary material of Ignatiadis et al. (2016) (with slightly stronger assumption on the smoothness of the  $F_g$ 's), the FDR controlling result of Corollary 2.5.1 gives a slightly sharper bound ( $\pi_0 \alpha$  instead of  $\alpha$ ) in (ED) case.

The power optimality stated in Corollary 2.5.1 is new and was not shown in Ignatiadis et al. (2016). It thus supports the fact that IHW should be used under the assumption (ED) and when  $\pi_0$  is close to 1 or not estimated.

### 2.5.3 Comparison to other existing procedures

For any estimators  $\hat{\pi}_{g,0} \in [0, 1]$ , any weighting satisfying  $\sum_g \frac{m_g}{m} w_g \leq 1$  also satisfies  $\sum_g \frac{m_g}{m} \hat{\pi}_{g,0} w_g \leq 1$ , that is  $\hat{K}_{\text{NE}} \subset \hat{K}$ . Hence, any MWBH procedure estimating  $\frac{m_{g,0}}{m_g}$  by 1 uses a weight function valued in  $\hat{K}$ . This immediately yields the following corollary.

**Corollary 2.5.2.** *Let us assume that Assumptions 2.2.1 to 2.2.6 are fulfilled, with the additional assumption that (ME) holds. Then*

$$\lim_{m \rightarrow \infty} \text{Pow}(\text{ADDOW}) \geq \limsup_{m \rightarrow \infty} \text{Pow}(R),$$

for any  $R \in \{\text{BH}, \text{IHW}\}$ .

The next corollary simply states that ADDOW outperforms many procedures of the "weighting with  $\pi_0$  adaptation" literature.

**Corollary 2.5.3.** *Let us assume that Assumptions 2.2.1 to 2.2.6 are fulfilled, with the additional assumption that (ME) holds. Then*

$$\lim_{m \rightarrow \infty} \text{Pow}(\text{ADDOW}) \geq \limsup_{m \rightarrow \infty} \text{Pow}(R),$$

for any  $R \in \{\text{Pro 1}, \text{Pro 2}, \text{HZZ}, \text{ABH}\}$ .

The results for Pro2, HZZ and ABH follow directly from Theorem 2.5.2 because these are MWBH procedures. The proof for Pro1 (which is not of the MWBH type) can be found in Section 2.D.

## 2.5.4 Results for the stabilized version

Next theorem shows that, asymptotically, the procedure  $s\text{ADDOW}_\beta$  is the same as ADDOW. Our result is true even if  $\beta = \beta_m \xrightarrow{m \rightarrow \infty} 0$  provided that the convergence is not too fast. It is proven in Section 2.E.

**Theorem 2.5.3.** *Let us assume that Assumptions 2.2.1 to 2.2.6 are fulfilled. Take a sequence  $(\beta_m)_{m \geq 1}$  such that  $\beta_m \geq a \exp(-bm^{1-\nu})$  for some  $a \in (0, 1]$ ,  $b > 0$  and  $\nu > 0$ .*

*Then  $\phi_{\beta_m} \rightarrow 1$  almost surely. In particular, all Theorems and Corollaries of Sections 2.5.1 and 2.5.3 hold when replacing ADDOW with  $s\text{ADDOW}_{\beta_m}$ .*

# 2.6 Numerical experiments

## 2.6.1 Simulation setting

We consider the one-sided Gaussian framework described in Section 2.2.4 for  $G = 2$  groups. The parameters are thus given by  $m_1$ ,  $m_2$ ,  $m_{1,0}$ ,  $m_{2,0}$ ,  $\mu_1$ ,  $\mu_2$ , and  $\alpha$ . For the stabilisation,  $q_{\beta,m}$  is estimated with realizations of  $Z_{0m}$  (as defined in equation (2.4.1)),

where  $Z_{0m}$  and  $Z_m$  are computed as suprema on  $\{k/m, 1 \leq k \leq m\}$  instead of  $[0, 1]$  for an easier computation. Our experiments have been performed by using the three following scenarios, for which the values of  $\mu_1$  and  $\mu_2$  are defined according to a parameter  $\bar{\mu}$ . Each simulation of each scenario is replicated 1000 times.

- Scenario 1:  $\mu_1 = \bar{\mu}$  and  $\mu_2 = 2\bar{\mu}$ ,  $\alpha = 0.05$ ,  $\beta = 0.001$ ,  $m_1 = m_2 = 2000$ ,  $m_{1,0}/m_1 = 0.7$  and  $m_{2,0}/m_2 = 0.8$ . Furthermore the values of  $\bar{\mu}$  range from 0.5 to 3 with jumps of size 0.25. Here,  $q_{\beta,m}$  is estimated with 10000 realizations of  $Z_{0m}$ . The methods compared in this scenario are detailed below.
- Scenario 2:  $\mu_1 = 2$  and  $\mu_2 = \bar{\mu}$ ,  $\alpha = 0.7$ ,  $m_1 = 1000$  and  $m_2 = 9000$ ,  $m_{1,0}/m_1 = 0.05$  and  $m_{2,0}/m_2 = 0.85$ . Furthermore  $\bar{\mu} \in \{1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3\}$ . In this scenario, we compare only BH, ADDOW in the (CE) case (with  $\hat{\pi}_{g,0} = \pi_{g,0}$ ) and ADDOW in the (NE) case (that is, IHW, with  $\hat{\pi}_{g,0} = 1$ ).
- Scenario 3:  $\mu_1 = \bar{\mu}$  and  $\mu_2 = 2\bar{\mu}$ ,  $\alpha = 0.2$ ,  $\beta = 0.05$ ,  $m_1 = m_2 = m/2$ ,  $m_{g,0}/m_g = 0.8$ , and  $\bar{\mu} \in \{0.01, 3\}$ . Furthermore,  $m \in \{500, 1000, 2000, 3000, 4000, 5000, 8000\}$  for  $\bar{\mu} = 3$  and, for  $\bar{\mu} = 0.01$ ,  $m$  takes the same values plus  $10^4, 2.10^4, 3.10^4$ . Here,  $q_{\beta,m}$  is estimated with 1000 realizations of  $Z_{0m}$ . In this scenario, only BH, ADDOW and sADDOW $_{\beta}$  in the (NE) case are compared.

In scenario 1, four groups of procedures are compared. The difference between the four groups lies in the way  $\pi_0$  is estimated. Group 1 corresponds to the (NE) case:  $\hat{\pi}_{g,0} = 1$ . Group 2 corresponds to the (CE) case, with an oracle estimator:  $\hat{\pi}_{g,0} = \pi_{g,0}$ . Groups 3 and 4 use the Storey estimator  $\hat{\pi}_{g,0}(\lambda)$  defined in Equation (2.2.3), for different yet usual (see e.g. [Storey, 2002](#) and [Blanchard and Roquain, 2009](#)) values of  $\lambda$ . We took  $\lambda = 1/2$  for Group 3 and  $\lambda = \alpha$  for Group 4. Inside each group, the following procedures are computed:

- ABH as defined in section 2.3.2 (which is BH in Group 1)
- HZZ as defined in section 2.3.2 (except in Group 1 where it is not defined)
- Pro2 as defined in section 2.3.2 (defined only based on BH in Group 1)
- ADDOW (which is equal to IHW in Group 1).

Additionally, in Groups 1 and 2, the oracle weights  $W_{or}^*$  given by equation 2.3.5 are computed and the resulting procedure MWBH( $W_{or}^*$ ) is also computed.

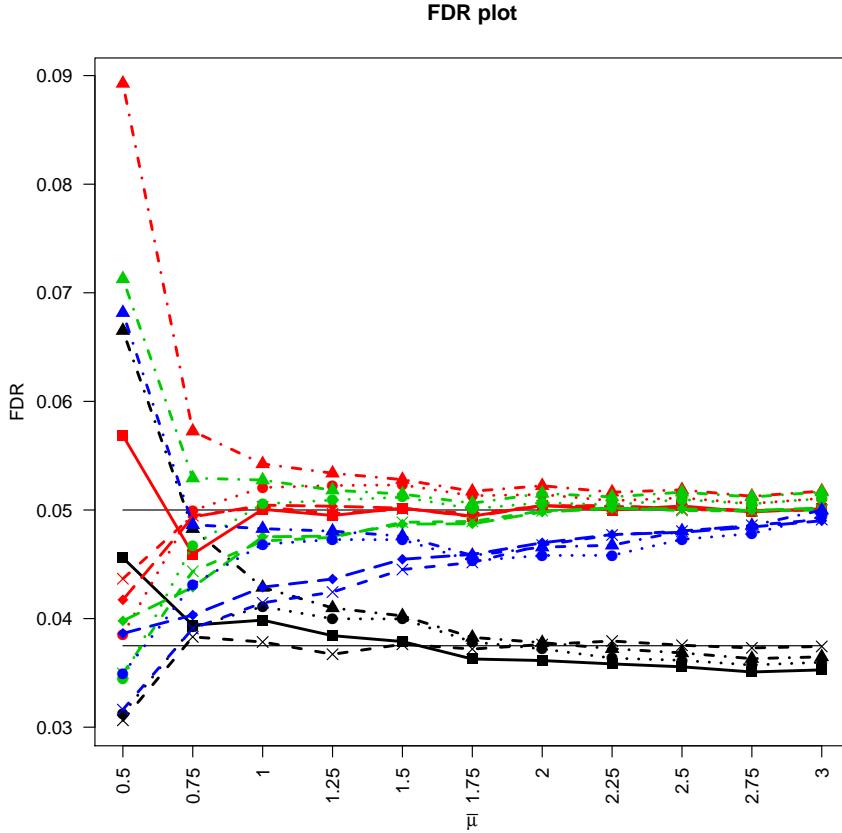


Fig. 2.2 FDR against  $\bar{\mu}$  in scenario 1. Group 1 in black; Group 2 in red; Group 3 in green; Group 4 in blue. The type of procedure depends on the point shape: MWBH ( $W_{or}^*$ ) (squares); ADDOW (triangles); Pro2 (disks); HZZ (diamonds) and finally BH/ABH (crosses). Horizontal lines:  $\alpha$  and  $\pi_0\alpha$  levels. See Section 2.6.1.

## 2.6.2 FDR control

The FDR of all above procedures are compared in Figure 2.2, Figure 2.3a and Figure 2.3b.

First, Figure 2.3b shows that the convergence of the FDR holds for moderate  $m$ . This supports the theoretical finding of Corollary 2.5.1 showing that the FDR shall converge to  $\pi_0\alpha$  in scenario 3. This Figure also shows that when the signal is strong, sADDOW $_\beta$  behaves as ADDOW, which is well expected for the definition of  $\phi_\beta$ . While Figure 2.2 also supports Theorem 2.5.1 for large signal ( $\bar{\mu} \geq 2$ ), we see that the FDR control of data-driven weighted procedures (ADDOW, Pro2) can deteriorate as  $\bar{\mu}$  decreases. This is due to an overfitting phenomenon. The overfitting is also brought to light in Groups 1 and 2 by the comparison between ADDOW and its oracle MWBH ( $W_{or}^*$ ), which always achieves FDR control (except for  $\bar{\mu} = 0.5$ ).

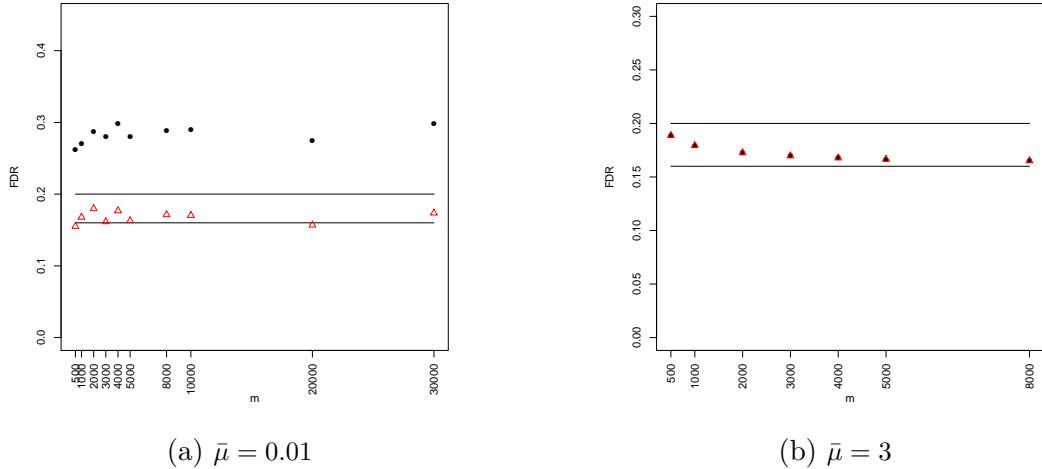


Fig. 2.3 FDR against  $m$  in scenario 3. Group 1, ADDOW (black dots) and  $sADDOW_\beta$  (red triangles). Horizontal lines:  $\alpha$  and  $\pi_0\alpha$  levels.

As  $\bar{\mu}$  get smaller, the overfitting seems to increase and the FDR control seems to get violated. Let us underline that this does not contradict our theory because considering a small  $\bar{\mu}$  might imply a smaller convergence rate while  $m$  stays  $\lesssim 10^4$  in scenarios 1 and 3. Fortunately, in this regime, it is apparent from that the regularization process correctly addresses the overfitting by maintaining the FDR control holds true. Again, this is well expected because  $sADDOW_\beta$  simply corresponds to BH in that regime, see equation (2.4.2).

### 2.6.3 Power

Now that the FDR control has been studied, let us compare the procedures in terms of power. First, to better emphasize the benefit of adaptation, the power is rescaled in the following way: we define the normalized difference of power with respect to BH, or DiffPow, by

$$\text{DiffPow}(R) = \frac{m}{m_1} (\text{Pow}(R) - \text{Pow}(\text{BH})) ,$$

for any procedure  $R$ .

Figure 2.4 displays the power of all the procedures defined in Section 2.6.1. Figures 2.5a and 2.5b display only a subset of them, for clarity. We can make several observations:

- Procedures of Group 2 are more powerful than their equivalent in Group 3, which are better than their equivalent in Group 4, which are better than in Group 1 (see e.g. Figure 2.5a). In particular, the difference between Group 2 and Group 1

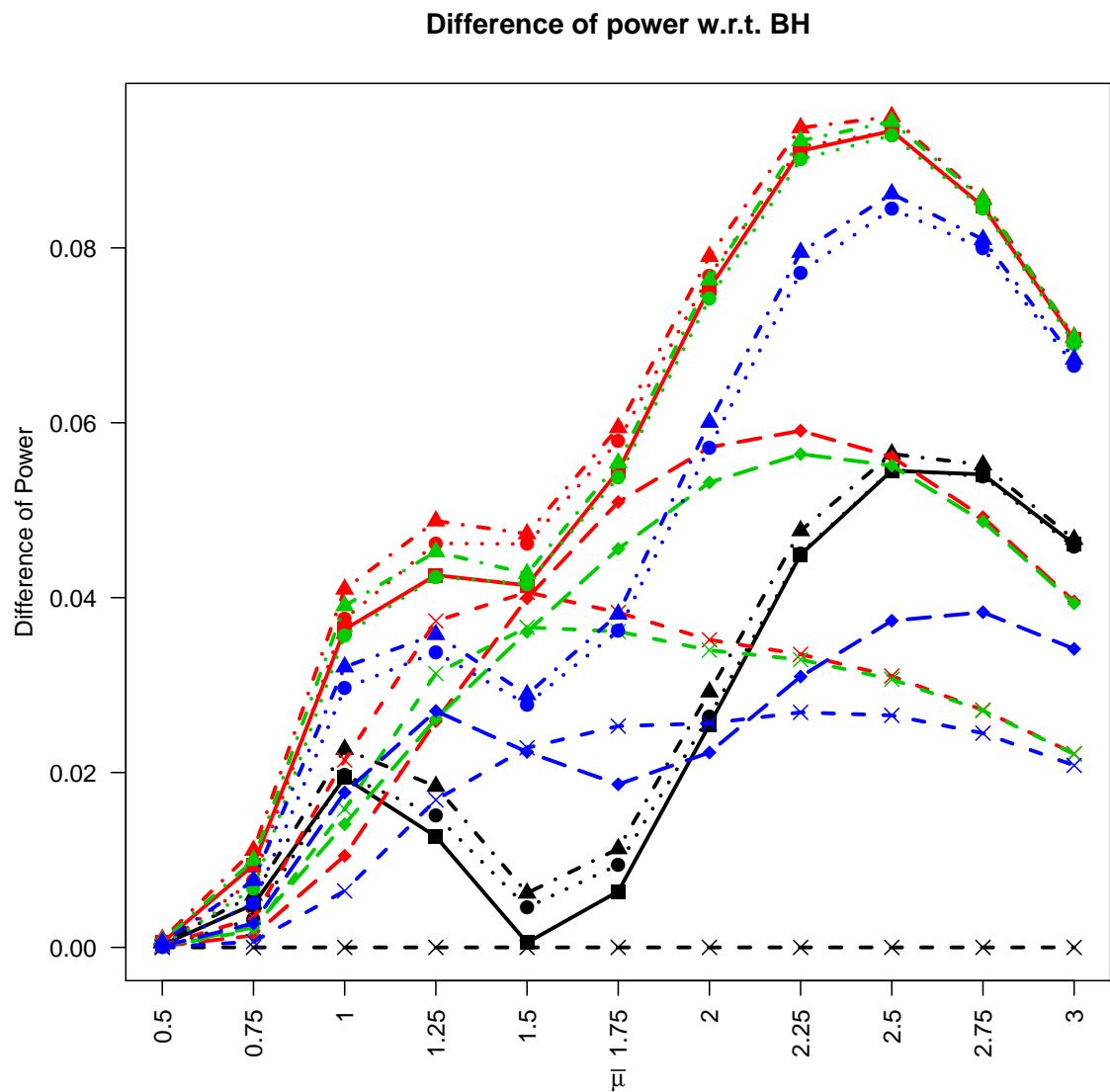


Fig. 2.4 DiffPow against  $\bar{\mu}$  in scenario 1. Same legend as Figure 2.2.

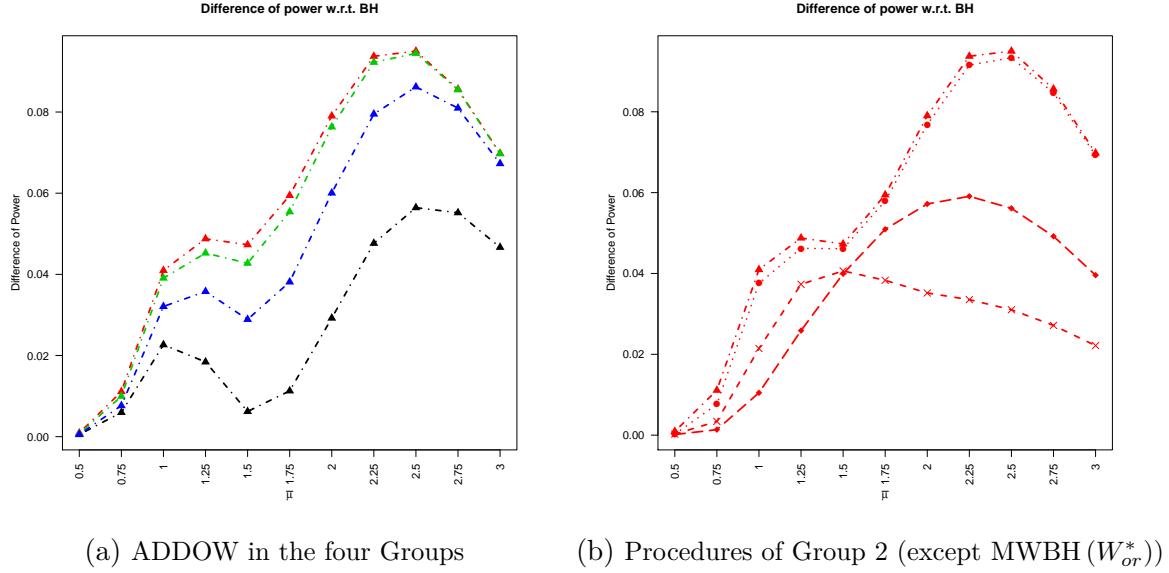


Fig. 2.5 Details of Figure 2.4 where only a subset of procedures is plotted.

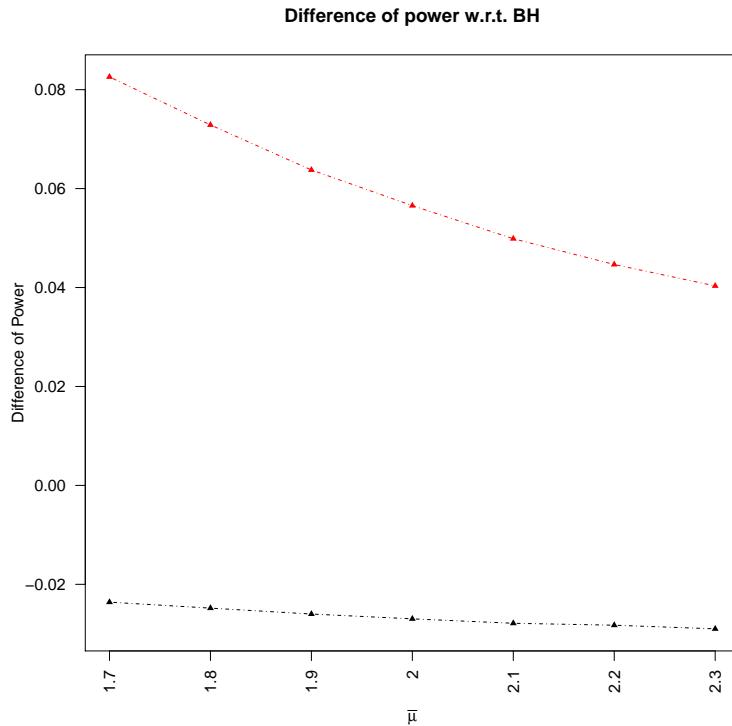


Fig. 2.6 DiffPow of ADDOW against  $\bar{\mu}$  in scenario 2. The (NE) case is in black and the (CE) case in red.

is huge. This illustrates the importance of incorporating the knowledge of  $\pi_0$  to improve power.

- In all groups (that is for any choice of  $\hat{\pi}_{g,0}$ ), ADDOW achieves the best power (see e.g. Figure 2.5b), which supports Theorem 2.5.2. Additionnaly, maybe surprisingly, Pro2 behaves quite well, with a power close to the one of ADDOW and despite its theoretical sub-optimality.
- Inside Group 2, 3 or 4, comparing ABH and HZZ to ADDOW and Pro2 shows the benefit of adding the  $F_g$  adaptation to the  $\pi_0$  adaptation: the ADDOW and Pro2 have better power than ABH and HZZ for all signals (see e.g. Figure 2.5b). In Groups 2 and 3, we can see a zone of moderate signal (around  $\bar{\mu} = 1.5$ ) where the two categories of procedures are close. That is the same zone where HZZ becomes better than ABH. We deduce that in that zone the optimal weighting is the same as the uniform  $\hat{w}^{(1)}$  weighting of ABH.
- The comparison of the DiffPow between IHW and ABH or HZZ from Group 2 in Figure 2.4 shows the difference between adapting only to the  $F_g$ 's versus adapting only to  $\pi_0$ . No method is generally better than the other: as we see in the plot, it depends on the signal strength. We also see that neither ABH nor HZZ is better than the other.
- For all signals, methods of Group 3 are close to their equivalent of Group 2, which indicates that using  $\lambda = 1/2$  gives a good estimate of  $\pi_{g,0}$  in practice (see e.g. Figure 2.5a). Furthermore, the larger the signal is, the more methods of Group 3 and 4 get closer to Group 2.

Finally, let us discuss Figure 2.6. The graph is rather unequivocal and shows that the parameter choice of scenario 2 implies that IHW has a power smaller than BH (ADDOW in (CE) case stays better as expected). Let us recall our interpretation proposed in remark 2.3.1: IHW favors the large and sparse second group of hypotheses whereas the optimal power is achieved by favoring the small first group of hypotheses which contains almost only signal. As a WBH procedure with weights (1,1), BH does not favor any group. Figure 2.6 demonstrates the limitation of the heuristic that “maximizing the number of rejections maximizes power” by providing a direct counterexample, and underlines the necessity of estimating the  $\pi_{g,0}$  when nothing lets us think that (ED) may be met.

## 2.7 Concluding remarks

In this paper we presented a new class of data-driven step-up procedures, ADDOW, that generalizes IHW by incorporating  $\pi_{g,0}$  estimators in each group. We showed that while this procedure asymptotically controls the FDR at the targeted level, it has the best power among all MWBH procedures when the  $\pi_0$  estimation can be made consistently. In particular it dominates all the existing procedures of the weighting literature and solves the  $p$ -values weighting issue in a group-structured multiple testing problem. As a by-product, our work established the optimality of IHW in the case of homogeneous  $\pi_0$  structure. Finally we proposed a stabilization variant designed to deal with the case where only few discoveries can be made (very small signal strength or sparsity). Some numerical simulations illustrated that our properties are also valid in a finite sample framework, provided that the number of tests and the signal strength are large enough.

**Assumptions** Our assumptions are rather mild: basically we only added the concavity of the  $F_g$  to the assumptions of [Ignatiadis et al. \(2016\)](#). Notably we dropped the other regularity assumptions on  $F_g$  that were made in [Roquain and van de Wiel \(2009\)](#) while keeping all the useful properties on  $W^*$  in the (NE) case. Note that the criticality assumption is often made in the literature, see [Ignatiadis et al. \(2016\)](#) (assumption 5 of the supplementary material), [Zhao and Zhang \(2014\)](#) (assumption A.1), or the assumption of Theorem 4 in [Hu et al. \(2010\)](#). Finally, the weak dependence assumption is extensively used in our paper. An interesting direction could be to extend our result to some strong dependent cases, for instance by assuming the PRDS (positive regression dependence), as some previous work already studied properties of MWBH procedures under that assumption, see [Roquain and Van De Wiel \(2008\)](#).

**Computational aspects** The actual maximization problem of ADDOW is difficult, it involves a mixed integer linear programming that may take a long time to resolve. Some regularization variant may be needed for applications. To this end, we can think to use the least concave majorant (LCM) instead of the empirical c.d.f. in equation (2.3.1) (as proposed in modification (E1) of IHW in [Ignatiadis et al., 2016](#)). As we show in Section 2.8, ADDOW can be extended to that case (see especially Section 2.8.1) and our results are still valid for this new regularized version of ADDOW.

**Toward nonasymptotic results** Interesting direction for future research can be to investigate the convergence rate in our asymptotic results. One possible direction can be to use the work of [Neuvial \(2008\)](#). However, it would require to compute the Hadamard

derivative of the functional involved in our analysis, which might be very challenging. Finally, another interesting future work could be to develop other versions of ADDOW that ensure finite sample FDR control property: this certainly requires to use a different optimization process, which will make the power optimality difficult to maintain.

## 2.8 Proofs of Theorems 2.5.1 and 2.5.2

### 2.8.1 Further generalization

Define for any  $u$  and  $W$

$$\widehat{H}_W(u) = m^{-1} |R_{u,W} \cap \mathcal{H}_0| = m^{-1} \sum_{g=1}^G \sum_{i=1}^{m_g} \mathbb{1}_{\{p_{g,i} \leq \alpha u W_g(u), H_{g,i}=0\}}$$

and

$$\widehat{P}_W(u) = m^{-1} |R_{u,W} \cap \mathcal{H}_1| = \widehat{G}_W(u) - \widehat{H}_W(u),$$

so that  $\text{FDP}(R_{u,W}) = \frac{\widehat{H}_W(u)}{\widehat{G}_W(u) \vee m^{-1}}$  and  $\text{Pow}(R_{u,W}) = \mathbb{E}[\widehat{P}_W(u)]$  (recall that MWBH( $W$ ) is  $R_{\tilde{u}_W, W}$ ). Also define  $\widehat{D}_g(t) = m_g^{-1} \sum_{i=1}^{m_g} \mathbb{1}_{\{p_{g,i} \leq t\}}$  so that  $\widehat{G}_W(u) = \sum_g \frac{m_g}{m} \widehat{D}_g(\alpha u W_g(u))$ .

For the sake of generality  $\widehat{D}_g$  is not the only estimator of  $D_g$  (defined in equation (2.B.1)) that we will use to prove our results (for example, we can use the LCM of  $\widehat{D}_g$ , denoted  $\text{LCM}(\widehat{D}_g)$ , see Section 2.7). So let us increase slightly the scope of the MWBH class by defining  $\widetilde{G}_W(u) = \sum_g \frac{m_g}{m} \widetilde{D}_g(\alpha u W_g(u))$  for any estimator  $\widetilde{D}_g$  such that  $\widetilde{D}_g$  is nondecreasing,  $\widetilde{D}_g(0) = 0$ ,  $\widetilde{D}_g(1) = 1$  and  $\|\widetilde{D}_g - D_g\| \xrightarrow{\mathbb{P}} 0$ , where  $\|\cdot\|$  is the sup norm for the bounded functions on their definition domain. Note that at least  $(D_g)_g$ ,  $(\widehat{D}_g)_g$  (by Lemma 2.C.1), and  $(\text{LCM}(\widehat{D}_g))_g$  (by Lemma 2.C.6) are eligible.

If  $W$  is such that  $\widetilde{G}_W$  is nondecreasing, we then define the generalized MWBH as

$$\text{GMWBH}\left((\widetilde{D}_g)_g, W\right) = R_{\tilde{u}_W, W} \text{ where } \tilde{u}_W = \mathcal{I}\left(\widetilde{G}_W\right).$$

If  $(\widetilde{D}_g)_g$  is such that we can define, for all  $u \in [0, 1]$ ,

$$\widetilde{W}^*(u) \in \arg \max_{w \in \hat{K}} \widetilde{G}_w(u), \quad (2.8.1)$$

we define the generalized ADDOW by

$$\text{GADDOW}\left((\widetilde{D}_g)_g\right) = \text{GMWBH}\left((\widetilde{D}_g)_g, \widetilde{W}^*\right),$$

the latter being well defined because  $\tilde{G}_{\tilde{W}^*}$  is nondecreasing (by a proof similar to the one of Lemma 2.A.6). Note that for any continuous  $\tilde{D}_g$ , such as  $\text{LCM}(\widehat{D}_g)$  or  $D_g$  itself, the arg max in (2.8.1) is non empty and GADDOW can then be defined.

What we show below are more general theorems, valid for any GADDOW  $((\tilde{D}_g)_g)$ . Our proofs combined several technical lemmas deferred to Sections 2.B and 2.C, which are based on the previous work of Roquain and van de Wiel (2009); Hu et al. (2010); Zhao and Zhang (2014).

*Remark 2.8.1.* GADDOW  $((\tilde{D}_g)_g)$  when  $\tilde{D}_g = \text{LCM}(\widehat{D}_g)$  and  $\hat{\pi}_{g,0} = 1$  is exactly the same as IHW with modification (E1) defined in the supplementary material of Ignatiadis et al. (2016). In our notation, the latter is WBH  $(\widetilde{W}^*(\tilde{u}_{\widetilde{W}^*}))$ , which is the same as GADDOW  $((\tilde{D}_g)_g)$  because  $\tilde{u}_{\widetilde{W}^*} = \tilde{u}_{\widetilde{W}^*}(\tilde{u}_{\widetilde{W}^*})$  (same proof as in Remark 2.8.2).

### 2.8.2 Proof of Theorem 2.5.1

We have

$$\text{FDP} \left( \text{GMWBH} \left( (\tilde{D}_g)_g, \widetilde{W}^* \right) \right) = \frac{\widehat{H}_{\widetilde{W}^*}(\tilde{u})}{\widehat{G}_{\widetilde{W}^*}(\tilde{u}) \vee m^{-1}} \in [0, 1],$$

where  $\tilde{u}$  is defined as in (2.C.6) so by Lemma 2.C.5 we deduce that

$$\text{FDP} \left( \text{GADDOW} \left( (\tilde{D}_g)_g \right) \right) \xrightarrow[m \rightarrow \infty]{\mathbb{P}} \frac{H_{\widetilde{W}^*}^\infty(u^*)}{G_{\widetilde{W}^*}^\infty(u^*)} = \frac{H_{\widetilde{W}^*}^\infty(u^*)}{u^*},$$

and then

$$\lim_{m \rightarrow \infty} \text{FDR} \left( \text{GADDOW} \left( (\tilde{D}_g)_g \right) \right) = u^{*-1} H_{\widetilde{W}^*}^\infty(u^*),$$

where  $G_{\widetilde{W}^*}^\infty$ ,  $H_{\widetilde{W}^*}^\infty$  and  $u^*$  are defined in Section 2.B.

If  $\alpha \geq \bar{\pi}_0$ ,  $u^* = 1$  by Lemma 2.B.2 and  $\alpha u^* W_g^*(u^*) \geq 1$  by Lemma 2.B.1 so  $u^{*-1} H_{\widetilde{W}^*}^\infty(u^*) = \pi_0 \leq \bar{\pi}_0 \leq \alpha$ .

If  $\alpha \leq \bar{\pi}_0$ ,  $\alpha u^* W_g^*(u^*) \leq 1$  by Lemma 2.B.1 so  $U(\alpha u^* W_g^*(u^*)) = \alpha u^* W_g^*(u^*)$  for all  $g$  and then

$$\begin{aligned} u^{*-1} H_{\widetilde{W}^*}^\infty(u^*) &= \alpha \sum_g \pi_g \pi_{g,0} W_g^*(u^*) \\ &\leq \alpha \sum_g \pi_g \bar{\pi}_{g,0} W_g^*(u^*) = \alpha. \end{aligned} \tag{2.8.2}$$

Moreover if (ME) holds (that is, there exists  $C \geq 1$  such that  $\bar{\pi}_{g,0} = C\pi_{g,0}$  for all  $g$ ), we write

$$\begin{aligned} u^{*-1}H_{W^*}^\infty(u^*) &= \alpha \sum_g \pi_g \pi_{g,0} W_g^*(u^*) \\ &= \frac{\alpha}{C} \sum_g \pi_g \bar{\pi}_{g,0} W_g^*(u^*) = \frac{\alpha}{C}. \end{aligned} \quad (2.8.3)$$

The equalities in (2.8.2) and (2.8.3) are due to  $\sum_g \pi_g \bar{\pi}_{g,0} W_g^*(u^*) = 1$  (by Lemma 2.B.1).

### 2.8.3 Proof of Theorem 2.5.2

First, in any case,

$$\hat{P}_{\tilde{W}^*}(\tilde{u}) = \hat{G}_{\tilde{W}^*}(\tilde{u}) - \hat{H}_{\tilde{W}^*}(\tilde{u}) \xrightarrow{a.s.} G_{W^*}^\infty(u^*) - H_{W^*}^\infty(u^*) = P_{W^*}^\infty(u^*)$$

by Lemma 2.C.5, where  $P_{W^*}^\infty$  is defined in Section 2.B. Hence:

$$\lim_{m \rightarrow \infty} \text{Pow}\left(\text{GADDOW}\left((\tilde{D}_g)_g\right)\right) = P_{W^*}^\infty(u^*).$$

For the rest of the proof, we assume we are in case (ME), which implies by Lemma 2.B.3 that  $W^*(u) \in \arg \max_{w \in K^\infty} P_w^\infty(u)$  for all  $u$ , and that  $P_{W^*}^\infty$  is nondecreasing. We also split the proof in two parts. For the first part we assume that for all  $m$ ,  $\hat{W}$  is a weight vector  $\hat{w} \in \hat{K}$  therefore not depending on  $u$ . In the second part we will conclude with a general sequence of weight functions.

**Part 1**  $\hat{W} = \hat{w} \in \hat{K}$  for all  $m$ . Let  $\ell = \limsup \text{Pow}(\text{MWBH}(\hat{w}))$ . Up to extracting a subsequence, we can assume that  $\ell = \lim \mathbb{E}[\hat{P}_{\hat{w}}(\hat{u}_{\hat{w}})]$  and  $\hat{\pi}_{g,0} \xrightarrow{a.s.} \bar{\pi}_{g,0}$  for all  $g$ . Define the event

$$\tilde{\Omega} = \left\{ \begin{array}{ll} \forall g, \hat{\pi}_{g,0} &\longrightarrow \bar{\pi}_{g,0} \\ \sup_{w \in \mathbb{R}_+^G} \|\hat{P}_w - P_w^\infty\| &\longrightarrow 0 \\ \sup_{w \in \mathbb{R}_+^G} \|\hat{G}_w - G_w^\infty\| &\longrightarrow 0 \end{array} \right\}$$

then  $\mathbb{P}(\tilde{\Omega}) = 1$  (by Lemma 2.C.1),  $\ell = \lim \mathbb{E}[\hat{P}_{\hat{w}}(\hat{u}_{\hat{w}}) \mathbf{1}_{\tilde{\Omega}}]$  and by reverse Fatou Lemma  $\ell \leq \mathbb{E}[\limsup \hat{P}_{\hat{w}}(\hat{u}_{\hat{w}}) \mathbf{1}_{\tilde{\Omega}}]$ .

Now consider that  $\tilde{\Omega}$  occurs and fix a realization of it, the following of this part 1 is deterministic. Let  $\ell' = \limsup \hat{P}_{\hat{w}}(\hat{u}_{\hat{w}})$ . The sequences  $(\frac{m}{m_g \hat{\pi}_{g,0}})$  are converging and then bounded, hence the sequence  $(\hat{w})$  is also bounded. By compacity, once again up to extracting a subsequence, we can assume that  $\ell' = \lim \hat{P}_{\hat{w}}(\hat{u}_{\hat{w}})$  and that  $\hat{w}$  converges to a

given  $w^{cv}$ . By taking  $m \rightarrow \infty$  in the relation  $\sum \frac{m_g}{m} \hat{\pi}_{g,0} \hat{w}_g \leq 1$ , it appears that  $w^{cv}$  belongs to  $K^\infty$ .  $\|\hat{G}_{\hat{w}} - G_{w^{cv}}^\infty\| \leq \sup_w \|\hat{G}_w - G_w^\infty\| + \|G_{\hat{w}}^\infty - G_{w^{cv}}^\infty\| \rightarrow 0$  so by Remark 2.B.2  $\hat{u}_{\hat{w}} \rightarrow u_{w^{cv}}^\infty$  and finally

$$\begin{aligned} \left| \hat{P}_{\hat{w}}(\hat{u}_{\hat{w}}) - P_{w^{cv}}^\infty(u_{w^{cv}}^\infty) \right| &\leq \sup_{w \in \mathbb{R}_+^G} \left\| \hat{P}_w - P_w^\infty \right\| + \left| P_{\hat{w}}^\infty(\hat{u}_{\hat{w}}) - P_{w^{cv}}^\infty(u_{w^{cv}}^\infty) \right| \\ &\longrightarrow 0, \end{aligned}$$

by continuity of  $F_g$  and because  $\tilde{\Omega}$  is realized. So  $\ell' = P_{w^{cv}}^\infty(u_{w^{cv}}^\infty) \leq P_{W^*}^\infty(u_{w^{cv}}^\infty)$  by maximality. Note also that  $G_{w^{cv}}^\infty(\cdot) \leq G_{W^*}^\infty(\cdot)$  which implies that  $u_{w^{cv}}^\infty \leq u_{W^*}^\infty = u^*$  so  $\ell' \leq P_{W^*}^\infty(u^*)$  because  $P_{W^*}^\infty$  is nondecreasing. Finally  $\limsup \hat{P}_{\hat{w}}(\hat{u}_{\hat{w}}) \mathbf{1}_{\tilde{\Omega}} \leq P_{W^*}^\infty(u^*)$  for any realization of  $\Omega$ , by integrating we get that  $\ell \leq P_{W^*}^\infty(u^*)$  which concludes that part 1.

**Part 2** Now consider the case where  $\widehat{W}$  is a weight function  $u \mapsto \widehat{W}(u)$ . Observe that

$$\hat{u}_{\widehat{W}} = \hat{G}_{\widehat{W}}(\hat{u}_{\widehat{W}}) = \hat{G}_{\widehat{W}(\hat{u}_{\widehat{W}})}(\hat{u}_{\widehat{W}}),$$

so by definition of  $\mathcal{I}(\cdot)$ ,  $\hat{u}_{\widehat{W}} \leq \hat{u}_{\widehat{W}(\hat{u}_{\widehat{W}})}$ , and then

$$\hat{P}_{\widehat{W}}(\hat{u}_{\widehat{W}}) = \hat{P}_{\widehat{W}(\hat{u}_{\widehat{W}})}(\hat{u}_{\widehat{W}}) \leq \hat{P}_{\widehat{W}(\hat{u}_{\widehat{W}})}\left(\hat{u}_{\widehat{W}(\hat{u}_{\widehat{W}})}\right).$$

As a consequence,  $\text{Pow}\left(\text{MWBH}\left(\widehat{W}\right)\right) \leq \text{Pow}\left(\text{MWBH}\left(\widehat{W}(\hat{u}_{\widehat{W}})\right)\right)$ . Finally, apply part 1 to the weight vector sequence  $(\widehat{W}(\hat{u}_{\widehat{W}}))$  to conclude.

*Remark 2.8.2.* We just showed that for every MWBH procedure, there is a corresponding WBH procedure with better power. In particular, by defining  $\hat{u} = u_{\widehat{W}^*}$  the ADDOW threshold, we showed that  $\hat{u} \leq \hat{u}_{\widehat{W}^*(\hat{u})}$ . But  $\hat{G}_{\widehat{W}^*} \geq \hat{G}_{\hat{w}}$  and then  $\hat{u} \geq u_{\hat{w}}$  for any  $\hat{w}$ . Hence  $\hat{u} = \hat{u}_{\widehat{W}^*(\hat{u})}$  and ADDOW is equal to the WBH procedure associated to the weight vector  $\widehat{W}^*(\hat{u})$ .

*Remark 2.8.3.* We actually proved a stronger result, as we can replace the statement  $\widehat{W} : [0, 1] \rightarrow \hat{K}$  by  $\widehat{W} : [0, 1] \rightarrow \hat{K}^{\text{alt}}$  where  $\hat{K}^{\text{alt}} = \left\{ w \in \mathbb{R}_+^G : \sum_g \frac{m_g}{m} \hat{\pi}_{g,0}^{\text{alt}} w_g \leq 1 \right\}$  and the  $\hat{\pi}_{g,0}^{\text{alt}}$  are such that  $\hat{\pi}_{g,0}^{\text{alt}} \xrightarrow{\mathbb{P}} \bar{\pi}_{g,0}^{\text{alt}}$  for some  $\bar{\pi}_{g,0}^{\text{alt}} \geq \bar{\pi}_{g,0}$ .

## Appendix 2.A Lemmas and proofs of Section 2.2

**Lemma 2.A.1.** *For all  $g$ ,  $F_g$  is continuous.*

*Proof.*  $F_g$  is concave so it is continuous over  $\mathbb{R} \setminus \{0, 1\}$ .  $F_g$  is continuous in 0 because it is càdlàg.  $F_g$  is continuous in 1 by concavity and monotonicity.  $\square$

**Lemma 2.A.2.** *Take a real valued sequence  $(\lambda_m)$  with  $\lambda_m \in (0, 1)$ , converging to 1, such that  $\frac{1}{\sqrt{m}} = o(1 - \lambda_m)$  and  $\frac{m_{g,0}}{m_g} = \pi_{g,0} + o(1 - \lambda_m)$  for all  $g$ . If  $f_g(1^-) = 0$  for all  $g$  and the p-values inside each group are mutually independent, then*

$$\forall g \in \{1, \dots, G\}, \hat{\pi}_{g,0}(\lambda_m) \xrightarrow{\mathbb{P}} \pi_{g,0}.$$

*Proof.* First note that  $\frac{m_{g,1}}{m_g} - \pi_{g,1} = \pi_{g,0} - \frac{m_{g,0}}{m_g} = o(1 - \lambda_m)$ .

Thus we have

$$\begin{aligned} |\hat{\pi}_{g,0}(\lambda_m) - \pi_{g,0}| &= \left| \frac{1 - \frac{1}{m_g} \sum_i \mathbf{1}_{\{p_{g,i} \leq \lambda_m\}} + \frac{1}{m}}{1 - \lambda_m} - \pi_{g,0} \right| \\ &\leq \frac{\lambda_m \left| \pi_{g,0} - \frac{m_{g,0}}{m_g} \right| + \frac{m_{g,0}}{m_g} \left| \lambda_m - \frac{1}{m_{g,0}} \sum_i \mathbf{1}_{\{p_{g,i} \leq \lambda_m, H_{g,i}=0\}} \right|}{1 - \lambda_m} \\ &\quad + \frac{\left| \pi_{g,1} - \frac{m_{g,1}}{m_g} \right| + \frac{m_{g,1}}{m_g} \left| F_g(\lambda_m) - \frac{1}{m_{g,1}} \sum_i \mathbf{1}_{\{p_{g,i} \leq \lambda_m, H_{g,i}=1\}} \right|}{1 - \lambda_m} \\ &\quad + \frac{m_{g,1} \frac{1 - F_g(\lambda_m)}{1 - \lambda_m} + \frac{1}{m(1 - \lambda_m)}}{1 - \lambda_m} \\ &\leq \frac{m_{g,0}}{m_g} \frac{\sup_{x \in [0,1]} \left| x - \frac{1}{m_{g,0}} \sum_i \mathbf{1}_{\{p_{g,i} \leq x, H_{g,i}=0\}} \right|}{1 - \lambda_m} \\ &\quad + \frac{m_{g,1}}{m_g} \frac{\sup_{x \in [0,1]} \left| F_g(x) - \frac{1}{m_{g,1}} \sum_i \mathbf{1}_{\{p_{g,i} \leq x, H_{g,i}=1\}} \right|}{1 - \lambda_m} + o(1). \end{aligned}$$

The two suprema of the last display, when multiplied by  $\sqrt{m}$ , converge in distribution (by Kolmogorov-Smirnov's theorem). So when divided by  $1 - \lambda_m$  they converge to 0 in distribution and then in probability (because  $\frac{1}{1 - \lambda_m} = o(\sqrt{m})$ ).  $\square$

**Definition 2.A.1.** The critical alpha value is

$$\alpha^* = \inf_{w \in K^\infty} \frac{1}{\sum_g \pi_g w_g (\pi_{g,0} + \pi_{g,1} f_g(0^+))},$$

where  $K^\infty = \{w \in \mathbb{R}_+^G : \sum_g \pi_g \bar{\pi}_{g,0} w_g \leq 1\}$ .

**Lemma 2.A.3.**  $\alpha^*$  always satisfies  $\alpha^* < 1$ .

*Proof.* We only need to show that for one  $w \in K^\infty$ , we have

$$\sum_g \pi_g w_g (\pi_{g,0} + \pi_{g,1} f_g(0^+)) > 1.$$

Let us show that this is true for every  $w \in K^\infty$  such that  $\sum_g \pi_g \bar{\pi}_{g,0} w_g = 1$ , e.g. the  $w$  defined by  $w_g = \frac{1}{\bar{\pi}_{g,0}}$  for all  $g$ . We use the fact that  $f_g(0^+) > \frac{F_g(1) - F_g(0)}{1-0} = 1$  by the strict concavity of  $F_g$ . Then  $\pi_{g,0} + \pi_{g,1} f_g(0^+) > 1$  and

$$\sum_g \pi_g w_g (\pi_{g,0} + \pi_{g,1} f_g(0^+)) > \sum_g \pi_g w_g \geq \sum_g \pi_g \bar{\pi}_{g,0} w_g = 1. \quad \square$$

Recall that  $\mathcal{I}(\cdot)$  is defined as  $\mathcal{I}(h) = \sup \{u \in [0, 1] : h(u) \geq u\}$  on the function space:

$$\mathcal{F} = \{h : [0, 1] \rightarrow [0, 1] : h(0) = 0, h \text{ is nondecreasing}\} \quad (2.A.1)$$

which has the natural order  $h_1 \leq h_2 \iff h_1(u) \leq h_2(u) \forall u \in [0, 1]$ .  $\mathcal{F}$  is also normed with the sup norm  $\|\cdot\|$ .

**Lemma 2.A.4.** *For all  $h \in \mathcal{F}$ ,  $\mathcal{I}(h)$  is a maximum and  $h(\mathcal{I}(h)) = \mathcal{I}(h)$ . Moreover,  $\mathcal{I}(\cdot)$ , seen as a map on  $\mathcal{F}$ , is nondecreasing and continuous on each continuous  $h_0 \in \mathcal{F}$  such that either  $u \mapsto h_0(u)/u$  is decreasing over  $(0, 1]$ , or  $\mathcal{I}(h_0) = 0$ .*

*Proof.*  $\mathcal{I}(h)$  is a maximum because there exists  $\epsilon_n \rightarrow 0$  such that

$$h(\mathcal{I}(h)) \geq h(\mathcal{I}(h) - \epsilon_n) \geq \mathcal{I}(h) - \epsilon_n \rightarrow \mathcal{I}(h).$$

So  $h(\mathcal{I}(h)) \geq \mathcal{I}(h)$ . Then  $h(h(\mathcal{I}(h))) \geq h(\mathcal{I}(h))$  thus  $h(\mathcal{I}(h)) \leq \mathcal{I}(h)$  by the definition of  $\mathcal{I}(h)$  as a supremum.

Next, if  $h_1 \leq h_2$ ,  $\mathcal{I}(h_1) = h_1(\mathcal{I}(h_1)) \leq h_2(\mathcal{I}(h_1))$  so  $\mathcal{I}(h_1) \leq \mathcal{I}(h_2)$  by defintion of  $\mathcal{I}(h_2)$ .

Now take a continuous  $h_0 \in \mathcal{F}$  such that either  $u \mapsto h_0(u)/u$  is decreasing or  $\mathcal{I}(h_0) = 0$ , and  $h$  any element of  $\mathcal{F}$ . Let  $\gamma > 0$ , let  $u_- = \mathcal{I}(h_0) - \gamma$  and  $u_+ = \mathcal{I}(h_0) + \gamma$ . We want to prove that there exists an  $\eta_\gamma$  such that  $\|h - h_0\| \leq \eta_\gamma$  implies  $u_- \leq \mathcal{I}(h) \leq u_+$ .

If  $u_+ > 1$  then obviously  $\mathcal{I}(h) \leq u_+$ . If not, let  $s_\gamma = \max_{u' \in [u_+, 1]} (h_0(u') - u')$ . It is a maximum by continuity over a compact and is such that  $s_\gamma < 0$ , because  $s_\gamma \geq 0$  would contradict the maximality of  $\mathcal{I}(h_0)$ .

Then, for all  $u' \in [u_+, 1]$ ,

$$h(u') - u' \leq h_0(u') - u' + \|h - h_0\|,$$

and then

$$\sup_{u' \in [u_+, 1]} (h(u') - u') \leq s_\gamma + \|h - h_0\|.$$

Hence, as soon as  $\|h - h_0\| \leq \frac{1}{2}|s_\gamma|$ ,  $\sup_{u' \in [u_+, 1]} (h(u') - u') < 0$  and  $\mathcal{I}(h) < u_+$ .

If  $u_- \leq 0$ , which is always the case if  $\mathcal{I}(h_0) = 0$ , then  $\mathcal{I}(h) \geq u_-$ . If  $u_- > 0$ ,  $u \mapsto h_0(u)/u$  is decreasing and

$$\frac{h_0(u_-)}{u_-} > \frac{h_0(\mathcal{I}(h_0))}{\mathcal{I}(h_0)} = 1,$$

so  $h_0(u_-) > u_-$ . We can then write the following:

$$h(u_-) - u_- \geq h_0(u_-) - u_- - \|h - h_0\| > 0,$$

as soon as  $\|h - h_0\| \leq \frac{1}{2}(h_0(u_-) - u_-)$ . This implies  $\mathcal{I}(h) > u_-$ . Taking

$$\eta_\gamma = \frac{1}{2} \min \left( |s_\gamma| \mathbb{1}_{\{u_+ \leq 1\}} + \mathbb{1}_{\{u_+ > 1\}}, (h_0(u_-) - u_-) \mathbb{1}_{\{u_- > 0\}} + \mathbb{1}_{\{u_- \leq 0\}} \right)$$

completes the proof.  $\square$

**Lemma 2.A.5.** *Let a weight function  $W : [0, 1] \rightarrow \mathbb{R}_+^G$ . For each  $r$  between 1 and  $m$  denote the  $W(r/m)$ -weighted  $p$ -values  $p_{g,i}^{[r]} = p_{g,i}/W_g(r/m)$  (with the convention  $p_{g,i}/0 = \infty$ ), order them  $p_{(1)}^{[r]} \leq \dots \leq p_{(m)}^{[r]}$  and note  $p_{(0)}^{[r]} = 0$ .*

*Then  $\hat{u}_W = m^{-1} \max \left\{ r \geq 0 : p_{(r)}^{[r]} \leq \alpha \frac{r}{m} \right\}$ .*

*Proof.* Let us denote  $\hat{r} = \max \left\{ r \geq 0 : p_{(r)}^{[r]} \leq \alpha \frac{r}{m} \right\}$  and show  $\hat{u}_W = \hat{r}/m$  by double inequality. First, we have

$$\begin{aligned} \hat{G}_W \left( \frac{\hat{r}}{m} \right) &= m^{-1} \sum_{g=1}^G \sum_{i=1}^{m_g} \mathbb{1}_{\{p_{g,i} \leq \alpha \frac{\hat{r}}{m} W_g(\frac{\hat{r}}{m})\}} \\ &= m^{-1} \sum_{g=1}^G \sum_{i=1}^{m_g} \mathbb{1}_{\{p_{g,i}^{[\hat{r}]} \leq \alpha \frac{\hat{r}}{m}\}} \\ &= m^{-1} \sum_{r=1}^m \mathbb{1}_{\{p_{(r)}^{[\hat{r}]} \leq \alpha \frac{\hat{r}}{m}\}} \geq \hat{r}/m, \end{aligned}$$

because  $p_{(1)}^{[\hat{r}]}, \dots, p_{(\hat{r})}^{[\hat{r}]} \leq \alpha \frac{\hat{r}}{m}$ . Then  $\hat{r}/m \leq \hat{u}_W$  by definition of  $\hat{u}_W$ . Second, we know that  $\hat{u}_W$  can be written as  $\hat{\kappa}/m$  because  $\hat{u}_W = \hat{G}_W(\hat{u}_W)$ , so we want to show that  $\hat{\kappa} \leq \hat{r}$  which

is implied by  $p_{(\hat{\kappa})}^{[\hat{\kappa}]} \leq \alpha \frac{\hat{\kappa}}{m}$ . The latter is true because

$$\sum_{r=1}^m \mathbb{1}_{\left\{p_{(r)}^{[\hat{\kappa}]} \leq \alpha \frac{\hat{\kappa}}{m}\right\}} = m \hat{G}_W \left( \frac{\hat{\kappa}}{m} \right) = m \hat{G}_W (\hat{u}_W) \geq \hat{\kappa}.$$

□

**Lemma 2.A.6.**  $\hat{G}_{\hat{W}^*}$  is nondecreasing.

*Proof.* Let  $u \leq u'$ .  $\hat{G}_{\hat{W}^*}(u') = \max_{w \in \hat{K}} \hat{G}_w(u')$  so by denoting  $w = \hat{W}^*(u)$  we have  $\hat{G}_{\hat{W}^*}(u') \geq \hat{G}_w(u')$ . Furthermore,

$$\hat{G}_w(u') = \frac{1}{m} \sum_{g=1}^G \sum_{i=1}^{m_g} \mathbb{1}_{\{p_{g,i} \leq \alpha u' w_g\}} \geq \frac{1}{m} \sum_{g=1}^G \sum_{i=1}^{m_g} \mathbb{1}_{\{p_{g,i} \leq \alpha u w_g\}} = \hat{G}_{\hat{W}^*}(u),$$

which entails  $\hat{G}_{\hat{W}^*}(u') \geq \hat{G}_{\hat{W}^*}(u)$ . □

## Appendix 2.B Asymptotical weighting

Define, for a weight function  $W : [0, 1] \rightarrow \mathbb{R}_+^G$ , possibly random,

$$P_W^\infty : u \mapsto \sum_{g=1}^G \pi_g \pi_{g,1} F_g(\alpha u W_g(u));$$

$$G_W^\infty : u \mapsto \sum_{g=1}^G \pi_g D_g(\alpha u W_g(u));$$

and

$$H_W^\infty(u) = G_W^\infty(u) - P_W^\infty(u),$$

where

$$D_g : t \mapsto \pi_{g,0} U(t) + \pi_{g,1} F_g(t) \quad (2.B.1)$$

is strictly concave on  $[0, 1]$  because  $F_g$  is and  $\pi_{g,1} > 0$ . Note that, if  $W$  is a fixed deterministic weight function,  $P_W^\infty$  and  $G_W^\infty$  are the uniform limits of  $P_W^{(m)}$  and  $G_W^{(m)}$  when  $m \rightarrow \infty$ . If  $W$  is such that  $G_W^\infty$  is nondecreasing, we also define

$$u_W^\infty = \mathcal{I}(G_W^\infty). \quad (2.B.2)$$

Recall that  $K^\infty = \{w \in \mathbb{R}_+^G : \sum_g \pi_g \bar{\pi}_{g,0} w_g \leq 1\}$ . It is the asymptotic version of  $\hat{K}$ . We now define oracle optimal weights over  $K^\infty$  for  $G_W^\infty(u)$  and  $P_W^\infty(u)$ , for all  $u > 0$ .

**Lemma 2.B.1.** Fix an  $u \in [0, 1]$ . Then  $\arg \max_{w \in K^\infty} G_w^\infty(u)$  is non empty.

If  $0 < \alpha u \leq \bar{\pi}_0$ , it is a singleton. In this case, its only element  $w^*$  belongs to  $[0, \frac{1}{\alpha u}]^G$  and satisfies  $\sum_g \pi_g \bar{\pi}_{g,0} w_g^* = 1$ . If  $\alpha u \geq \bar{\pi}_0$  it is included in  $[\frac{1}{\alpha u}, \infty)^G$ .

Finally,  $\max_{w \in K^\infty} G_w^\infty(u) \leq 1$  with equality if and only if  $\alpha u \geq \bar{\pi}_0$ .

The same statements are true for  $P_w^\infty$ , except that the upper bound of  $\max_{w \in K^\infty} P_w^\infty(u)$ , which is achieved if and only if  $\alpha u \geq \bar{\pi}_0$ , is not 1 but  $1 - \pi_0$ .

*Proof.* The function  $w \mapsto G_w^\infty(u)$  is continuous over the compact  $K^\infty$  so it has a maximum. Note that  $\max_{w \in K^\infty} G_w^\infty(0) = 0$  and  $\arg \max_{w \in K^\infty} G_w^\infty(0) = K^\infty$ . For the rest of the proof  $u$  is greater than 0.

First we show that any  $w^* \in \arg \max_{w \in K^\infty} G_w^\infty(u)$  belongs to  $[0, \frac{1}{\alpha u}]^G$  or  $[\frac{1}{\alpha u}, \infty)^G$ . If not, there is  $w^* \in \arg \max_{w \in K^\infty} G_w^\infty(u)$  such that  $\alpha uw_{g_1}^* > 1$  and  $\alpha uw_{g_2}^* < 1$  for some  $g_1, g_2 \leq G$ . Now then we define  $\tilde{w}$  such that  $\tilde{w}_g = w_g^*$  for all  $g \notin \{g_1, g_2\}$ ,  $\tilde{w}_{g_1} = \frac{1}{\alpha u}$  and

$$\tilde{w}_{g_2} = w_{g_2}^* + \left( w_{g_1}^* - \frac{1}{\alpha u} \right) \frac{\pi_{g_1} \bar{\pi}_{g_1,0}}{\pi_{g_2} \bar{\pi}_{g_2,0}} > w_{g_2}^*.$$

So  $\tilde{w}$  belongs to  $K^\infty$  and satisfies

$$\begin{aligned} G_{\tilde{w}}^\infty(u) &= \sum_{g \neq g_1, g_2} \pi_g D_g(\alpha uw_g^*) + \pi_{g_1} + \pi_{g_2} D_{g_2}(\alpha u \tilde{w}_{g_2}) \\ &> \sum_{g \neq g_1, g_2} \pi_g D_g(\alpha uw_g^*) + \pi_{g_1} + \pi_{g_2} D_{g_2}(\alpha uw_{g_2}^*) = G_{w^*}^\infty(u), \end{aligned}$$

because  $D_g$  is increasing over  $[0, 1]$  and then constant equal to 1. This contradicts the definition of  $w^*$  so is impossible.

Next we distinct three cases.

(i)  $\alpha u = \bar{\pi}_0$ . Then  $w_0 = (\frac{1}{\alpha u}, \dots, \frac{1}{\alpha u}) = (\frac{1}{\bar{\pi}_0}, \dots, \frac{1}{\bar{\pi}_0})$  is obviously an element of  $\arg \max_{w \in K^\infty} G_w^\infty(u)$  because

$$G_{w_0}^\infty(u) = \sum_{g=1}^G \pi_g D_g(1) = 1,$$

and we easily check that  $\sum_g \pi_g \bar{\pi}_{g,0} (w_0)_g = 1$ . Thus for every  $w \in K^\infty$  distinct from  $w_0$ , there must exist a  $g_1 \in \{1, \dots, G\}$  such that  $\alpha uw_{g_1} < 1$ , so  $D_{g_1}(\alpha uw_{g_1}) < 1$  and  $G_w^\infty(u) < \sum_g \pi_g = 1$ :  $w_0$  is the only element of  $\arg \max_{w \in K^\infty} G_w^\infty(u)$ .

(ii)  $\alpha u < \bar{\pi}_0$ . If a  $w^* \in \arg \max_{w \in K^\infty} G_w^\infty(u)$  exists in  $[\frac{1}{\alpha u}, \infty)^G$ , then  $w_g^* \geq \frac{1}{\alpha u} > \frac{1}{\bar{\pi}_0}$  and  $\sum_g \pi_g \bar{\pi}_{g,0} w_g^* > 1$  which is impossible. So

$$\arg \max_{w \in K^\infty} G_w^\infty(u) = \arg \max_{w \in K^\infty \cap [0, \frac{1}{\alpha u}]^G} G_w^\infty(u).$$

The function  $w \mapsto G_w^\infty(u)$  is strictly concave over the convex set  $K^\infty \cap [0, \frac{1}{\alpha u}]^G$  because  $\pi_{g,1} > 0$  and  $D_g$  is strictly concave over  $[0, 1]$  for all  $g$ , hence the maximum is unique.

We showed that the only  $w^* \in \arg \max_{w \in K^\infty} G_w^\infty(u)$  is not in  $[\frac{1}{\alpha u}, \infty)^G$  so there exists  $g_1 \leq G$  such that  $\alpha u w_{g_1}^* < 1$  thus  $G_{w^*}^\infty(u) < 1$ . Furthermore  $\sum_g \pi_g \bar{\pi}_{g,0} w_g^* = 1$  : if not there would exist a  $\tilde{w}$  with  $\tilde{w}_{g_1} > w_{g_1}^*$  (for the same  $g_1$  as in previous sentence) and  $\tilde{w}_g = w_g^*$  for all  $g \neq g_1$  such that  $\tilde{w} \in K^\infty$  and  $G_{\tilde{w}}^\infty(u) > G_{w^*}^\infty(u)$  which is impossible.

(iii)  $\alpha u > \bar{\pi}_0$ . So  $u > \frac{\bar{\pi}_0}{\alpha}$  and obviously

$$\max_{w \in K^\infty} G_w^\infty(u) \geq \max_{w \in K^\infty} G_w^\infty\left(\frac{\bar{\pi}_0}{\alpha}\right) = G_{w_0}^\infty\left(\frac{\bar{\pi}_0}{\alpha}\right) = 1,$$

as stated in case (i). So  $\max_{w \in K^\infty} G_w^\infty(u) = 1$  and the vectors  $w^*$  of  $\arg \max_{w \in K^\infty} G_w^\infty(u)$  are the ones fulfilling  $D_g(\alpha u w_g^*) = 1$  for all  $g$  that is  $w^* \in [\frac{1}{\alpha u}, \infty)^G$ .

The proof is similar for  $P^\infty$ , by replacing  $D_g$  by  $\pi_{g,1} F_g$ .  $\square$

From now on,  $W^*(u)$  denotes an element of  $\arg \max_{w \in K^\infty} G_w^\infty(u)$  (just like we write  $\widehat{W}^*(u)$  as an element of  $\arg \max_{w \in \hat{K}} \widehat{G}_w(u)$ ), our results will not depend on the chosen element of the argmax. Next Lemma gives some properties on the function  $G_{W^*}^\infty$ , among them  $G_{W^*}^\infty$  is nondecreasing which allow us to define

$$u^* = u_{W^*}^\infty = \mathcal{I}(G_{W^*}^\infty). \quad (2.B.3)$$

**Lemma 2.B.2.**  $G_{W^*}^\infty$  is nondecreasing and  $u^* > 0$ .  $G_{W^*}^\infty$  is strictly concave over  $[0, \frac{\bar{\pi}_0}{\alpha} \wedge 1]$  and, if  $\alpha \geq \bar{\pi}_0$ , constant equal to 1 over  $[\frac{\bar{\pi}_0}{\alpha}, 1]$ .

In particular, (i)  $u^* = 1$  if and only if  $\alpha \geq \bar{\pi}_0$ , (ii) the function  $u \mapsto G_{W^*}^\infty(u)/u$  is decreasing over  $(0, 1]$ , (iii)  $G_{W^*}^\infty$  is continuous over  $[0, 1]$ .

*Proof.*  $G_{W^*}^\infty$  is nondecreasing by exactly the same argument as in the proof of Lemma 2.A.6. The result can be strengthened thanks to Lemma 2.B.1, by writing, for  $u < u' \leq \frac{\bar{\pi}_0}{\alpha} \wedge 1$ , that  $G_{W^*(u)}^\infty(u') > G_{W^*(u)}^\infty(u)$  because  $1 > G_{W^*}^\infty(u)$ . So  $G_{W^*}^\infty$  is increasing on  $[0, \frac{\bar{\pi}_0}{\alpha} \wedge 1]$ .

To prove that  $u^* > 0$ , take some  $w \in K^\infty$  such that

$$\alpha > \frac{1}{\sum_g \pi_g w_g (\pi_{g,0} + \pi_{g,1} f_g(0^+))} \geq \alpha^*.$$

Because the expression above is continuous of the  $w_g$ , they can always be chosen nonzero. We have  $u^* \geq u_w^\infty$  because  $G_{W^*}^\infty \geq G_w^\infty$ . Then we have, for  $x > 0$ ,  $x \rightarrow 0^+$ ,

$$\begin{aligned} \frac{G_w^\infty(x) - G_w^\infty(0)}{x - 0} &= \frac{G_w^\infty(x)}{x} = \sum_g \pi_g \pi_{g,0} \alpha w_g + \sum_g \pi_g \pi_{g,1} \alpha w_g \frac{F_g(\alpha x w_g)}{\alpha x w_g} \\ &\rightarrow \alpha \sum_g \pi_g w_g (\pi_{g,0} + \pi_{g,1} f_g(0^+)) > 1, \end{aligned}$$

so  $G_w^\infty(u) > u$  in the neighborhood of  $0^+$ , which entails  $u_w^\infty > 0$ .

Now take  $a, b \in [0, \frac{\bar{\pi}_0}{\alpha} \wedge 1]$  with  $a < b$  and  $\lambda \in (0, 1)$ , by Lemma 2.B.1, we have that  $\alpha a W_g^*(a), \alpha b W_g^*(b) \leq 1$  and then, for all  $g$ :

$$D_g (\lambda \alpha a W_g^*(a) + (1 - \lambda) \alpha b W_g^*(b)) \geq \lambda D_g (\alpha a W_g^*(a)) + (1 - \lambda) D_g (\alpha b W_g^*(b)).$$

Moreover, because  $G_{W^*}^\infty(a) < G_{W^*}^\infty(b)$ , for at least one  $g_1$  we have  $a W_{g_1}^*(a) \neq b W_{g_1}^*(b)$  and by strict concavity of  $D_{g_1}$  the inequality above is strict for  $g_1$ . Then define  $\tilde{w}_g = \frac{\lambda a W_g^*(a) + (1 - \lambda) b W_g^*(b)}{\lambda a + (1 - \lambda) b}$ . We have  $\tilde{w} \in K^\infty$  and then for all  $g$ :

$$\pi_g D_g (\alpha(\lambda a + (1 - \lambda) b) \tilde{w}_g) \geq \lambda \pi_g D_g (\alpha a W_g^*(a)) + (1 - \lambda) \pi_g D_g (\alpha b W_g^*(b)),$$

the inequality being strict for  $g_1$ . Finally by summing:

$$G_{W^*}^\infty(\lambda a + (1 - \lambda) b) \geq G_{\tilde{w}}^\infty(\lambda a + (1 - \lambda) b) > \lambda G_{W^*}^\infty(a) + (1 - \lambda) G_{W^*}^\infty(b).$$

Additionally,  $G_{W^*}^\infty(u) = 1$  for  $\alpha u \geq \bar{\pi}_0$  comes from Lemma 2.B.1. The fact that  $u^* = 1 \iff \alpha \geq \bar{\pi}_0$  follows directly from the previous statements and Lemma 2.B.1. The decreasingness of  $u \mapsto G_{W^*}^\infty(u)/u$  is straightforward from strict concavity properties because it is the slope of the line between the origin and the graph of  $G_{W^*}^\infty$  at abscissa  $u > 0$ . Previous statements imply that  $G_{W^*}^\infty$  is continuous at least over  $(0, \frac{\bar{\pi}_0}{\alpha} \wedge 1)$  and, if  $\alpha \geq \bar{\pi}_0$ , over  $[\frac{\bar{\pi}_0}{\alpha}, 1]$ .  $K^\infty$  is bounded, let  $B$  such that  $|w_g| \leq B$  for all  $w \in K^\infty$ , then  $G_{W^*}^\infty(u) \leq \sum_g \frac{m_g}{m} D_g(\alpha u B) \rightarrow 0$  when  $u \rightarrow 0$  which gives the continuity in 0. As in the proof of Lemma 2.A.1, the continuity in  $\frac{\bar{\pi}_0}{\alpha} \wedge 1$  is given by the combination of concavity and nondecrease.  $\square$

*Remark 2.B.1.* The case  $\alpha \geq \bar{\pi}_0$  is rarely met in practice because  $\alpha$  is chosen small and the signal is assumed to be sparse (so  $\bar{\pi}_0$  is large) but it is kept to cover all situations. It confirms the intuitive idea that in this situation the best strategy is to reject all hypotheses because then the FDP is equal to  $\pi_0 \leq \bar{\pi}_0 \leq \alpha$ .

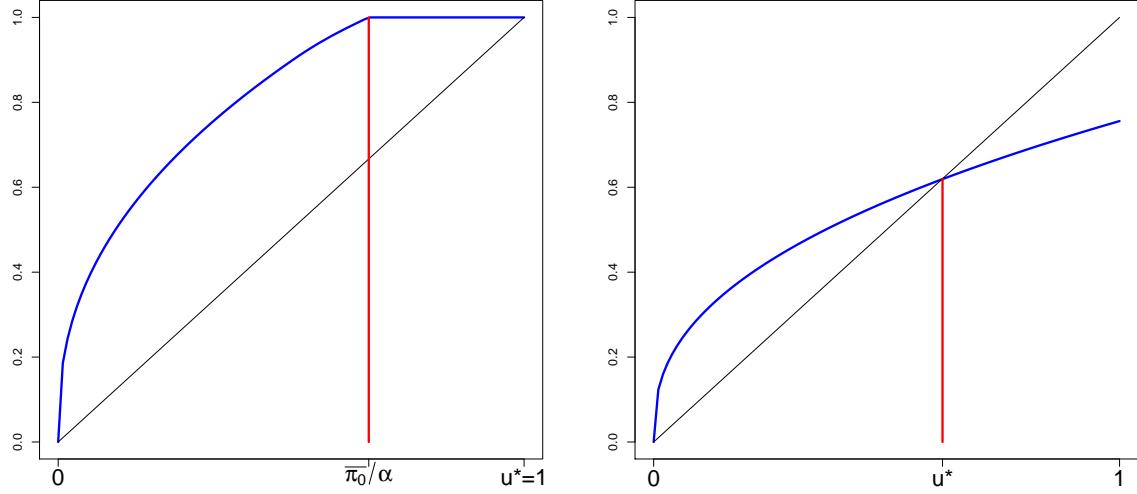


Fig. 2.7 Plot of  $u \mapsto G_{W^*}^\infty(u)$  when  $\alpha \geq \bar{\pi}_0$  (left panel) and  $\alpha < \bar{\pi}_0$  (right panel).

*Remark 2.B.2.* For a weight vector  $w \in \mathbb{R}_+^G$ ,  $G_w^\infty$  is obviously continuous. Moreover if  $w \neq 0$ , let  $M = \max_{0 \leq u \leq 1} G_w^\infty(u) \leq 1$  and  $u^\diamond = \min\{u : G_w^\infty(u) = M\} > 0$ , then  $G_w^\infty$  is strictly concave over  $[0, u^\diamond]$  and constant equal to  $M$  on  $[u^\diamond, 1]$ , hence  $u \mapsto G_w^\infty(u)/u$  is decreasing. So whether  $w = 0$  or not,  $\mathcal{I}(\cdot)$  is continuous in  $G_w^\infty$  by Lemma 2.A.4.

*Remark 2.B.3.* The proof of the strict concavity of  $G_{W^*}^\infty$  can easily be adapted to show the (non necessary strict) concavity of  $\tilde{G}_{W^*}$  when  $\tilde{D}_g = \text{LCM}(\widehat{D}_g)$ .

Figure 2.7 illustrates all the properties stated in Lemma 2.B.2, with the two cases  $\alpha \geq \bar{\pi}_0$  and  $\alpha < \bar{\pi}_0$ .

The next Lemma justifies the intuitive idea that maximizing the rejections and the power is the same thing (as exposed in Section 2.3.2), but only under (ME).

**Lemma 2.B.3.** *If (ME) holds, for all  $u \in [0, 1]$ ,*

$$\arg \max_{w \in K^\infty} G_w^\infty(u) = \arg \max_{w \in K^\infty} P_w^\infty(u).$$

*In particular,  $P_{W^*}^\infty$  is continuous nondecreasing.*

*Proof.* First,  $\arg \max_{w \in K^\infty} G_w^\infty(0) = \arg \max_{w \in K^\infty} P_w^\infty(0) = K^\infty$ , so assume  $u > 0$ . If  $\alpha u \geq \bar{\pi}_0$ ,  $\max_{w \in K^\infty} G_w^\infty(u) = 1$  and  $\max_{w \in K^\infty} P_w^\infty(u) = 1 - \pi_0$  by Lemma 2.B.1, thus  $\arg \max_{w \in K^\infty} G_w^\infty(u)$  and  $\arg \max_{w \in K^\infty} P_w^\infty(u)$  are both equal to the set of weights  $w \in K^\infty$  such that  $\alpha uw_g \geq 1$  for all  $g$ .

Now if  $\alpha u \leq \bar{\pi}_0$ , both  $\arg \max$  are singletons. Take  $w^*$  the only element of  $\arg \max_{w \in K^\infty} P_w^\infty(u)$ . Recall that there exists  $C \geq 1$  such that, for all  $1 \leq g \leq G$ ,  $\bar{\pi}_{g,0} = C\pi_{g,0}$ , and write, for all  $w \in K^\infty$ ,

$$\begin{aligned} G_w^\infty(u) &= \sum_g \pi_g \bar{\pi}_{g,0} U(\alpha u w_g) + P_w^\infty(u) \\ &\leq \alpha u \sum_g \pi_g \bar{\pi}_{g,0} w_g + P_{w^*}^\infty(u) \\ &= \frac{\alpha u}{C} \sum_g \pi_g \bar{\pi}_{g,0} w_g + P_{w^*}^\infty(u) \\ &\leq \frac{\alpha u}{C} \times 1 + P_{w^*}^\infty(u) \\ &= \sum_g \pi_g \bar{\pi}_{g,0} U(\alpha u w_g^*) + P_{w^*}^\infty(u) = G_{w^*}^\infty(u), \end{aligned}$$

because  $\sum_g \pi_g \bar{\pi}_{g,0} w_g^* = 1$  and  $\alpha u w_g^* \leq 1$  for all  $g$ , by Lemma 2.B.1. This means that  $w^*$  is also the unique element of  $\arg \max_{w \in K^\infty} G_w^\infty(u)$ . Finally the properties on  $P_{W^*}^\infty$  are obtained by the same proof as Lemma 2.B.2.  $\square$

The next lemma is only a deterministic tool used in the proof of Lemma 2.C.4. Define the distance  $d$  of a weight vector  $w$  to a subset  $S$  of  $\mathbb{R}_+^G$  by  $d(w, S) = \inf_{\bar{w} \in S} \max_g |w_g - \bar{w}_g|$ . Let  $M_u = \arg \max_{w \in K^\infty} G_w^\infty(u)$  to lighten notations.

**Lemma 2.B.4.** *Take some  $u \in (0, 1]$ . Then we have:*

$$\forall \epsilon > 0, \exists \xi > 0, \forall w \in K^\infty, |G_w^\infty(u) - G_{W^*}^\infty(u)| \leq \xi \Rightarrow d(w, M_u) < \epsilon.$$

In particular, if  $\alpha u \leq \bar{\pi}_0$ ,

$$\forall \epsilon > 0, \exists \xi > 0, \forall w \in K^\infty, |G_w^\infty(u) - G_{W^*}^\infty(u)| \leq \xi \Rightarrow \max_g |w_g - W_g^*(u)| < \epsilon, \quad (2.B.4)$$

and if  $\alpha u \geq \bar{\pi}_0$ ,

$$\forall \epsilon > 0, \exists \xi > 0, \forall w \in K^\infty, |G_w^\infty(u) - G_{W^*}^\infty(u)| \leq \xi \Rightarrow (\forall g, \alpha u w_g > 1 - \epsilon). \quad (2.B.5)$$

*Proof.* If the statement is false, there exists some  $\epsilon > 0$  and some sequence  $(w_n)_{n \geq 1}$  converging to a  $w^\ell$  in  $K^\infty$  (because  $K^\infty$  is compact), such that  $d(w_n, M_u) \geq \epsilon$  and

$$|G_{w_n}^\infty(u) - G_{W^*}^\infty(u)| \rightarrow 0.$$

By continuity of  $D_g$ ,  $G_{w^\ell}^\infty(u) = G_{W^*}^\infty(u)$  so  $w^\ell \in M_u$  which contradicts  $d(w^\ell, M_u) \geq \epsilon$ . If  $\alpha u \leq \bar{\pi}_0$ ,  $M_u$  is a singleton by Lemma 2.B.1, hence (2.B.4). However, if  $\alpha u \geq \bar{\pi}_0$ ,  $M_u = \{w \in K^\infty : \alpha uw_g \geq 1 \forall g\}$  by Lemma 2.B.1, hence (2.B.5).  $\square$

## Appendix 2.C Convergence lemmas

Recall that  $\|\cdot\|$  is the sup norm for the bounded functions on their definition domain:  $\|f\| = \sup_{u \in [0,1]} |f(u)|$  or  $\|f\| = \sup_{t \in \mathbb{R}} |f(t)|$ .

**Lemma 2.C.1.** *The following quantities converge to 0 almost surely:*

$\sup_{w \in \mathbb{R}_+^G} \|\widehat{H}_w - H_w^\infty\|$ ,  $\sup_{w \in \mathbb{R}_+^G} \|\widehat{P}_w - P_w^\infty\|$ ,  $\sup_{w \in \mathbb{R}_+^G} \|\widehat{G}_w - G_w^\infty\|$ , and  $\|\widehat{D}_g - D_g\|$ , for all  $g \in \{1, \dots, G\}$ .

Furthermore, for any  $(\widetilde{D}_g)_g$  such that  $\|\widetilde{D}_g - D_g\| \xrightarrow{\mathbb{P}} 0$ ,

$$\sup_{w \in \mathbb{R}_+^G} \|\widetilde{G}_w - G_w^\infty\| \xrightarrow{\mathbb{P}} 0. \quad (2.C.1)$$

*Proof.* By using the same proof as the one of the Glivenko-Cantelli theorem, we get from (2.2.1) and (2.2.2) that, for all  $g$ ,

$$\left\| \frac{1}{m_{g,0}} \sum_{i=1}^{m_g} \mathbb{1}_{\{p_{g,i} \leq \cdot, H_{g,i}=0\}} - U \right\| \xrightarrow{a.s.} 0,$$

and

$$\left\| \frac{1}{m_{g,1}} \sum_{i=1}^{m_g} \mathbb{1}_{\{p_{g,i} \leq \cdot, H_{g,i}=1\}} - F_g \right\| \xrightarrow{a.s.} 0.$$

Next, we write that

$$\begin{aligned} \left\| \frac{1}{m_g} \sum_{i=1}^{m_g} \mathbb{1}_{\{p_{g,i} \leq \cdot, H_{g,i}=0\}} - \pi_{g,0} U \right\| &\leq \left| \frac{m_{g,0}}{m_g} - \pi_{g,0} \right| \\ &\quad + \pi_{g,0} \left\| \frac{1}{m_{g,0}} \sum_{i=1}^{m_g} \mathbb{1}_{\{p_{g,i} \leq \cdot, H_{g,i}=0\}} - U \right\| \\ &\xrightarrow{a.s.} 0, \end{aligned}$$

and similarly  $\left\| \frac{1}{m_g} \sum_{i=1}^{m_g} \mathbb{1}_{\{p_{g,i} \leq \cdot, H_{g,i}=1\}} - \pi_{g,1} F_g \right\| \xrightarrow{a.s.} 0$ . So by summing,  $\|\widehat{D}_g - D_g\| \xrightarrow{a.s.} 0$ . Apply the triangular inequality once again to get  $\left\| \frac{1}{m} \sum_{i=1}^{m_g} \mathbb{1}_{\{p_{g,i} \leq \cdot, H_{g,i}=0\}} - \pi_g \pi_{g,0} U \right\| \xrightarrow{a.s.} 0$ ,

which implies

$$\begin{aligned} \sup_{w \in \mathbb{R}_+^G} \|\widehat{H}_w - H_w^\infty\| &\leq \sum_{g=1}^G \left\| \frac{1}{m} \sum_{i=1}^{m_g} \mathbf{1}_{\{p_{g,i} \leq \cdot, H_{g,i}=0\}} - \pi_g \pi_{g,0} U \right\| \\ &\xrightarrow{a.s.} 0. \end{aligned}$$

Similarly  $\sup_{w \in \mathbb{R}_+^G} \|\widehat{P}_w - P_w^\infty\| \xrightarrow{a.s.} 0$  and  $\sup_{w \in \mathbb{R}_+^G} \|\widehat{G}_w - G_w^\infty\| \xrightarrow{a.s.} 0$  by sum.

Finally,

$$\sup_{w \in \mathbb{R}_+^G} \|\widetilde{G}_w - G_w^\infty\| \leq \sum_g \left( \left| \frac{m_g}{m} - \pi_g \right| + \pi_g \|\widetilde{D}_g - D_g\| \right) \xrightarrow{\mathbb{P}} 0. \quad \square$$

From now on  $\widetilde{D}_g$  is assumed to converge uniformly to  $D_g$  in probability and that  $\widetilde{W}^*(u) \in \arg \max_{w \in \hat{K}} \widetilde{G}_w(u)$  exists for all  $u$ .

Next Lemma is the main technical one (with the longest proof).

**Lemma 2.C.2.** *We have the following convergence in probability:*

$$\|\widetilde{G}_{\widetilde{W}^*} - G_{\widetilde{W}^*}^\infty\| \xrightarrow{\mathbb{P}} 0.$$

*Proof.* First,

$$\|\widetilde{G}_{\widetilde{W}^*} - G_{\widetilde{W}^*}^\infty\| \leq \sup_{w \in \mathbb{R}_+^G} \|\widetilde{G}_w - G_w^\infty\| + \|G_{\widetilde{W}^*}^\infty - G_{\widetilde{W}^*}^\infty\|,$$

where the first term tends to 0 by (2.C.1), so we work on the second term.

The main idea is to use the maximality of  $\widetilde{G}_w(u)$  in  $\widetilde{W}^*(u)$  and the maximality of  $G_w^\infty(u)$  in  $W^*(u)$ . The problem is that one is a maximum over  $\hat{K}$  and the other is over  $K^\infty$ . The solution consists in defining small variations of  $\widetilde{W}^*(u)$  and  $W^*(u)$  to place them respectively in  $K^\infty$  and  $\hat{K}$ .

Let  $\widetilde{W}_g^\dagger(u) = \frac{m_g \hat{\pi}_{g,0}}{m \pi_g \bar{\pi}_{g,0}} \widetilde{W}_g^*(u)$ . Then  $\widetilde{W}_g^\dagger(u) \in K^\infty$  and

$$\begin{aligned} \|\widetilde{W}_g^\dagger - \widetilde{W}_g^*\| &= \left| \frac{m_g \hat{\pi}_{g,0}}{m \pi_g \bar{\pi}_{g,0}} - 1 \right| \|\widetilde{W}_g^*\| \\ &\leq \left| \frac{m_g \hat{\pi}_{g,0}}{m \pi_g \bar{\pi}_{g,0}} - 1 \right| \frac{m}{m_g \hat{\pi}_{g,0}} \xrightarrow{\mathbb{P}} 0 \text{ because } \frac{m_g \hat{\pi}_{g,0}}{m} \xrightarrow{\mathbb{P}} \pi_g \bar{\pi}_{g,0}, \end{aligned}$$

which in turn implies that

$$\begin{aligned} \|G_{\tilde{W}^\dagger}^\infty - G_{\tilde{W}^*}^\infty\| &\leq \sum_g \pi_g \sup_u |D_g(\alpha u \tilde{W}_g^\dagger(u)) - D_g(\alpha u \tilde{W}_g^*(u))| \\ &\xrightarrow{\mathbb{P}} 0, \end{aligned} \quad (2.C.2)$$

because  $D_g$  is uniformly continuous over  $\mathbb{R}_+$ . Likewise, we define  $W_g^\dagger(u) = \frac{m\pi_g \bar{\pi}_{g,0}}{m_g \hat{\pi}_{g,0}} W_g^*(u)$ . Therefore  $W^\dagger(u) \in \hat{K}$ ,

$$\|W_g^\dagger - W_g^*\| \leq \left| \frac{m\pi_g \bar{\pi}_{g,0}}{m_g \hat{\pi}_{g,0}} - 1 \right| \frac{1}{\pi_g \bar{\pi}_{g,0}} \xrightarrow{\mathbb{P}} 0,$$

and

$$\|G_{W^\dagger}^\infty - G_{W^*}^\infty\| \leq \sum_g \pi_g \sup_u |D_g(\alpha u W_g^\dagger(u)) - D_g(\alpha u W_g^*(u))| \xrightarrow{\mathbb{P}} 0. \quad (2.C.3)$$

With (2.C.1) and (2.C.2), we deduce that

$$\begin{aligned} \|\tilde{G}_{\tilde{W}^\dagger} - \tilde{G}_{\tilde{W}^*}\| &\leq \|\tilde{G}_{\tilde{W}^\dagger} - G_{\tilde{W}^\dagger}^\infty\| + \|G_{\tilde{W}^\dagger}^\infty - G_{\tilde{W}^*}^\infty\| \\ &\quad + \|G_{\tilde{W}^*}^\infty - \tilde{G}_{\tilde{W}^*}\| \\ &\xrightarrow{\mathbb{P}} 0, \end{aligned} \quad (2.C.4)$$

and likewise with (2.C.1) and (2.C.3) we have

$$\|\tilde{G}_{W^\dagger} - \tilde{G}_{W^*}\| \xrightarrow{\mathbb{P}} 0. \quad (2.C.5)$$

Combining (2.C.1), (2.C.2), (2.C.4), (2.C.5), and the maximalities of  $\tilde{G}_{\tilde{W}^*}(u)$  and  $G_{W^*}^\infty(u)$  will finish the proof. As a start, write

$$\|G_{\tilde{W}^*}^\infty - G_{W^*}^\infty\| \leq \|G_{\tilde{W}^*}^\infty - G_{\tilde{W}^\dagger}^\infty\| + \|G_{\tilde{W}^\dagger}^\infty - G_{W^*}^\infty\|,$$

with  $\|G_{\tilde{W}^*}^\infty - G_{\tilde{W}^\dagger}^\infty\| \xrightarrow{\mathbb{P}} 0$  by (2.C.2), and, for all  $u$ ,

$$|G_{\tilde{W}^\dagger}^\infty(u) - G_{W^*}^\infty(u)| = G_{W^*}^\infty(u) - G_{\tilde{W}^\dagger}^\infty(u),$$

by maximality of  $G_{W^*}^\infty(u)$  over  $K^\infty$ . Then

$$\begin{aligned} \sup_u (G_{W^*}^\infty(u) - G_{W^\dagger}^\infty(u)) &\leq \sup_u (G_{W^*}^\infty(u) - \tilde{G}_{W^*}(u)) \\ &\quad + \sup_u (\tilde{G}_{W^*}(u) - \tilde{G}_{\tilde{W}^\dagger}(u)) \\ &\quad + \sup_u (\tilde{G}_{\tilde{W}^\dagger}(u) - G_{\tilde{W}^\dagger}^\infty(u)), \end{aligned}$$

with  $\sup_u (G_{W^*}^\infty(u) - \tilde{G}_{W^*}(u)) \xrightarrow{\mathbb{P}} 0$  and  $\sup_u (\tilde{G}_{\tilde{W}^\dagger}(u) - G_{\tilde{W}^\dagger}^\infty(u)) \xrightarrow{\mathbb{P}} 0$  by (2.C.1).

Finally,

$$\begin{aligned} \sup_u (\tilde{G}_{W^*}(u) - \tilde{G}_{\tilde{W}^\dagger}(u)) &\leq \sup_u (\tilde{G}_{W^*}(u) - \tilde{G}_{W^\dagger}(u)) \\ &\quad + \sup_u (\tilde{G}_{W^\dagger}(u) - \tilde{G}_{\tilde{W}^*}(u)) \\ &\quad + \sup_u (\tilde{G}_{\tilde{W}^*}(u) - \tilde{G}_{\tilde{W}^\dagger}(u)), \end{aligned}$$

with  $\sup_u (\tilde{G}_{W^*}(u) - \tilde{G}_{W^\dagger}(u)) \xrightarrow{\mathbb{P}} 0$  (2.C.5) and  $\sup_u (\tilde{G}_{\tilde{W}^*}(u) - \tilde{G}_{\tilde{W}^\dagger}(u)) \xrightarrow{\mathbb{P}} 0$  (2.C.4).

As a consequence there exists a random variable  $V_m \xrightarrow{\mathbb{P}} 0$  such that

$$\|\tilde{G}_{\tilde{W}^*} - G_{W^*}^\infty\| \leq \sup_u (\tilde{G}_{W^\dagger}(u) - \tilde{G}_{\tilde{W}^*}(u)) + V_m,$$

but  $\tilde{G}_{W^\dagger}(u) - \tilde{G}_{\tilde{W}^*}(u) \leq 0$  by maximality of  $\tilde{G}_{\tilde{W}^*}(u)$  over  $\hat{K}$ , so

$$\|\tilde{G}_{\tilde{W}^*} - G_{W^*}^\infty\| \leq V_m \xrightarrow{\mathbb{P}} 0. \quad \square$$

Next Lemma is a direct application of Lemma 2.A.4. Recall that  $u^* = u_{W^*}^\infty$  (see (2.B.3)) and let

$$\tilde{u} = \tilde{u}_{\tilde{W}^*} = \mathcal{I}(\tilde{G}_{\tilde{W}^*}) \tag{2.C.6}$$

**Lemma 2.C.3.** *We have the following convergences in probability:*

$$\left\{ \begin{array}{ccc} \tilde{u} & \xrightarrow{\mathbb{P}} & u^* \\ \tilde{G}_{\tilde{W}^*}(\tilde{u}) & \xrightarrow{\mathbb{P}} & G_{W^*}^\infty(u^*). \end{array} \right.$$

*Proof.*  $u \mapsto G_{W^*}^\infty(u)/u$  is nondecreasing and  $G_{W^*}^\infty$  is continuous by Lemma 2.B.2 so by Lemma 2.A.4  $\mathcal{I}(\cdot)$  is continuous in  $G_{W^*}^\infty$ : let  $\gamma > 0$  and  $\eta_\gamma$  as in the proof of Lemma 2.A.4,

then

$$\mathbb{P}(|\tilde{u} - u^*| \leq \gamma) \geq \mathbb{P}\left(\|\tilde{G}_{\tilde{W}^*} - G_{W^*}^\infty\| \leq \eta_\gamma\right) \xrightarrow{\text{Lemma 2.C.2}} 1.$$

Second result follows immediately because  $\tilde{G}_{\tilde{W}^*}(\tilde{u}) = \tilde{u}$  and  $G_{W^*}^\infty(u^*) = u^*$  by Lemma 2.A.4.  $\square$

#### Lemma 2.C.4.

- (i) If  $\alpha \leq \bar{\pi}_0$ ,  $\tilde{W}^*(\tilde{u}) \xrightarrow{\mathbb{P}} W^*(u^*)$ .
- (ii) If  $\alpha \geq \bar{\pi}_0$ , the inferior limit in probability of  $\alpha\tilde{u}\tilde{W}_g(\tilde{u})$  is greater than or equal to 1, uniformly in  $g$ , which reads formally:

$$\forall \epsilon > 0, \mathbb{P}\left(\forall g, \alpha\tilde{u}\tilde{W}_g(\tilde{u}) > 1 - \epsilon\right) \rightarrow 1.$$

*Proof.* First, we use the same trick as in the proof of Lemma 2.C.2: let  $\tilde{W}_g^\dagger(u) = \frac{m_g \bar{\pi}_{g,0}}{m \bar{\pi}_{g,0}} \tilde{W}_g^*(u)$  such that  $\tilde{W}^\dagger(u) \in K^\infty$  and  $\|\tilde{W}_g^* - \tilde{W}_g^\dagger\| \xrightarrow{\mathbb{P}} 0$ .

Let us show that  $\left|G_{\tilde{W}^\dagger(\tilde{u})}^\infty(u^*) - G_{W^*}^\infty(u^*)\right| \xrightarrow{\mathbb{P}} 0$  to apply then Lemma 2.B.4 (always possible because  $u^* > 0$ ). We have

$$\begin{aligned} \left|G_{\tilde{W}^\dagger(\tilde{u})}^\infty(u^*) - G_{W^*}^\infty(u^*)\right| &\leq \left|G_{\tilde{W}^\dagger(\tilde{u})}^\infty(u^*) - G_{\tilde{W}^*(\tilde{u})}^\infty(\tilde{u})\right| \\ &\quad + \left|G_{\tilde{W}^*(\tilde{u})}^\infty(\tilde{u}) - \tilde{G}_{\tilde{W}^*}(\tilde{u})\right| \\ &\quad + \left|\tilde{G}_{\tilde{W}^*}(\tilde{u}) - G_{W^*}^\infty(u^*)\right|. \end{aligned}$$

First term converges to 0 because for all  $g$ ,  $D_g$  is uniformly continuous and

$$\begin{aligned} |\alpha u^* \tilde{W}_g^\dagger(\tilde{u}) - \alpha \tilde{u} \tilde{W}_g^*(\tilde{u})| &\leq |\alpha u^* \tilde{W}_g^\dagger(\tilde{u}) - \alpha u^* \tilde{W}_g^*(\tilde{u})| + |\alpha u^* \tilde{W}_g^*(\tilde{u}) - \alpha \tilde{u} \tilde{W}_g^*(\tilde{u})| \\ &\leq \|\tilde{W}_g^\dagger - \tilde{W}_g^*\| + |u^* - \tilde{u}| \frac{m}{m_g \hat{\pi}_{g,0}} \xrightarrow{\mathbb{P}} 0. \end{aligned} \tag{2.C.7}$$

Apply (2.C.1) to the second term and Lemma 2.C.3 to the third.

(i) If  $\alpha \leq \bar{\pi}_0$ , then  $\alpha u^* \leq \bar{\pi}_0$  and by equation (2.B.4),  $\tilde{W}^\dagger(\tilde{u}) \xrightarrow{\mathbb{P}} W^*(u^*)$ . But for all  $g$

$$\left|\tilde{W}_g^*(\tilde{u}) - W_g^*(u^*)\right| \leq \|\tilde{W}_g^* - \tilde{W}_g^\dagger\| + \left|\tilde{W}_g^\dagger(\tilde{u}) - W_g^*(u^*)\right|,$$

and then  $\tilde{W}^*(\tilde{u}) \xrightarrow{\mathbb{P}} W^*(u^*)$ .

(ii) If  $\alpha \geq \bar{\pi}_0$ ,  $u^* = 1$  by Lemma 2.B.2 and by equation (2.B.5),

$$\forall \epsilon > 0, \mathbb{P} \left( \forall g, \alpha u^* \tilde{W}_g^\dagger(\tilde{u}) > 1 - \frac{\epsilon}{2} \right) \longrightarrow 1.$$

By equation (2.C.7) we also have

$$\forall \epsilon > 0, \mathbb{P} \left( \forall g, \left| \alpha u^* \tilde{W}_g^\dagger(\tilde{u}) - \alpha \tilde{u} \tilde{W}_g^*(\tilde{u}) \right| \leq \frac{\epsilon}{2} \right) \longrightarrow 1,$$

and by combining the two we get the desired result.  $\square$

**Lemma 2.C.5.** *We have the following convergences in probability:*

$$\hat{G}_{\tilde{W}^*}(\tilde{u}) \xrightarrow{\mathbb{P}} G_{W^*}^\infty(u^*),$$

$$\hat{H}_{\tilde{W}^*}(\tilde{u}) \xrightarrow{\mathbb{P}} H_{W^*}^\infty(u^*).$$

*Proof.* We have

$$\left| \hat{G}_{\tilde{W}^*}(\tilde{u}) - G_{W^*}^\infty(u^*) \right| \leq \sup_{w \in \mathbb{R}_+^G} \left\| \hat{G}_w - G_w^\infty \right\| + \left| G_{\tilde{W}^*}^\infty(\tilde{u}) - G_{W^*}^\infty(u^*) \right|.$$

Hence, by Lemma 2.C.1, we only need to show that  $H_{W^*}^\infty(\tilde{u}) \xrightarrow{\mathbb{P}} H_{W^*}^\infty(u^*)$ .

(i) If  $\alpha \leq \bar{\pi}_0$ ,  $\tilde{u} \xrightarrow{\mathbb{P}} u^*$  and  $\tilde{W}^*(\tilde{u}) \xrightarrow{\mathbb{P}} W^*(u^*)$  by Lemma 2.C.4. Then  $\alpha \tilde{u} \tilde{W}^*(\tilde{u}) \xrightarrow{\mathbb{P}} \alpha u^* W^*(u^*)$ . We get the desired convergence by  $D_g$ 's continuity.

(ii) If  $\alpha \geq \bar{\pi}_0$ ,  $u^* = 1$  and  $\alpha u^* W_g^*(u^*) \geq 1$  for all  $g$  so  $G_{W^*}^\infty(u^*) = 1$ . Then by Lemma 2.C.4  $D_g(\alpha \tilde{u} \tilde{W}_g^*(\tilde{u})) \xrightarrow{\mathbb{P}} 1$  which means that  $G_{\tilde{W}^*}^\infty(\tilde{u}) \xrightarrow{\mathbb{P}} \sum_g \pi_g 1 = 1$ .

The proof for  $\hat{H}$  is similar, just replace  $D_g$  by  $\pi_{g,0} U$  (and 1 by  $\pi_{g,0}$ ).  $\square$

The last lemma states that  $\text{LCM}(\widehat{D}_g)$  is a valid estimator of  $D_g$  to use in GADDOW.

**Lemma 2.C.6.** *Assume that  $\widetilde{D}_g = \text{LCM}(\widehat{D}_g)$ . Then  $\widetilde{D}_g$  is nondecreasing,  $\widetilde{D}_g(0) = 0$ ,  $\widetilde{D}_g(1) = 1$  and  $\left\| \widetilde{D}_g - D_g \right\| \xrightarrow{\mathbb{P}} 0$ .*

*Proof.*  $\widetilde{D}_g(0) = \widehat{D}_g(0) = 0$  and  $\widetilde{D}_g(1) = \widehat{D}_g(1) = 1$  from the closed form given in Lemma 1 in Carolan (2002). Let  $a, b \in [0, 1]$ ,  $a < b$ , and let

$$C(t) = \begin{cases} \widetilde{D}_g(t + b - a) & \text{if } t + b - a \leq 1 \\ 1 & \text{if } t + b - a \geq 1. \end{cases}$$

Then  $C$  is concave, and

$$C(t) \geq \begin{cases} \widehat{D}_g(t+b-a) & \geq \widehat{D}_g(t) \text{ if } t+b-a \leq 1 \\ 1 & \geq \widehat{D}_g(t) \text{ if } t+b-a \geq 1, \end{cases}$$

because  $\widehat{D}_g$  is non decreasing. So by definition of the LCM,  $C(t) \geq \widetilde{D}_g(t)$  for all  $t \in [0, 1]$ . In particular,

$$\widetilde{D}_g(b) = C(a) \geq \widetilde{D}_g(a),$$

and  $\widetilde{D}_g$  is nondecreasing. Finally, the convergence comes from  $\|\widetilde{D}_g - D_g\| \leq \|\widehat{D}_g - D_g\|$ , see also [Carolan \(2002\)](#).  $\square$

## Appendix 2.D Proof of Corollary 2.5.3 for Pro 1

First,  $\hat{w}^{(1)} \xrightarrow{\mathbb{P}} w^{(1)}$  where  $w^{(1)} = \left(\frac{1}{\bar{\pi}_0}, \dots, \frac{1}{\bar{\pi}_0}\right)$  and  $\hat{w}^{(2)} \xrightarrow{\mathbb{P}} w^{(2)}$  where, for all  $g$ ,  $w_g^{(2)} = \frac{\bar{\pi}_{g,1}}{\bar{\pi}_{g,0}(1-\bar{\pi}_0)}$ . By using Lemma 2.C.1 and the continuity of  $D_g$ , we get that  $\|\widehat{G}_{\hat{w}^{(1)}} - G_{w^{(1)}}^\infty\| \xrightarrow{\mathbb{P}} 0$  and  $\|\widehat{G}_{\hat{w}^{(2)}} - G_{w^{(2)}}^\infty\| \xrightarrow{\mathbb{P}} 0$  and then by Lemma 2.A.4 we get that  $\hat{u}_{\hat{w}^{(1)}} \xrightarrow{\mathbb{P}} u_{w^{(1)}}^\infty$  and  $\hat{u}_{\hat{w}^{(2)}} \xrightarrow{\mathbb{P}} u_{w^{(2)}}^\infty$  so  $\hat{u}_M \xrightarrow{\mathbb{P}} u_M$  where  $u_M = \max(u_{w^{(1)}}^\infty, u_{w^{(2)}}^\infty)$ .

Define again  $\widehat{W}_g^\dagger(u) = \frac{m_g \bar{\pi}_{g,0}}{m \pi_g \bar{\pi}_{g,0}} \widehat{W}_g^*(u)$  and note that the power of Pro1 is  $\mathbb{E} [\widehat{P}_{\widehat{W}^*}(\hat{u}_M)]$ . We have

$$\begin{aligned} \widehat{P}_{\widehat{W}^*}(\hat{u}_M) &\leq \sup_{w \in \mathbb{R}_+^G} \|\widehat{P}_w - P_w^\infty\| + \|P_{\widehat{W}^*}^\infty - P_{\widehat{W}^\dagger}^\infty\| + P_{\widehat{W}^\dagger}^\infty(\hat{u}_M) \\ &\leq \sup_{w \in \mathbb{R}_+^G} \|\widehat{P}_w - P_w^\infty\| + \|P_{\widehat{W}^*}^\infty - P_{\widehat{W}^\dagger}^\infty\| + P_{W^*}^\infty(\hat{u}_M) \\ &\xrightarrow{\mathbb{P}} P_{W^*}^\infty(u_M), \end{aligned}$$

because  $P_{W^*}^\infty$  is continuous by Lemma 2.B.3.

Note that  $u^* \geq u_M$  (because  $G_{W^*}^\infty \geq G_{w^{(1)}}^\infty$  and  $G_{W^*}^\infty \geq G_{w^{(2)}}^\infty$ ) to conclude.

## Appendix 2.E Proof of Theorem 2.5.3

First note that  $\mathbf{1} = (1, \dots, 1) \in \hat{K}_{\text{NE}}$ . Fix a given  $u_0 \in (0, 1)$ , say  $u_0 = 1/2$ . Then, by Lemma 2.C.1,

$$\sup_{w \in \hat{K}_{\text{NE}}} \sup_{u \in [0, 1]} (\widehat{G}_w(u) - \alpha u) \geq \widehat{G}_{\mathbf{1}}(u_0) - \alpha u_0 \xrightarrow{a.s} G_{\mathbf{1}}^\infty(u_0) - \alpha u_0. \quad (2.E.1)$$

Then, denoting  $K_1 = G_{\mathbf{1}}^\infty(u_0) - \alpha u_0$ , we have

$$\begin{aligned} K_1 &= \sum_{g=1}^G \pi_g (\pi_{g,0}\alpha u_0 + \pi_{g,1}F_g(\alpha u_0) - \alpha u_0) \\ &= \sum_{g=1}^G \pi_g \pi_{g,1} (F_g(\alpha u_0) - \alpha u_0) > 0, \end{aligned}$$

because  $\pi_{g,1} > 0$  and, by strict concavity, for any  $x \in (0, 1)$ ,

$$\frac{F_g(x)}{x} = \frac{F_g(x) - F_g(0)}{x - 0} > \frac{F_g(1) - F_g(0)}{1 - 0} = 1.$$

By multiplying both terms of (2.E.1) by  $\sqrt{m}$  we get that  $Z_m \geq \sqrt{m}Y_m$  for some variable  $Y_m$  checking  $Y_m \xrightarrow[m \rightarrow \infty]{a.s.} K_1 > 0$ .

Next, recall that

$$Z_{0m} = \sqrt{m} \sup_{u \in [0, 1]} \left( m^{-1} \sum_{g=1}^G \sum_{i=1}^{m_g} \mathbb{1}_{\{U_{g,i} \leq \alpha u \tilde{W}_g^*(u)\}} - \alpha u \right),$$

where the  $U_{g,i}$  are uniform variables over  $[0, 1]$  with, for all  $g$ ,  $U_{g,1}, \dots, U_{g,m_g}$  independent, and

$$\tilde{W}^*(u) \in \arg \max_{w \in \hat{K}_{\text{NE}}} m^{-1} \sum_{g=1}^G \sum_{i=1}^{m_g} \mathbb{1}_{\{U_{g,i} \leq \alpha u w_g\}}.$$

Define also  $\hat{U}_{g,m_g} : t \mapsto m_g^{-1} \sum_{i=1}^{m_g} \mathbb{1}_{\{U_{g,i} \leq t\}}$ . We then have

$$\begin{aligned} Z_{0m} &= \sqrt{m} \sup_{u \in [0, 1]} \left( \sum_{g=1}^G \frac{m_g}{m} \hat{U}_{g,m_g} (\alpha u \tilde{W}_g^*(u)) - \alpha u \right) \\ &= \sqrt{m} \sup_{u \in [0, 1]} \left( \sum_{g=1}^G \frac{m_g}{m} (\hat{U}_{g,m_g} (\alpha u \tilde{W}_g^*(u)) - \alpha u \tilde{W}_g^*(u)) \right) \end{aligned} \tag{2.E.2}$$

$$\begin{aligned} &\leq \sqrt{m} \sum_{g=1}^G \frac{m_g}{m} \sup_{t \in \mathbb{R}^+} (\hat{U}_{g,m_g}(t) - t) \\ &\leq \sqrt{m} \sum_{g=1}^G \frac{m_g}{m} \sup_{t \in [0, 1]} (\hat{U}_{g,m_g}(t) - U(t)), \end{aligned} \tag{2.E.3}$$

where the equality in (2.E.2) comes from  $\sum_g \frac{m_g}{m} \widetilde{W}_g^*(u) = 1$ , and the inequality in (2.E.3) comes from  $U(t) = \min(1, t) \leq t$ . Therefore

$$Z_{0m} \leq |Z_{0m}| \leq \sqrt{m} \sum_{g=1}^G \frac{m_g}{m} \|\widehat{U}_{g,m_g} - U\| = \sum_{g=1}^G \sqrt{\frac{m_g}{m}} \sqrt{m_g} \|\widehat{U}_{g,m_g} - U\|.$$

Therefore, for all  $c > 0$ ,

$$\begin{aligned} \mathbb{P}(Z_{0m} > c) &\leq \mathbb{P}\left(\sum_{g=1}^G \sqrt{\frac{m_g}{m}} \sqrt{m_g} \|\widehat{U}_{g,m_g} - U\| > c\right) \\ &\leq \mathbb{P}\left(\exists g : \sqrt{m_g} \|\widehat{U}_{g,m_g} - U\| > \sqrt{\frac{m}{m_g}} \frac{c}{G}\right) \\ &\leq \sum_{g=1}^G \mathbb{P}\left(\sqrt{m_g} \|\widehat{U}_{g,m_g} - U\| > \sqrt{\frac{m}{m_g}} \frac{c}{G}\right). \end{aligned}$$

Now, applying  $G$  times the Dvoretzky-Kiefer-Wolfowitz-Massart inequality ([Dvoretzky et al., 1956](#); [Massart, 1990](#)), we derive

$$\begin{aligned} \mathbb{P}(Z_{0m} > c) &\leq \sum_{g=1}^G 2 \exp\left(-2 \frac{m}{m_g} \frac{c^2}{G^2}\right) \\ &\leq 2G \exp\left(-2 \min_{1 \leq g \leq G} \left(\frac{m}{m_g}\right) \frac{c^2}{G^2}\right). \end{aligned}$$

Now define

$$c_m = \frac{G}{\sqrt{2}} \sqrt{\max_{1 \leq g \leq G} \left(\frac{m_g}{m}\right) \log\left(\frac{2G}{\beta_m}\right)} \leq K_2 \sqrt{K_3 - \log(\beta_m)} \text{ for some } K_2, K_3 > 0.$$

From above,  $\mathbb{P}(Z_{0m} > c_m) \leq \beta_m$  which in turn implies  $q_{\beta_m, m} \leq c_m$ , because by definition

$$q_{\beta_m, m} = \min\{x : \mathbb{P}(Z_{0m} > x) \leq \beta_m\}.$$

Finally,  $\phi_{\beta_m} = \mathbb{1}_{\{Z_m > q_{\beta_m, m}\}} \geq \mathbb{1}_{\{\sqrt{m} Y_m > c_m\}}$ , and  $c_m \underset{m \rightarrow \infty}{=} o(\sqrt{m})$  since  $\beta_m \geq ae^{-bm^{1-\nu}}$ , which proves that  $\phi_{\beta_m} \rightarrow 1$  almost surely.

Now showing that  $\text{sADDOW}_{\beta_m}$  has same asymptotical FDR and power as ADDOW is easy, because on one hand,

$$\begin{aligned} |\text{FDP}(\text{sADDOW}_{\beta_m}) - \text{FDP}(\text{ADDOW})| &= |(\phi_{\beta_m} - 1) \text{FDP}(\text{ADDOW}) \\ &\quad + (1 - \phi_{\beta_m}) \text{FDP}(\text{BH})| \\ &\leq 2 |1 - \phi_{\beta_m}| \xrightarrow{a.s.} 0, \end{aligned}$$

and on the other hand

$$\text{Pow}(\text{sADDOW}_{\beta_m}) = \mathbb{E} \left[ \phi_{\beta_m} \hat{P}_{\hat{W}^*}(\hat{u}) + (1 - \phi_{\beta_m}) \hat{P}_1(u_1) \right],$$

with

$$\left| \phi_{\beta_m} \hat{P}_{\hat{W}^*}(\hat{u}) + (1 - \phi_{\beta_m}) \hat{P}_1(u_1) - \hat{P}_{\hat{W}^*}(\hat{u}) \right| \leq 2 |1 - \phi_{\beta_m}| \xrightarrow{a.s.} 0.$$



# Chapter 3

## New FDR bounds for discrete and heterogeneous tests

This chapter corresponds to the published work ([Döhler et al., 2018](#)), which is a joint work with Sebastian Döhler and Etienne Roquain. The manual of the associated R package `DiscreteFDR` is provided in Appendix [C](#).

**Abstract** To find interesting items in genome-wide association studies or next generation sequencing data, a crucial point is to design powerful false discovery rate (FDR) controlling procedures that suitably combine discrete tests (typically binomial or Fisher tests). In particular, recent research has been striving for appropriate modifications of the classical Benjamini-Hochberg (BH) step-up procedure that accommodate discreteness and heterogeneity of the data. However, despite an important number of attempts, these procedures did not come with theoretical guarantees. In this paper, we provide new FDR bounds that allow us to fill this gap. More specifically, these bounds make it possible to construct BH-type procedures that incorporate the discrete and heterogeneous structure of the data and provably control the FDR for any fixed number of null hypotheses (under independence). Markedly, our FDR controlling methodology also allows to incorporate the quantity of signal in the data (corresponding therefore to a so-called  $\pi_0$ -adaptive procedure) and to recover some prominent results of the literature. The power advantage of the new methods is demonstrated in a numerical experiment and for some appropriate real data sets.

### 3.1 Introduction

Multiple testing procedures are now routinely used to find significant items in massive and complex data. An important focus has been given to methods controlling the false discovery rate (FDR) because this scalable type I error rate “survives” to high dimension. Since the original procedure of [Benjamini and Hochberg \(1995\)](#), much effort has been undertaken to design FDR controlling procedures that adapt to various underlying structures of the data, such as the quantity of signal, the signal strength and the dependencies, among others.

In this work, our motivation is to deal with adaptation to discrete and heterogeneous data. This type of data arises in many relevant applications, in particular when data are represented by counts. Examples can be found in clinical studies (see e.g. [Westfall and Wolfinger, 1997](#)), genome-wide association studies (GWAS) (see e.g. [Dickhaus et al., 2012](#)) and next generation sequencing data (NGS) (see e.g. [Chen and Doerge, 2015b](#)). It is well known (see e.g. [Westfall and Wolfinger, 1997](#)) that using discrete test statistics can generate a severe power loss, already at the stage of the single tests. A consequence is that using “blindly” the BH procedure with discrete  $p$ -values will control the FDR in a too conservative manner. Therefore, more powerful procedures that avoid this conservatism are much sought after in applications, see for instance [Karp et al. \(2016\)](#), [van den Broek et al. \(2015\)](#) and [Dickhaus et al. \(2012\)](#).

In the literature, building multiple testing procedures that take into account the discreteness of the test statistics has a long history that can be traced back to Tukey and [Mantel \(1980\)](#). Some null hypotheses can be *a priori* excluded from the study because the corresponding tests are unable to produce sufficiently small  $p$ -values. This results in a multiplicity reduction that should increase the power. While this idea has been exploited in [Tarone \(1990\)](#) and in a more general manner in [Westfall and Wolfinger \(1997\)](#) for family-wise error rate, a first attempt was made for FDR in [Gilbert \(2005\)](#). More recently, [Heyse \(2011\)](#) has proposed a more powerful solution, relying on the following averaged cumulative distribution function (c.d.f.):

$$\bar{F}(t) = \frac{1}{m} \sum_{i=1}^m F_i(t), \quad t \in [0, 1], \tag{3.1.1}$$

where each  $F_i$  corresponds to the c.d.f. of the  $i$ -th test  $p$ -value under the null hypothesis. To illustrate the potential benefit of using  $\bar{F}$ , Figure 3.1 displays this function for the pharmacovigilance data from [Heller and Gur \(2011\)](#) (see Section 3.5 for more details). It is important to note that heterogeneity and discreteness structures are both essential

in (3.1.1): on the one hand, without any heterogeneity (all the  $F_i$ 's are equal), we have  $\bar{F}(t) = F_1(t)$  and there is no benefit in averaging the null; on the other hand, without discreteness, the  $F_i$ 's are essentially invertible and the  $p$ -values can be transformed to be (continuous) uniform under the null, so that the standard BH procedure can be applied. Both structures commonly arise when multiple conditional tests are performed, for which the heterogeneity and discreteness come from marginal counts of contingency tables, e.g., for multiple Fisher exact tests (see simulations in Section 3.6). The critical values of the Heyse procedure can be obtained by inverting  $\bar{F}$  at the values  $\alpha k/m, 1 \leq k \leq m$ . Thus, the smaller the  $\bar{F}$ -values, the larger the critical values. For the example depicted in Figure 3.1, Heyse critical values improve the BH critical values roughly by a factor 3, thereby yielding a potentially strong rejection enhancement. Furthermore, since the functions  $F_i$ 's are known in practice, so is  $\bar{F}$ . Hence, the user has a good prior idea of the improvements reachable by this discrete approach. Unfortunately, the Heyse procedure does not rigorously control the FDR in general; counter-examples are provided in [Heller and Gur \(2011\)](#) and [Döhler \(2016\)](#) (and also in Appendix 3.B.1).

Meanwhile, different solutions have been explored by modifying directly the  $p$ -values, either by randomization (see [Habiger, 2015](#) and references therein), or by shrinking them to build so-called mid  $p$ -values (see [Heller and Gur, 2011](#) and references therein). While randomized approaches possess attractive theoretical properties, they are often criticized for their lack of reproducibility (see e.g. [Berger, 1996](#) and [Ripamonti et al., 2017](#)). Other approaches incorporate discreteness and heterogeneity by constructing less conservative FDR estimates, see e.g. [Pounds and Cheng \(2006\)](#), or by combining grouping and weighting approaches, see [Chen and Doerge \(2015b\)](#).

Overall, although many new procedures have been proposed in the literature, only few of them have been proved to achieve a rigorous FDR control under standard conditions, especially in the finite sample case. To the best of our knowledge, we can only refer to the discretized version of the procedure of [Benjamini and Liu \(1999\)](#) introduced by [Heller and Gur \(2011\)](#) and to the asymptotic work of [Ferreira \(2007\)](#). Our paper offers a solution to this problem by presenting new procedures that achieve both theoretical validity and good practical performance. These procedures are readily implemented in computer software and are therefore easy to apply. Moreover, since neither randomization nor any additional choice of tuning parameters is necessary, their results are easy to interpret.

The paper is organized as follows: after having precisely defined the setting in Section 3.2, we introduce in Section 3.3 new procedures relying on the following modifications

of the  $\bar{F}$  function:

$$\bar{F}_{\text{SU}}(t) = \frac{1}{m} \sum_{i=1}^m \frac{F_i(t)}{1 - F_i(\tau_m)}; \quad \bar{F}_{\text{SD}}(t) = \frac{1}{m} \sum_{i=1}^m \frac{F_i(t)}{1 - F_i(t)}, \quad t \in [0, 1],$$

(with the convention  $1/0 = +\infty$ ), where an appropriate choice of  $\tau_m$  is made. To feel how light these modifications are, Figure 3.1 displays these functions and shows they are very close to the original  $\bar{F}$  for small values of  $t$ . In addition, we also introduce more powerful "adaptive" versions, meaning that the derived critical values are designed in a way that "implicitly estimates" the overall proportion of true null hypotheses and thus may outperform the original Heyse procedure. Next, in Section 3.4, we establish rigorous FDR control of the corresponding non-adaptive and adaptive procedures under standard conditions. Our proofs, presented in Section 3.8, rely on new bounds on FDR that generalize some prominent results of the multiple testing literature. These bounds are the main mathematical contributions of the paper and are interesting in their own right, beyond the discrete setting. Also, to explore in detail the improvement of our procedures, we analyse both real and simulated data in Sections 3.5 and 3.6. Finally, while some additional procedures are presented in Appendix 3.A, other complementary results are provided in Appendices 3.B, 3.C and 3.D.

## 3.2 Preliminaries

### 3.2.1 General model

Let us observe a random variable  $X$ , defined on a probabilistic space and valued in an observation space  $(\mathcal{X}, \mathfrak{X})$ . We consider a set  $\mathcal{P}$  of possible distributions for the distribution of  $X$  and we denote the true one by  $P$ . We assume that  $m$  null hypotheses  $H_{0,i}$ ,  $1 \leq i \leq m$ , are available for  $P$  and we denote the corresponding set of true null hypotheses by  $\mathcal{H}_0(P) = \{1 \leq i \leq m : H_{0,i} \text{ is satisfied by } P\}$ . We also denote by  $\mathcal{H}_1(P)$  the complement of  $\mathcal{H}_0(P)$  in  $\{1, \dots, m\}$  and by  $m_0(P) = |\mathcal{H}_0(P)|$  the number of true nulls.

We assume that the user has at hand a set of  $p$ -values to test each null, that is, a set of random variables  $\{p_i(X), 1 \leq i \leq m\}$ , valued in  $[0, 1]$ . Throughout the paper, we also make the important (but classical) following assumption:

$$\begin{aligned} \{p_i(X), i \in \mathcal{H}_0\} &\text{ consists of independent variables} \\ &\text{and is independent of } \{p_i(X), i \in \mathcal{H}_1\}. \end{aligned} \tag{Indep}$$

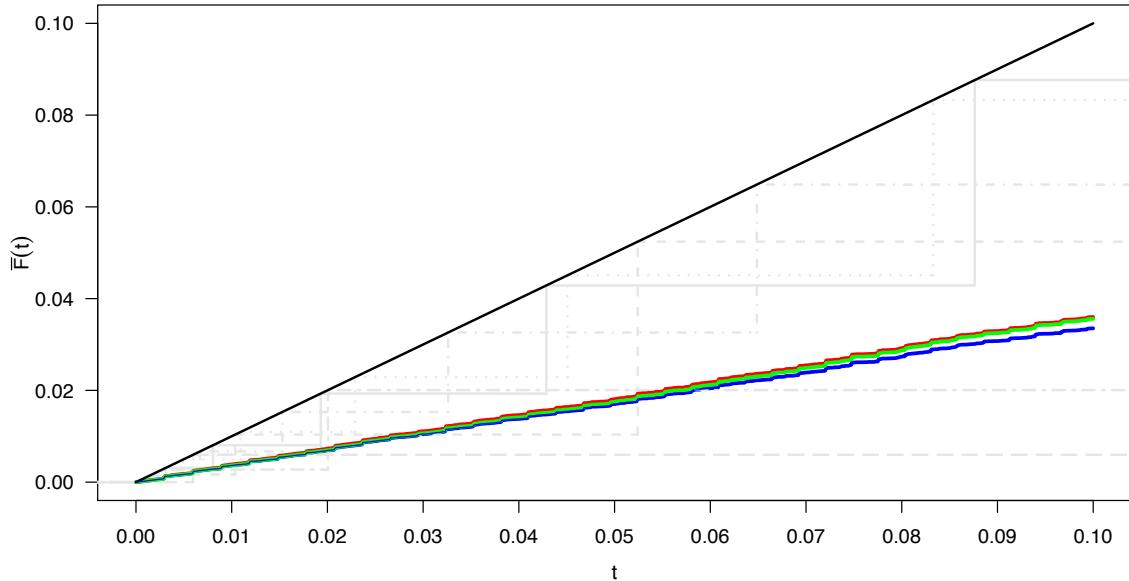


Fig. 3.1 Plots of variants of  $\bar{F}$  for the pharmacovigilance data. The solid black line corresponds to the uniform case, the discrete variants are represented by blue (for  $\bar{F}$ ), green (for  $\bar{F}_{SD}$ ) and red (for  $\bar{F}_{SU}$ ) solid lines. Some  $F_i$ 's are displayed in light grey by using different line types.

Note that (Indep) is satisfied when all the  $p$ -values  $p_i(X)$ ,  $1 \leq i \leq m$ , are mutually independent. Nevertheless, this setting also encompasses situations where there are some dependencies between the  $p$ -values under the alternative.

Now, we denote  $\mathcal{F} = \{F_i, 1 \leq i \leq m\}$ , where for each  $i \in \{1, \dots, m\}$ , we let

$$F_i(t) = \sup_{P \in \mathcal{P} : i \in \mathcal{H}_0(P)} \mathbb{P}_{X \sim P}(p_i(X) \leq t), \quad t \in [0, 1], \quad 1 \leq i \leq m,$$

which is assumed to be *known*. Note that we necessarily have  $F_i(\cdot)$  non decreasing,  $F_i(t) \in [0, 1]$ ,  $F_i(1) = 1$  and we add the technical condition  $F_i(0) = 0$ . Loosely, each  $F_i$  corresponds to the (least favorable) cumulative distribution function of  $p_i$  under the null. Above, we have taken the supremum to cover the case where the null hypothesis is composite: in that situation, each  $F_i$  is adjusted according to the least favorable configuration within the null  $H_{0,i}$ .

Here are some conditions on  $\mathcal{F}$  that will be useful to compare some of the studied procedures (these conditions are *not* assumed in our results unless explicitly mentioned):

$$F_i(t) \leq t, \quad t \in [0, 1], \quad 1 \leq i \leq m, \quad (3.2.1)$$

$$F_i(t) = t, \quad t \in [0, 1], \quad 1 \leq i \leq m. \quad (3.2.2)$$

Condition (3.2.1) ensures that the  $p$ -values have marginals stochastically lower-bounded by a uniform variable under the null, called a *super-uniform* distribution in the sequel. This is the classical setting which is used in most of the work dealing with FDR controlling theory, see e.g. [Benjamini and Hochberg \(1995\)](#). Condition (3.2.2) is more restrictive: if each null hypothesis is a singleton, it is equivalent to the  $p$ -values having uniform marginals under the null.

### 3.2.2 Discrete and continuous modelling

In order to describe the overall support of  $p$ -value distributions we assume one of the two following situations to be at hand throughout the paper (except in Section 3.4 which is written in a more general manner):

- Continuous case: for all  $i \in \{1, \dots, m\}$ ,  $F_i$  is continuous. In that case, we let  $\mathcal{A}_i = [0, 1]$ ,  $1 \leq i \leq m$  and  $\mathcal{A} = \cup_{i=1}^m \mathcal{A}_i = [0, 1]$ , which corresponds to the overall  $p$ -value support.
- Discrete case: each  $p$ -value  $p_i$  (both under the null and alternative) takes values in some finite set  $\mathcal{A}_i$ . We denote  $\mathcal{A} = \cup_{i=1}^m \mathcal{A}_i$  the overall  $p$ -value support.

The continuous setting is typically valid in situations where the  $p$ -values are calibrated from test statistics having a continuous distribution under the null. In this situation, (3.2.2) is often satisfied. The discrete setting typically arises in situations where the  $p$ -values are calibrated from test statistics having a finitely supported distribution under the null. In this situation, we generally have that (3.2.2) holds true only on the support of  $F_i$ , that is,

$$F_i(t) = t, \quad t \in \mathcal{A}_i, \quad 1 \leq i \leq m. \quad (3.2.3)$$

In the discrete framework, let us underline that while (3.2.3) will typically hold, the equality  $F_i(t) = t$ ,  $t \in \mathcal{A}$  will fail in general because  $\mathcal{A}$  contains points of  $\mathcal{A}_j$  for  $j \neq i$ . As a result,  $\bar{F}(t)$  defined by (3.1.1) will be smaller than  $t$  in general (see Figure 3.1), which is exactly the property that we want to exploit in this paper.

To illustrate the above framework, we provide below two simple examples (for more advanced examples, see for instance [Chen and Doerge, 2015b](#)).

*Example 3.2.1* (Gaussian testing). Observe  $X = (X_i)_{1 \leq i \leq m}$  with independent coordinates and marginals  $X_i \sim \mathcal{N}(\mu_i, 1)$ , where  $\mu_i \in \mathbb{R}$  is the parameter of interest,  $1 \leq i \leq m$ . In that situation, a possible hypothesis testing problem is to consider the nulls  $H_{0,i} : \mu_i \leq 0$  against  $H_{1,i} : \mu_i > 0$ . Then  $p_i(X) = 1 - \Phi(X_i)$ ,  $1 \leq i \leq m$ , is a family of  $p$ -values satisfying (3.2.2) (where  $\Phi$  denotes the c.d.f. of a standard Gaussian variable).

*Example 3.2.2* (Binomial testing). Observe  $X = (X_i)_{1 \leq i \leq m}$  with independent coordinates and marginals  $X_i \sim \mathcal{B}(n_i, \theta_i)$ , where  $n_i \geq 1$  is known and  $\theta_i \in (0, 1)$  is the parameter of interest,  $1 \leq i \leq m$ . In that situation, a possible hypothesis testing problem is to consider the nulls  $H_{0,i} : \theta_i \leq 1/2$  against  $H_{1,i} : \theta_i > 1/2$ . Then  $p_i(X) = T_i(X_i)$ ,  $1 \leq i \leq m$ , define a family of  $p$ -values where  $T_i(x) = 2^{-n_i} \sum_{j=x}^{n_i} \binom{n_i}{j}$  is the upper-tail distribution function of a binomial distribution of parameters  $(n_i, 1/2)$ . The support of the  $p$ -values under the null and alternative is given by the values  $2^{-n_i} \sum_{j=K_i-k}^{n_i} \binom{n_i}{j}$ ,  $1 \leq k \leq K_i$ , where  $K_i = n_i + 1$  and  $1 \leq i \leq m$ . We easily check in that case that (3.2.2) is violated while (3.2.1) and (3.2.3) hold.

### 3.2.3 Step-wise procedures

First define a critical value sequence as any nondecreasing sequence  $\tau = (\tau_k)_{1 \leq k \leq m} \in [0, 1]^m$  (with  $\tau_0 = 0$  by convention).

The *step-up procedure* of critical value sequence  $\tau$ , denoted by  $\mathbf{SU}(\tau)$ , rejects the  $i$ -th hypothesis if  $p_i \leq \tau_{\hat{k}}$ , with  $\hat{k} = \max\{k \in \{0, 1, \dots, m\} : p_{(k)} \leq \tau_k\}$ , where  $p_{(1)} \leq p_{(2)} \leq \dots \leq p_{(m)}$  denote the ordered  $p$ -values (with the convention  $p_{(0)} = 0$ ).

The *step-down procedure* of critical value sequence  $\tau$ , denoted by  $\mathbf{SD}(\tau)$ , rejects the  $i$ -th hypothesis if  $p_i \leq \tau_{\tilde{k}}$ , with  $\tilde{k} = \max\{k \in \{0, 1, \dots, m\} : \forall k' \leq k, p_{(k')} \leq \tau_{k'}\}$ . It is straightforward to check that, for the same set of critical values, the step-up version always rejects more hypotheses than the step-down version. More comments and illustrations on step-wise procedures can be found in [Blanchard et al. \(2014\)](#) and [Dickhaus \(2014\)](#), among others.

### 3.2.4 False discovery rate

We measure the quantity of false positives of a step-up (resp. step-down) procedure by using the false discovery rate (FDR), introduced and popularized by [Benjamini and Hochberg \(1995\)](#), which is defined as the averaged proportion of errors among the

rejected hypotheses. More formally, for some procedure  $R$  rejecting the  $i$ -th hypothesis if  $p_i \leq \hat{t}(X)$  (for some threshold  $\hat{t}(X)$ ), we let

$$\text{FDR}(R, P) = \mathbb{E}_{X \sim P} \left[ \frac{\sum_{i \in \mathcal{H}_0(P)} \mathbf{1}_{\{p_i \leq \hat{t}(X)\}}}{1 \vee \sum_{i=1}^m \mathbf{1}_{\{p_i \leq \hat{t}(X)\}}} \right], \quad P \in \mathcal{P}. \quad (3.2.4)$$

The main contribution of this work is to propose procedures that control the FDR at a prescribed level  $\alpha$  and that incorporate the knowledge of the  $F_i$ 's in a way that increases the number of discoveries.

### 3.3 Procedures

In this section we briefly review some existing methods for FDR control and introduce our new procedures.

#### 3.3.1 Existing methods

We use the following methods as starting points for constructing new procedures.

- [BH]: the seminal procedure proposed in [Benjamini and Hochberg \(1995\)](#), corresponding to the step-up procedure  $\mathbf{SU}(\tau)$ , with critical values  $\tau_k = \alpha k / m$ ,  $1 \leq k \leq m$ ;
- [BR- $\lambda$ ],  $\lambda \in (0, 1)$ : an adaptive version of the BH procedure that was proposed in [Blanchard and Roquain \(2009\)](#), corresponding to the step-up procedure  $\mathbf{SU}(\tau)$ , with critical values

$$\tau_k = \left( (1 - \lambda) \frac{\alpha k}{m - k + 1} \right) \wedge \lambda, \quad 1 \leq k \leq m; \quad (3.3.1)$$

- [GBS]: an adaptive version of the BH procedure that has been proposed in [Gavrilov et al. \(2009\)](#), corresponding to the step-down procedure  $\mathbf{SD}(\tau)$ , with critical values

$$\tau_k = \frac{\alpha k}{m - (1 - \alpha)k + 1}, \quad 1 \leq k \leq m; \quad (3.3.2)$$

- [Heyse]: the step-up procedure  $\mathbf{SU}(\tau)$  using critical values given by

$$\tau_k = \max\{t \in \mathcal{A} : \bar{F}(t) \leq \alpha k / m\}, \quad 1 \leq k \leq m; \quad (3.3.3)$$

where  $\bar{F}$  is defined by (3.1.1). This procedure was proposed in Heyse (2011).

The rationale behind the critical values of [BR- $\lambda$ ] and [GBS] is that they are intended to mimic the oracle critical values  $\tau_k = \alpha k / m_0(P)$ ,  $1 \leq k \leq m$ , which are less conservative than those of [BH] when  $m_0(P)/m$  is not close to 1, see e.g. Benjamini et al. (2006); Blanchard and Roquain (2009) for more details on this issue. Also, among adaptive procedures, [GBS] satisfies a kind of optimality as a finite sample version of the asymptotically optimal rejection curve, see Finner et al. (2009).

Let us now comment on [Heyse]. First, in the continuous setting where (3.2.1) holds,  $\bar{F}(t) \leq t$ ,  $t \in [0, 1]$ , and thus the critical values given by (3.3.3) satisfy  $\tau_k \geq \alpha k / m$ ,  $1 \leq k \leq m$ , which means that [Heyse] rejects at least as many hypotheses as [BH]. When (3.2.2) additionally holds, we have  $\bar{F}(t) = t$ ,  $t \in [0, 1]$ , and the two critical value sequences are the same. Second, in the discrete setting where (3.2.1) holds,  $\mathcal{A}$  is finite and  $\tau_k$  is not necessarily greater than  $\alpha k / m$  anymore. However, [Heyse] is also less conservative (or equal) than [BH] in the latter case, as stated in the following result (proved in Appendix 3.B for completeness).

**Lemma 3.3.1.** *Consider the model of Section 3.2.1 assuming (3.2.1), both in the continuous and discrete setting described in Section 3.2.2. Then the set of nulls rejected by [Heyse] is larger than the one of [BH] (almost surely). Furthermore, under (3.2.3), these two rejection sets are equal (almost surely) if  $F_i = F_j$  for all  $i \neq j$ .*

The equality case of Lemma 3.3.1 was provided in Proposition 2.3 of Heller and Gur (2011). It can be seen as a limitation of Heyse procedure in the homogeneous case. In the heterogeneous case, however,  $\bar{F}(t)$  is smaller than  $t$  (see Figure 3.1) and [Heyse] can substantially improve [BH] (see Figure 3.2).

While [Heyse] incorporates the knowledge of the  $F_i$ 's in a natural way (see also Remark 3.3.1 below), it is not correctly calibrated for a rigorous FDR control (see Appendix 3.B.1). We propose suitable modifications of [Heyse] in the next sections.

*Remark 3.3.1* (Empirical Bayes point of view on the Heyse procedure).

We claim that [Heyse] corresponds to a suitable empirical Bayes procedure. To see this, consider the “binomial example” of Section 3.2.2, but assume now that the counts  $n_1, \dots, n_m$  are observed from a sample  $N_1, \dots, N_m$  i.i.d. of an *a priori* distribution  $\nu$ . Unconditionally, the  $p$ -values  $p_i$ ,  $i \in \mathcal{H}_0$ , are thus i.i.d. with c.d.f.  $\bar{F}_0 = \sum_{n \geq 0} \nu(\{n\}) F_{0,n}$ , where  $F_{0,n}$  is the c.d.f. jumping at each  $x_{k,n} = 2^{-n} \sum_{j=0}^{k-1} \binom{n}{j}$  with  $F_{0,n}(x_{k,n}) = x_{k,n}$ ,  $1 \leq k \leq n + 1$ . This suggests to normalize the  $p$ -values  $p_i$  as  $\bar{F}_0(p_i)$  which leads to the step-up procedure with critical values  $\tau_k = \max\{t : \bar{F}_0(t) \leq \alpha k / m\}$ . Following an empirical Bayes approach, the prior  $\nu$  can be estimated by  $\hat{\nu}(\{n\}) = m^{-1} \sum_{i=1}^m \mathbf{1}_{\{N_i=n\}}$ ,

which gives rise to the estimator of  $\bar{F}_0$  defined by  $\hat{\bar{F}}_0 = \sum_{n \geq 0} \hat{\nu}(\{n\}) F_{0,n} = m^{-1} \sum_{i=1}^m F_{0,N_i}$ , which is equal to  $\bar{F}$  given by (3.1.1). Hence, the corresponding (empirical Bayes) step-up procedure reduces to [Heyse].

### 3.3.2 Two new methods

We now present two procedures that aim at correcting [Heyse] :

- [HSU] (heterogeneous step-up) : the step-up procedure  $\mathbf{SU}(\tau)$  using the critical values defined in the following way:

$$\tau_m = \max \left\{ t \in \mathcal{A} : \frac{1}{m} \sum_{i=1}^m \frac{F_i(t)}{1 - F_i(t)} \leq \alpha \right\} \quad (3.3.4)$$

$$\tau_k = \max \left\{ t \in \mathcal{A} : t \leq \tau_m, \frac{1}{m} \sum_{i=1}^m \frac{F_i(t)}{1 - F_i(\tau_m)} \leq \alpha k / m \right\}, \quad 1 \leq k \leq m-1. \quad (3.3.5)$$

- [HSD] (heterogeneous step-down) : the step-down procedure  $\mathbf{SD}(\tau)$  using the critical values defined in the following way :

$$\tau_k = \max \left\{ t \in \mathcal{A} : \frac{1}{m} \sum_{i=1}^m \frac{F_i(t)}{1 - F_i(t)} \leq \alpha k / m \right\}, \quad 1 \leq k \leq m. \quad (3.3.6)$$

[HSU] can be seen as a correction of [Heyse]: the correction term in the critical values (3.3.5) lies in the additional denominator  $1 - F_i(\tau_m)$ . A consequence is that [HSU] can be more conservative than [BH]. However, the magnitude of this phenomenon is always small, as the next lemma shows (proved in Appendix 3.B for completeness).

**Lemma 3.3.2.** *Under the conditions of Lemma 3.3.1, the set of nulls rejected by [HSU] contains the one of [BH] taken at level  $\alpha/(1 + \alpha)$  (almost surely).*

For [HSD], the following result can be established.

**Lemma 3.3.3.** *Under the conditions of Lemma 3.3.1, the set of nulls rejected by [HSD] contains the one of the step-down procedure with critical values  $(\alpha k / m) / (1 + \alpha k / m)$ ,  $1 \leq k \leq m$  (almost surely).*

From (3.3.5) and (3.3.6) it is clear that the critical values of [HSD] are always at least as large as those for [HSU]. However, since the step-up direction is more powerful than the step-down direction (see Section 3.2.3) neither of the two generally dominates the other one.

*Remark 3.3.2.* We may ask whether we can construct a uniform improvement of [BH] that incorporates the  $F_i$ 's. There is indeed such a procedure, see procedure [RBH] in Appendix 3.A.1 for more details. However, the improvement brought by the  $F_i$ 's information is less substantial than for [HSU], so we have chosen to omit [RBH] from the main stream of the paper.

### 3.3.3 Adaptive versions

In this section, we define adaptive versions of [HSU] and [HSD] in the following way:

- [AHSU] (one-stage adaptive heterogeneous step-up): the step-up procedure  $\mathbf{SU}(\tau)$  using the critical values defined in the following way:  $\tau_m$  as in (3.3.4) and for  $1 \leq k \leq m - 1$ ,

$$\tau_k = \max \left\{ t \in \mathcal{A} : t \leq \tau_m, \left( \frac{F(t)}{1-F(\tau_m)} \right)_{(1)} + \cdots + \left( \frac{F(t)}{1-F(\tau_m)} \right)_{(m-k+1)} \leq \alpha k \right\}, \quad (3.3.7)$$

where each  $\left( \frac{F(t)}{1-F(\tau_m)} \right)_{(j)}$  denotes the  $j$ -th largest element of the range of values  $\left\{ \frac{F_i(t)}{1-F_i(\tau_m)}, 1 \leq i \leq m \right\}$ .

- [AHSD] (one-stage adaptive heterogeneous step-down): the step-down procedure  $\mathbf{SD}(\tau)$  using the critical values defined in the following way: for  $1 \leq k \leq m$ ,

$$\tau_k = \max \left\{ t \in \mathcal{A} : \left( \frac{F(t)}{1-F(t)} \right)_{(1)} + \cdots + \left( \frac{F(t)}{1-F(t)} \right)_{(m-k+1)} \leq \alpha k \right\}, \quad (3.3.8)$$

where each  $\left( \frac{F(t)}{1-F(t)} \right)_{(j)}$  denotes the  $j$ -th largest elements of the range of values  $\left\{ \frac{F_i(t)}{1-F_i(t)}, 1 \leq i \leq m \right\}$ .

Note that the critical values of [AHSU] and [AHSD] are clearly larger than or equal to those of their non-adaptive counterparts [HSU] and [HSD], respectively. This means that the adaptive versions are always less conservative. The following result establishes a connection of the adaptive procedures to the [BR- $\lambda$ ] and [GBS] procedures (proved in Appendix 3.B for completeness).

**Lemma 3.3.4.** *Under the conditions of Lemma 3.3.1, the following holds:*

- (i) the set of nulls rejected by [AHSU] contains the one of [BR- $\lambda$ ] (a.s.) for  $\lambda$  equals to (3.3.4);
- (ii) the set of nulls rejected by [AHSD] contains the one of [GBS] (a.s.);

The above lemma ensures that the user can incorporate the knowledge of the  $F_i$ 's in adaptive procedures with a “no loss” guarantee with respect to [BR] and [GBS].

*Remark 3.3.3.* We may ask whether we can build a procedure that is a uniform improvement of [BR- $\lambda$ ], for any fixed value of  $\lambda \in (0, 1)$ . We propose a solution in Appendix 3.A.2, called [HBR- $\lambda$ ]. It does not improve uniformly [HSU], but is an interesting variant of [AHSU].

## 3.4 New FDR bounds for heterogeneous nulls

In this section, we present new FDR bounds which are the main mathematical contributions of this paper and that are of independent interest. They generalize some classical bounds from super-uniform null distributions to arbitrary heterogeneous (not necessarily discrete) null distributions, and immediately yield FDR control of our new procedures.

### 3.4.1 Results

The following result holds. It only assumes independence between the  $p$ -values and *not* super-uniformity of the null distributions.

**Theorem 3.4.1.** *Consider any family  $\mathcal{F} = \{F_i, 1 \leq i \leq m\}$  as defined in Section 3.2.1 and assume (Indep). Consider any critical values  $\tau_k$ ,  $1 \leq k \leq m$  such that  $\forall i \in \{1, \dots, m\}$ ,  $F_i(\tau_m) < 1$ . Then, for all  $P \in \mathcal{P}$ , we have*

$$\begin{aligned} & \text{FDR}(\mathbf{SU}(\tau), P) \\ & \leq \min \left( \sum_{i=1}^m \max_{1 \leq k \leq m} \frac{F_i(\tau_k)}{k}, \max_{1 \leq k \leq m} \max_{\substack{A \subset \{1, \dots, m\} \\ |A|=m-k+1}} \left( \frac{1}{k} \sum_{i \in A} \frac{F_i(\tau_k)}{1 - F_i(\tau_m)} \right) \right); \end{aligned} \quad (3.4.1)$$

$$\begin{aligned} & \text{FDR}(\mathbf{SD}(\tau), P) \\ & \leq \min \left( \sum_{i=1}^m \max_{1 \leq k \leq m} \frac{F_i(\tau_k)}{k}, \max_{1 \leq k \leq m} \max_{\substack{A \subset \{1, \dots, m\} \\ |A|=m-k+1}} \left( \frac{1}{k} \sum_{i \in A} \frac{F_i(\tau_k)}{1 - F_i(\tau_k)} \right) \right). \end{aligned} \quad (3.4.2)$$

The proof of Theorem 3.4.1 is deferred to Section 3.8. It combines several techniques: the first tool is an expression of the FDR introduced by Ferreira (2007) (step-up case)

and [Roquain and Villers \(2011\)](#) (step-down case). A second idea comes from the work [Blanchard and Roquain \(2009\)](#) (step-up case) and [Gavrilov et al. \(2009\)](#) (step-down case), which introduced a new term (here, the denominator  $(1 - F_i(\cdot))$ ) to make the proof work. Finally, another inspiration is the study of [Roquain and van de Wiel \(2009\)](#) and [Döhler \(2016\)](#) that allowed to deal with heterogeneous FDR thresholding. Let us underline that the obtained proof is especially concise, which means that these different techniques fit together perfectly well, which is perhaps surprising at first glance, see Section 3.8.

Next, let us note that taking the maximum over the subset  $A$  in (3.4.1) and (3.4.2) allows us to adapt to the unknown number of true null hypotheses: loosely, if  $k - 1$  is the number of rejections,  $A$  corresponds to the acceptance set (hence of cardinality  $m - k + 1$ ), which “estimates”  $\mathcal{H}_0$  and thus the sums in (3.4.1) and (3.4.2) are indexed by a set “close” to the unknown set  $\mathcal{H}_0$ . Taking the maximum then corresponds to the least favorable possible  $\mathcal{H}_0$ .

Finally, let us underline again that the above bounds do not use the super-uniformity of the  $F_i$ 's which makes them quite general and flexible tools. Several examples are given below.

### 3.4.2 Application to adaptiveness and weighting

Let us now give some intuition behind these bounds and illustrate their generality by showing how they encompass previous work in the literature. First, assuming the super-uniformity  $F_i(t) \leq t$  for all  $t$  and  $i$ , these bounds entail

$$\text{FDR}(\mathbf{SU}(\tau), P) \leq m \max_{1 \leq k \leq m} \{\tau_k/k\}; \quad (3.4.3)$$

$$\text{FDR}(\mathbf{SU}(\tau), P) \leq \max_{1 \leq k \leq m} \frac{m - k + 1}{1 - \tau_m} \frac{\tau_k}{k}; \quad (3.4.4)$$

$$\text{FDR}(\mathbf{SD}(\tau), P) \leq \max_{1 \leq k \leq m} \frac{m - k + 1}{1 - \tau_k} \frac{\tau_k}{k}, \quad (3.4.5)$$

which immediately implies the fact that [BH], [BR- $\lambda$ ] (with  $\tau_m = \lambda$ ) and [GBS] all control the FDR at level  $\alpha$ . To this respect, bounds (3.4.3), (3.4.4) and (3.4.5) encompass Theorem 1 of [Benjamini and Hochberg \(1995\)](#), Theorem 9 of [Blanchard and Roquain \(2009\)](#) and Theorem 1.1 of [Gavrilov et al. \(2009\)](#), respectively.

Second, by removing the adaptative part of the bounds, that is, by replacing  $A$  by  $\{1, \dots, m\}$ , we obtain the simpler but more conservative bounds

$$\text{FDR}(\mathbf{SU}(\tau), P) \leq \max_{1 \leq k \leq m} \left( \frac{1}{k} \sum_{i=1}^m \frac{F_i(\tau_k)}{1 - F_i(\tau_m)} \right); \quad (3.4.6)$$

$$\text{FDR}(\mathbf{SD}(\tau), P) \leq \max_{1 \leq k \leq m} \left( \frac{1}{k} \sum_{i=1}^m \frac{F_i(\tau_k)}{1 - F_i(\tau_k)} \right). \quad (3.4.7)$$

Here, we show how these bounds can be used to recover some of the finite sample FDR controlling results of [Roquain and van de Wiel \(2009\)](#) for  $p$ -value weighting procedures. Assume that the  $p$ -values  $p_i$ ,  $1 \leq i \leq m$ , have uniform marginals under the null, that is, satisfy (3.2.2) and consider any family of c.d.f.  $(\Delta_i)_{1 \leq i \leq m}$ , with the additional property  $m^{-1} \sum_{i=1}^m \Delta_i(x) = x$ , for  $x \in [0, \alpha]$ . This family can be considered as “weighting” the  $p$ -values. It is a free parameter that adds an extra flexibility which can be useful in different contexts, see e.g. [Ignatiadis et al. \(2016\)](#) and [Durand \(2017\)](#). An important point is then to make sure that this weighting maintains the FDR control. For this, let us first modify the family  $(\Delta_i)_{1 \leq i \leq m}$  as follows:

$$\tilde{\Delta}_i(x) = \frac{\Delta_i(x)}{1 + \Delta_i(\alpha)}, \quad \text{so that} \quad \frac{\tilde{\Delta}_i(x)}{1 - \tilde{\Delta}_i(\alpha)} = \Delta_i(x), \quad x \in [0, 1], \quad 1 \leq i \leq m,$$

with the convention  $\tilde{\Delta}_i(1) = 1$  (to make  $\tilde{\Delta}_i$  meet the properties of a c.d.f.). Then we can consider the BH procedure using the transformed  $p$ -values  $\tilde{p}_i = \tilde{\Delta}_i^{-1}(p_i)$ ,  $1 \leq i \leq m$ , which can be interpreted as a “weighted BH procedure”, in the sense that each  $p$ -value  $p_i$  has an importance which is increased or diminished in the procedure according to the value of  $\tilde{\Delta}_i^{-1}$  at  $p_i$ . Since each  $\tilde{p}_i$  has for null c.d.f.  $\tilde{\Delta}_i$ , our bound (3.4.6) yields

$$\text{FDR} \leq \max_{1 \leq k \leq m} \left( \frac{1}{k} \sum_{i=1}^m \frac{\tilde{\Delta}_i(\alpha k/m)}{1 - \tilde{\Delta}_i(\alpha)} \right) = \max_{1 \leq k \leq m} \left( \frac{1}{k} \sum_{i=1}^m \Delta_i(\alpha k/m) \right) = \alpha,$$

which recovers the results of Theorem 4.1 in [Roquain and van de Wiel \(2009\)](#) (step-up part). The step-down part can be recovered from (3.4.7) in a similar way.

### 3.4.3 Application to the new procedures

To make a connection between Theorem 3.4.1 and our new procedures, especially [AHSU] and [AHSD] (see Section 3.3.3), observe that the following relations hold true:

$$\max_{\substack{A \subset \{1, \dots, m\} \\ |A|=m-k+1}} \left( \sum_{i \in A} \frac{F_i(\tau_k)}{1 - F_i(\tau_m)} \right) = \left( \frac{F(\tau_k)}{1 - F(\tau_m)} \right)_{(1)} + \dots + \left( \frac{F(\tau_k)}{1 - F(\tau_m)} \right)_{(m-k+1)} ;$$

$$\max_{\substack{A \subset \{1, \dots, m\} \\ |A|=m-k+1}} \left( \sum_{i \in A} \frac{F_i(\tau_k)}{1 - F_i(\tau_k)} \right) = \left( \frac{F(\tau_k)}{1 - F(\tau_k)} \right)_{(1)} + \dots + \left( \frac{F(\tau_k)}{1 - F(\tau_k)} \right)_{(m-k+1)} .$$

Therefore, Theorem 3.4.1 implies that our new procedures enjoy the desired FDR controlling property.

**Corollary 3.4.1.** *In the setting of Theorem 3.4.1, the procedures [HSU], [HSD], [AHSU], [AHSD] all control the FDR at level  $\alpha$ .*

Now let us focus on the discrete case. In that situation, recall that the individual  $p$ -values cannot be transformed (without randomization) to be uniform under the null. Rather, our Heyse-type procedures “average” the heterogeneous nulls. As a consequence, if some of the  $F_i$ ’s are really small, they will not contribute much to the average, offering some additional room for the other  $F_j$ ’s.

Finally, let us underline that our bounds can be useful for other discrete-type procedures. As a case in point, consider mid  $p$ -values which were introduced by Lancaster (1961) and are sometimes used for analysing discrete data (see e.g. Karp et al., 2016). These  $p$ -values are no longer super-uniform under the null hypotheses, however our theorem can accommodate such distributions in a natural way to still yield valid FDR controlling procedures.

## 3.5 Empirical data

To illustrate the performance of FDR-controlling procedures for discrete data, we analyse two classical data sets. In what follows, our main goal is to compare the performance of the new procedures [HSU] and [AHSU] to the classical [BH] and [Storey] and also to [Heyse]. The procedure [Storey] was proposed in Storey et al. (2004), and corresponds to the step-up procedure  $\mathbf{SU}(\tau)$ , with critical values  $\tau_k = \alpha k / \widehat{m}_0$ ,  $1 \leq k \leq m$ , where

$$\widehat{m}_0 = \widehat{m}_0(\lambda) = \frac{1 + \sum_{i=1}^m \mathbb{1}_{\{p_i > \lambda\}}}{1 - \lambda}$$

is an estimate of the number  $m_0$  of true null hypotheses among the  $m$  hypotheses. We use the standard value  $\lambda = \frac{1}{2}$ . All analyses were performed using the R language for statistical computing ([R Core Team, 2016](#)).

### 3.5.1 Pharmacovigilance data

This data set is derived from a database for reporting, investigating and monitoring adverse drug reactions due to the Medicines and Healthcare products Regulatory Agency in the United Kingdom. It contains the number of reported cases of amnesia as well as the total number of adverse events reported for each of the  $m = 2446$  drugs in the database. For more details we refer to [Heller and Gur \(2011\)](#) and to the accompanying R-package 'discreteMTP' ([Heller et al., 2012](#)), which also contains the data. [Heller and Gur \(2011\)](#) investigate the association between reports of amnesia and suspected drugs by performing for each drug a Fisher's exact test (one-sided) for testing association between the drug and amnesia while adjusting for multiplicity by using several (discrete) FDR procedures.

### 3.5.2 Next generation sequencing data

We also revisit the next generation sequencing (NGS) count data analyzed by [Chen and Doerge \(2015b\)](#), to which we also refer for more details. More specifically, we reanalyze the methylation data set for cytosines of Arabidopsis in [Lister et al. \(2008\)](#) which is part of the R package `fdrDiscreteNull` ([Chen and Doerge, 2015a](#)). This data set contains the counts for a biological entity under two different biological conditions or treatments. Following [Chen and Doerge \(2015b\)](#),  $m = 7421$  genes whose treatment-wise total counts are positive but row-total counts are no greater than 100 are analyzed using the exact binomial test, see [Chen and Doerge \(2015b\)](#).

### 3.5.3 Results

Table 3.1 summarizes the number of discoveries for the pharmacovigilance and NGS data when using the respective FDR procedures at level  $\alpha = 0.05$ . Compared to the classical [BH] procedure, the discrete procedures are able to detect three additional candidates linking amnesia and drugs in the pharmacovigilance data. This data set seems to contain very few signals so there is no benefit in using adaptive procedures, in fact the (finite sample) [Storey] procedure performs worse than the [BH] procedure. Note also that

Table 3.1 Number of rejections (discoveries) for the pharmacovigilance and Arabidopsis methylation data.

Data set	[BH]	[HSU]	[Heyse]	[Storey]	[AHSU]
Pharmacovigilance	24	27	27	22	27
Arabidopsis methylation	2097	2358	2379	2395	2446

our new procedures – while being correctly calibrated – still reject the same number of hypotheses as [Heyse].

In contrast, the Arabidopsis data seems to contain a large portion of signals so that in particular the [Storey] procedure performs much better than [BH]. The [HSU] and [Heyse] procedures also outperform [BH], while the [Storey] procedure is dominated by the [AHSU] procedure.

Figure 3.2 illustrates graphically the data and the critical constants of the involved multiple testing procedures. In particular, the benefit of taking discreteness into account

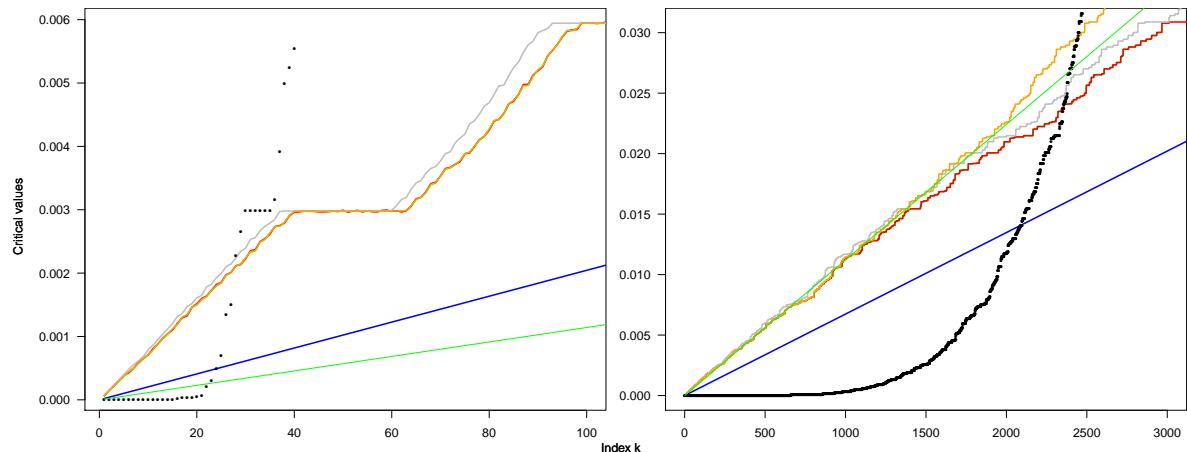


Fig. 3.2 Critical constants and sorted  $p$ -values (represented by black dots) for the pharmacovigilance (left panel) and Arabidopsis methylation data (right panel). The [BH], [HSU], [Heyse], [Storey] and [AHSU] critical constants are represented respectively by blue, red, grey, green, and orange solid lines.

becomes more apparent: for the pharmacovigilance data, the discrete critical values are considerably (by a factor of 2.5 – 3.5) larger than their respective classical counterparts. This leads to more powerful procedures. For the NGS data, we can observe quite clearly that the [HSU] critical constants are dominated by the [AHSU] constants, as explained in Section 3.3. This leads to roughly 100 additional rejections. Again, the discrete critical values are considerably larger than their respective classical counterparts. In Section 3.3.2, we mentioned that the correction factor  $1 - F_i(\tau_m)$ , introduced for guaranteeing FDR

control of [HSU], may lead to a procedure which is more conservative than [BH]. However, Figure 3.2 shows that – at least for the data sets considered here – this risk is by far compensated by the benefit of taking discreteness adequately into account.

## 3.6 Simulation study

We now investigate the power of the procedures from the previous section in a simulation study similar to those described in [Gilbert \(2005\)](#), [Heller and Gur \(2011\)](#) and [Döhler \(2016\)](#). Again, we focus on comparing the performance of the new discrete procedures to [BH], [Storey] and [Heyse].

### 3.6.1 Simulated Scenarios

We simulate a two-sample problem in which a vector of  $m$  independent binary responses (“adverse events”) is observed for each subject in two groups, where each group consists of  $N = 25$  subjects. Then, the goal is to simultaneously test the  $m$  null hypotheses  $H_{0i} : “p_{1i} = p_{2i}”$ ,  $i = 1, \dots, m$ , where  $p_{1i}$  and  $p_{2i}$  are the success probabilities for the  $i$ th binary response in group 1 and 2, respectively. Before we describe the simulation framework in more detail, we explain how this set-up leads to discrete and heterogeneous  $p$ -value distributions. Suppose we have simulated two vectors of dimension  $m$  where each component represents a count in  $\{0, \dots, 25\}$ . This data can be represented by  $m$  contingency tables. Now each hypothesis is tested using Fisher’s exact test (two-sided) for each contingency table, which is performed by conditioning on the (simulated) pair of marginal counts. Thus, we can determine for every contingency table  $i$  the discrete distribution function  $F_i$  of the  $p$ -values for Fisher’s exact test under the null hypothesis. For differing (simulated) contingency tables, these induced distributions will generally be heterogeneous and our inference is conditionally on the marginal counts.

We take  $m = 800, 2000$  where  $m = m_1 + m_2 + m_3$  and data are generated so that the response is  $Bernoulli(0.01)$  at  $m_1$  positions for both groups,  $Bernoulli(0.10)$  at  $m_2$  positions for both groups and  $Bernoulli(0.10)$  at  $m_3$  positions for group 1 and  $Bernoulli(q)$  at  $m_3$  positions for group 2 where  $q = 0.15, 0.25, 0.4$  represents weak, moderate and strong effects respectively. The null hypothesis is true for the  $m_1$  and  $m_2$  positions while the alternative hypothesis is true for the  $m_3$  positions. We also take different configurations for the proportion of false null hypotheses,  $m_3$  is set to be 10%, 30% and 80% of the value of  $m$ , which represents small, intermediate and large proportion of effects (the proportion of true nulls  $\pi_0$  is 0.9, 0.7, 0.2, respectively). Then,  $m_1$  is set to

be 20%, 50% and 80% of the number of true nulls (that is,  $m - m_3$ ) and  $m_2$  is taken accordingly as  $m - m_1 - m_3$ .

For each of the 54 possible parameter configurations specified by  $m, m_3, m_1$  and  $q$ , 10000 Monte Carlo trials are performed, that is, 10000 data sets are generated and for each data set, an unadjusted two-sided  $p$ -value from Fisher's exact test is computed for each of the  $m$  positions, and the multiple testing procedures mentioned above are applied at level  $\alpha = 0.05$ . The power of each procedure was estimated as the fraction of the  $m_3$  false null hypotheses that were rejected, averaged over the 10000 simulations. Note that while our procedures are designed to control the FDR conditionally on the marginal counts, our power results are presented in an unconditional way for the sake of simplicity. For random number generation the R-function *rbinom* was used. The two-sided  $p$ -values from Fisher's exact test were computed using the R-function *fisher.test*.

### 3.6.2 Results

We have computed the (average) power and FDR of the five procedures under investigation in all scenarios (see Tables 3.3 and 3.4 in Appendix 3.E for the full display). For weak and moderate effects, i.e.  $q = 0.15$  and  $q = 0.25$ , none of the procedure possesses relevant power. For strong effects, the results are summarized in Figure 3.3. (Since the power of the discrete procedures is slightly increasing in  $m_1$  for fixed  $m_3$  and  $q$ , we present – in order to avoid over-optimism – the configuration with smallest  $m_1$ ).

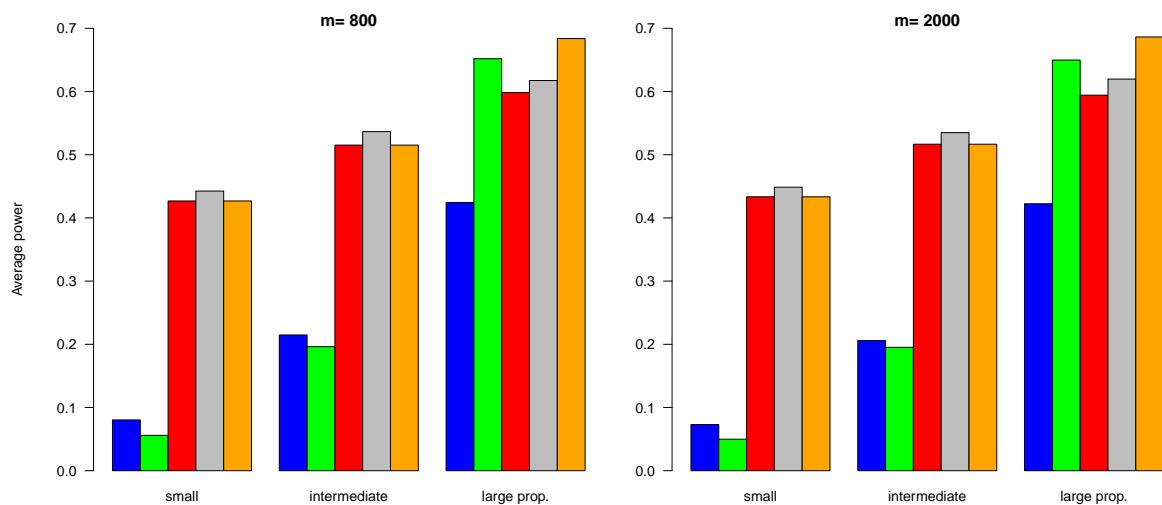


Fig. 3.3 Average power for the [BH], [Storey], [HSU], [Heyse] and [AHSU] procedures in the simulation study. The coloring is the same as in Figure 3.2.

The results are consistent with the findings of the previous section: the new discrete procedures are considerably more powerful than the [BH] procedure. When the proportion of alternatives is large, the [Storey] procedure provides large gains over [BH] but is still dominated by the discrete adaptive procedure [AHSU].

### 3.7 Conclusion and discussion

In this paper, we provided new bounds for the FDR of step-up and step-down procedures that use heterogeneous test statistics. This made it possible to define a new class of multiple testing procedures that provably control the FDR while incorporating the discreteness and heterogeneity of the tests statistics in a convenient way. We have shown that our approach can be seen as correcting and improving the approach of [Heyse \(2011\)](#): while it ensures a theoretical control, it can also make more rejections when the signal is strong enough.

Our new procedures are easily interpreted since they involve neither randomization nor any additional choice of tuning parameters (in Appendix 3.C we present a comparison with a randomized  $p$ -value approach). Furthermore, an R-package implementing them is currently being developed, which will make these methods available for the practitioner.

Additionally, our methodology can deal with other null distributions  $F_i$  that arise in the context of discrete testing: as a case in point, consider mid  $p$ -values which were introduced by [Lancaster \(1961\)](#) and are sometimes used for analysing discrete data (see e.g. [Karp et al., 2016](#)). These  $p$ -values are no longer super-uniform under the null hypotheses, however our methods can accommodate such distributions in a natural way to still yield valid FDR controlling procedures.

Finally, this paper opens several directions for future research, especially by trying to extend our arguments to other frameworks. For instance, an important point is to relax the independence requirement. To this respect, we believe that our procedures will inherit the behavior of BH procedure: while the FDR control is likely to be maintained under “realistic” dependence, formally proving such a result is probably a challenging problem. Another challenge is to develop mathematically valid plug-in procedures for discrete data. A first step in this direction is sketched in Appendix 3.D.

## 3.8 Proof of Theorem 3.4.1

### 3.8.1 Lemmas for step-down and step-up procedures

Let us introduce the following modifications of  $\mathbf{SU}(\tau)$  :

- $\mathbf{SU}^\sharp(\tau) = \mathbf{SU}(\tau^\sharp)$  the step-up with  $m$  critical values defined by  $(\tau_1^\sharp, \dots, \tau_m^\sharp) = (\tau_2, \dots, \tau_m, \tau_m)$ ;
- for some given index  $i \in \{1, \dots, m\}$ ,  $\mathbf{SU}^{\sharp,-i}(\tau) = \mathbf{SU}(\tau^{\sharp,-i})$  the step-up with  $m-1$  critical values defined by  $(\tau_1^{\sharp,-i}, \dots, \tau_{m-1}^{\sharp,-i}) = (\tau_2, \dots, \tau_m)$  and restricted to the  $p$ -values of the set  $\{p_j, j \neq i\}$ .

The following lemma holds (variation of a well known lemma, see e.g. [Ferreira and Zwinderman, 2006](#)) and is proved in Appendix 3.B for completeness.

**Lemma 3.8.1.** *For all  $i \in \{1, \dots, m\}$ , the following assertions are equivalent: (i)  $p_i \leq \tau_{\hat{k}}$ ; (ii)  $p_i \leq \tau_{\hat{k}^{\sharp,-i+1}}$ ; (iii)  $\hat{k}^{\sharp,-i} + 1 = \hat{k}$ , where  $\hat{k}^{\sharp,-i}$  denotes the number of rejected hypotheses of the procedure  $\mathbf{SU}^{\sharp,-i}(\tau)$ . Moreover, we have  $\{p_i > \tau_m\} \subset \{k^\sharp = \hat{k}^{\sharp,-i}\}$ , where  $k^\sharp$  denotes the number of rejected hypotheses of the procedure  $\mathbf{SU}^\sharp(\tau)$ .*

Let us introduce the following modifications of  $\mathbf{SD}(\tau)$  :

- for some given index  $i \in \{1, \dots, m\}$ ,  $\mathbf{SD}^{-i}(\tau) = \mathbf{SD}(\tau^{-i})$  the step-down procedure with  $m-1$  critical values defined by  $(\tau_1^{-i}, \dots, \tau_{m-1}^{-i}) = (\tau_1, \dots, \tau_{m-1})$  and restricted to the  $p$ -values of the set  $\{p_j, j \neq i\}$ .
- for some given index  $i \in \{1, \dots, m\}$ ,  $\mathbf{SD}^{\sharp,-i}(\tau) = \mathbf{SD}(\tau^{\sharp,-i})$  the step-down procedure with the  $m-1$  critical values  $(\tau_1^{\sharp,-i}, \dots, \tau_{m-1}^{\sharp,-i}) = (\tau_2, \dots, \tau_m)$  and restricted to the  $p$ -values of the set  $\{p_j, j \neq i\}$ .

The following lemma holds (variation of [Gavrilov et al., 2009; Roquain and Villers, 2011](#)) and is proved in Appendix 3.B for completeness:

**Lemma 3.8.2.** *For all  $i \in \{1, \dots, m\}$ , the following assertions are equivalent: (i)  $p_i \leq \tau_{\tilde{k}}$ ; (ii)  $p_i \leq \tau_{\tilde{k}+1}$ ; (iii)  $p_i \leq \tau_{\tilde{k}-i+1}$ ; (iv)  $\tilde{k}^{\sharp,-i} + 1 = \tilde{k}$ , where  $\tilde{k}^{-i}$  is the number of rejections of  $\mathbf{SD}^{-i}(\tau)$  and  $\tilde{k}^{\sharp,-i}$  is the number of rejections of  $\mathbf{SD}^{\sharp,-i}(\tau)$ . Moreover, we have  $\{p_i > \tau_{\tilde{k}-i+1}\} \subset \{\tilde{k} = \tilde{k}^{-i}\}$ .*

### 3.8.2 Proof of Theorem 3.4.1, step-up part

By using Lemma 3.8.1 (ii) and (iii), we obtain

$$\text{FDR}(\mathbf{SU}(\tau)) = \sum_{i \in \mathcal{H}_0} \mathbb{E} \left( \frac{\mathbb{1}_{\{p_i \leq \tau_{\hat{k}}\}}}{\hat{k}} \right) = \sum_{i \in \mathcal{H}_0} \mathbb{E} \left( \frac{\mathbb{1}_{\{p_i \leq \tau_{\hat{k}^\sharp, -i+1}\}}}{\hat{k}^\sharp, -i + 1} \right). \quad (3.8.1)$$

because  $p_i \leq \tau_{\hat{k}}$  is equivalent to  $p_i \leq \tau_{\hat{k}^\sharp, -i+1}$ , and both imply  $\hat{k}^\sharp, -i + 1 = \hat{k}$ . Now using independence between  $\hat{k}^\sharp, -i$  and  $p_i$ , we obtain

$$\begin{aligned} \sum_{i \in \mathcal{H}_0} \mathbb{E} \left( \frac{\mathbb{1}_{\{p_i \leq \tau_{\hat{k}^\sharp, -i+1}\}}}{\hat{k}^\sharp, -i + 1} \right) &= \sum_{i \in \mathcal{H}_0} \mathbb{E} \left( \mathbb{E} \left( \frac{\mathbb{1}_{\{p_i \leq \tau_{\hat{k}^\sharp, -i+1}\}}}{\hat{k}^\sharp, -i + 1} \mid \hat{k}^\sharp, -i \right) \right) \\ &= \sum_{i \in \mathcal{H}_0} \mathbb{E} \left( \frac{\mathbb{P}(p_i \leq \tau_{\hat{k}^\sharp, -i+1} \mid \hat{k}^\sharp, -i)}{\hat{k}^\sharp, -i + 1} \right) \\ &\leq \sum_{i \in \mathcal{H}_0} \mathbb{E} \left( \frac{F_i(\tau_{\hat{k}^\sharp, -i+1})}{\hat{k}^\sharp, -i + 1} \right), \end{aligned}$$

because for any  $i \in \mathcal{H}_0$ , and  $t$ , we have  $\mathbb{P}(p_i \leq t) \leq F_i(t)$ . Now, on the one hand,

$$\sum_{i \in \mathcal{H}_0} \mathbb{E} \left( \frac{F_i(\tau_{\hat{k}^\sharp, -i+1})}{\hat{k}^\sharp, -i + 1} \right) \leq \sum_{i=1}^m \mathbb{E} \left( \frac{F_i(\tau_{\hat{k}^\sharp, -i+1})}{\hat{k}^\sharp, -i + 1} \right) \leq \sum_{i=1}^m \max_{1 \leq k \leq m} \frac{F_i(\tau_k)}{k}.$$

Next, on the other hand, by using again (Indep) and that for any  $i \in \mathcal{H}_0$ , and  $t$ ,  $1 - \mathbb{P}(p_i \leq t) \geq 1 - F_i(t)$ ,

$$\begin{aligned} \sum_{i \in \mathcal{H}_0} \mathbb{E} \left( \frac{F_i(\tau_{\hat{k}^\sharp, -i+1})}{\hat{k}^\sharp, -i + 1} \right) &\leq \sum_{i \in \mathcal{H}_0} \mathbb{E} \left( \frac{F_i(\tau_{\hat{k}^\sharp, -i+1})}{\hat{k}^\sharp, -i + 1} \mathbb{E} \left( \frac{\mathbb{1}_{\{p_i > \tau_m\}}}{1 - F_i(\tau_m)} \mid \hat{k}^\sharp, -i \right) \right) \\ &= \sum_{i \in \mathcal{H}_0} \mathbb{E} \left( \frac{F_i(\tau_{\hat{k}^\sharp, -i+1})}{1 - F_i(\tau_m)} \frac{\mathbb{1}_{\{p_i > \tau_m\}}}{\hat{k}^\sharp, -i + 1} \right) \\ &\leq \sum_{i \in \mathcal{H}_0} \mathbb{E} \left( \frac{F_i(\tau_{k^\sharp+1})}{1 - F_i(\tau_m)} \frac{\mathbb{1}_{\{p_i > \tau_m\}}}{k^\sharp + 1} \mathbb{1}_{\{k^\sharp+1 \leq m\}} \right), \end{aligned}$$

where the latter inequality comes from the last assertion of Lemma 3.8.1. Now, since  $\tau_{k^\sharp+1} \leq \tau_m$ , we have that the last display is smaller than or equal to

$$\begin{aligned} & \mathbb{E} \left( \sum_{i \in \mathcal{H}_0} \frac{F_i(\tau_{k^\sharp+1})}{1 - F_i(\tau_m)} \frac{\mathbb{1}_{\{p_i > \tau_{k^\sharp+1}\}}}{k^\sharp + 1} \mathbb{1}_{\{k^\sharp+1 \leq m\}} \right) \\ & \leq \max_{0 \leq k \leq m-1} \max_{\substack{A \subset \{1, \dots, m\} \\ |A|=m-k}} \sum_{i \in A \cap \mathcal{H}_0} \frac{F_i(\tau_{k+1})}{1 - F_i(\tau_m)} \frac{1}{k+1}, \end{aligned} \quad (3.8.2)$$

by taking the maximum over all the possible realizations of the set  $A = \{1 \leq i \leq m : p_i > \tau_{k^\sharp+1}\} = \{1 \leq i \leq m : p_i > \tau_{k^\sharp}^\sharp\}$  which is the index set corresponding to the non-rejected null hypotheses of  $\mathbf{SU}(\tau^\sharp)$  (the latter being by definition of cardinality  $m - k^\sharp$ ). This concludes the proof.

### 3.8.3 Proof of Theorem 3.4.1, step-down part

It is similar to the step-up case, with some subtle changes:

$$\text{FDR}(\mathbf{SD}(\tau)) = \sum_{i \in \mathcal{H}_0} \mathbb{E} \left( \frac{\mathbb{1}_{\{p_i \leq \tau_{\tilde{k}}\}}}{\tilde{k}} \right) = \sum_{i \in \mathcal{H}_0} \mathbb{E} \left( \frac{\mathbb{1}_{\{p_i \leq \tau_{\tilde{k}-i+1}\}}}{\tilde{k}^{\sharp,-i} + 1} \right),$$

because  $p_i \leq \tau_{\tilde{k}}$  is equivalent to  $p_i \leq \tau_{\tilde{k}-i+1}$ , and both imply  $\tilde{k}^{\sharp,-i} + 1 = \tilde{k}$  (keep in mind that  $\tilde{k}^{\sharp,-i}$  might be different from  $\tilde{k}^{-i}$ ), by applying Lemma 3.8.2. Now using independence between  $(\tilde{k}^{-i}, \tilde{k}^{\sharp,-i})$  and  $p_i$ , we obtain

$$\begin{aligned} \sum_{i \in \mathcal{H}_0} \mathbb{E} \left( \frac{\mathbb{1}_{\{p_i \leq \tau_{\tilde{k}-i+1}\}}}{\tilde{k}^{\sharp,-i} + 1} \right) &= \sum_{i \in \mathcal{H}_0} \mathbb{E} \left( \mathbb{E} \left( \frac{\mathbb{1}_{\{p_i \leq \tau_{\tilde{k}-i+1}\}}}{\tilde{k}^{\sharp,-i} + 1} \mid (\tilde{k}^{-i}, \tilde{k}^{\sharp,-i}) \right) \right) \\ &= \sum_{i \in \mathcal{H}_0} \mathbb{E} \left( \frac{\mathbb{P}(p_i \leq \tau_{\tilde{k}-i+1} \mid (\tilde{k}^{-i}, \tilde{k}^{\sharp,-i}))}{\tilde{k}^{\sharp,-i} + 1} \right) \\ &\leq \sum_{i \in \mathcal{H}_0} \mathbb{E} \left( \frac{F_i(\tau_{\tilde{k}-i+1})}{\tilde{k}^{\sharp,-i} + 1} \right) \\ &\leq \sum_{i \in \mathcal{H}_0} \mathbb{E} \left( \frac{F_i(\tau_{\tilde{k}-i+1})}{\tilde{k}^{-i} + 1} \right), \end{aligned}$$

because  $\tilde{k}^{\sharp, -i} + 1 \geq \tilde{k}^{-i} + 1$  and because for  $i \in \mathcal{H}_0$ , and any  $t$ , we have  $\mathbb{P}(p_i \leq t) \leq F_i(t)$ . This gives the first part of the bound. Next, by using again (Indep), we obtain

$$\begin{aligned} \sum_{i \in \mathcal{H}_0} \mathbb{E} \left( \frac{F_i(\tau_{\tilde{k}^{-i}+1})}{\tilde{k}^{-i} + 1} \right) &\leq \sum_{i \in \mathcal{H}_0} \mathbb{E} \left( \frac{F_i(\tau_{\tilde{k}^{-i}+1})}{\tilde{k}^{-i} + 1} \mathbb{E} \left( \frac{\mathbb{1}_{\{p_i > \tau_{\tilde{k}^{-i}+1}\}}}{1 - F_i(\tau_{\tilde{k}^{-i}+1})} \mid (\tilde{k}^{-i}, \tilde{k}^{\sharp, -i}) \right) \right) \\ &= \sum_{i \in \mathcal{H}_0} \mathbb{E} \left( \frac{F_i(\tau_{\tilde{k}^{-i}+1})}{1 - F_i(\tau_{\tilde{k}^{-i}+1})} \frac{\mathbb{1}_{\{p_i > \tau_{\tilde{k}^{-i}+1}\}}}{\tilde{k}^{-i} + 1} \right). \end{aligned}$$

Now using the last assertion of Lemma 3.8.2, the last display is smaller than or equal to

$$\begin{aligned} &\mathbb{E} \left( \sum_{i \in \mathcal{H}_0} \frac{F_i(\tau_{\tilde{k}+1})}{1 - F_i(\tau_{\tilde{k}+1})} \frac{\mathbb{1}_{\{p_i > \tau_{\tilde{k}+1}\}}}{\tilde{k} + 1} \mathbb{1}_{\{\tilde{k}+1 \leq m\}} \right) \\ &\leq \mathbb{E} \left( \max_{0 \leq k \leq m-1} \max_{\substack{A \subset \{1, \dots, m\} \\ |A|=m-k}} \sum_{i \in A \cap \mathcal{H}_0} \frac{F_i(\tau_{k+1})}{1 - F_i(\tau_{k+1})} \frac{1}{k+1} \right), \end{aligned}$$

because  $\{1 \leq i \leq m : p_i > \tau_{\tilde{k}+1}\}$  is equal to  $\{1 \leq i \leq m : p_i > \tau_{\tilde{k}}\}$ , since both sets correspond to the set of non-rejected hypotheses of  $\mathbf{SD}(\tau)$ . Since  $\mathbf{SD}(\tau)$  rejects exactly  $\tilde{k}$  hypotheses, the proof is completed.

## Appendix 3.A Additional procedures

### 3.A.1 A rescaled BH procedure

The procedure [RBH] (rescaled BH) is defined as the step-up procedure using the critical values  $\tau_k = \lambda_\alpha k/m$ ,  $1 \leq k \leq m$ , where  $\lambda_\alpha = \max\{\lambda \in [0, 1] : \Psi(\lambda_\alpha) \leq \alpha\}$  for

$$\Psi(\lambda) = \min \left( \lambda, \max_{1 \leq k \leq m} \left( \frac{1}{k} \sum_{i=1}^m \frac{F_i(\lambda k/m)}{1 - F_i(\lambda)} \right) \right).$$

The following result is straightforward from Theorem 3.4.1 (SU part).

**Corollary 3.A.1.** *In the setting of Theorem 3.4.1 with the additional assumption (3.2.1), we have  $\forall P \in \mathcal{P}$ ,  $\text{FDR}(\text{RBH}, P) \leq \alpha$ .*

Moreover, if  $\alpha$  is such that the equality  $\Psi(\lambda_\alpha) = \alpha$  holds true, then  $\lambda_\alpha \geq \Psi(\lambda_\alpha) = \alpha$  and [RBH] always dominates [BH] in terms of critical values and therefore rejects at least as many hypotheses.

### 3.A.2 A heterogeneous BR procedure

The procedure [HBR- $\lambda$ ] (heterogeneous BR) is defined as the step-up procedure  $\mathbf{SU}(\tau)$  using the critical values defined in the following way: for  $k \in \{1, \dots, m\}$ ,

$$\tau_k = \max \left\{ t \in \mathcal{A} : (F(t))_{(1)} \leq \lambda, (F(t))_{(1)} + \dots + (F(t))_{(m-k+1)} \leq \alpha k (1 - \lambda) \right\},$$

where each  $(F(t))_{(j)}$  denotes the  $j$ -th largest elements of the set  $\{F_i(t), 1 \leq i \leq m\}$ . The following result is straightforward from Theorem 3.4.1 (SU part).

**Corollary 3.A.2.** *In the setting of Theorem 3.4.1, with the additional assumption (3.2.1), we have  $\forall P \in \mathcal{P}$ ,  $\text{FDR}(\text{HBR}, P) \leq \alpha$ . Moreover, the set of nulls rejected by [HBR- $\lambda$ ] is larger than the one of [BR- $\lambda$ ] (almost surely), with equality (almost surely) under (3.2.3) and  $F_i = F_j$  for all  $i \neq j$ .*

## Appendix 3.B Supplement

### 3.B.1 Counterexample

We present here a modification of the counterexample due to Krieger given in Heller and Gur (2011). Consider  $m = 3$   $p$ -value null distributions given by

$$\begin{aligned} P_1 &= 0.05 \cdot \delta_{\{0.05\}} + 0.16 \cdot \delta_{\{0.21\}} + 0.79 \cdot \delta_{\{1\}}; \\ P_2 &= 0.2 \cdot \delta_{\{0.2\}} + 0.09 \cdot \delta_{\{0.29\}} + 0.71 \cdot \delta_{\{1\}}; \\ P_3 &= \delta_{\{1\}}, \end{aligned}$$

where  $\delta_{\{x\}}$  denotes the Dirac distribution in  $x$ . It is easy to verify that (3.1.1) yields

$$\overline{F}(t) = \begin{cases} 0 & t < 0.05; \\ 0.05/3 & t \in [0.05, 0.2); \\ 0.25/3 & t \in [0.2, 0.21); \\ 0.41/3 & t \in [0.21, 0.29); \\ 0.50/3 & t \in [0.29, 1); \\ 1 & t \geq 1. \end{cases}$$

Then the critical values of [Heyse] at level  $\alpha = 0.25$  are given by  $\tau_1 = 0.2$ ,  $\tau_2 = \tau_3 = 0.29$ , see (3.3.3). Now consider an alternative distribution for  $P_3$  given by

$$Q_3 = \epsilon\delta_{\{0\}} + (1 - \epsilon)\delta_{\{0.3\}},$$

where  $\epsilon$  will be suitably chosen further on. Assume that the  $p$ -values  $p_1, p_2, p_3$  are independent, with  $p_i \sim P_i$  for  $i \in \{1, 2\}$  (hypotheses  $H_1$  and  $H_2$  true) and  $p_3 \sim Q_3$  (hypothesis  $H_3$  false).

On the one hand, let us focus on the event  $E^c = \{p_3 = 0.3\}$ . In this case,  $H_3$  is never rejected and the FDP of [Heyse] is 0 if and only if  $H_1$  and  $H_2$  are both not rejected and is equal to 1 otherwise. We partition  $E^c$  into the following different events:

- $E^c \cap \{p_1 = 0.05\}$ : in this case,  $p_{(1)} = 0.05 \leq \tau_1$  and at least  $H_1$  will be (falsely) rejected and FDP = 1;
- $E^c \cap \{p_1 = 0.21, p_2 \neq 1\}$ : in this case,  $p_{(1)} = 0.2 \leq \tau_1$  and at least  $H_2$  will be (falsely) rejected and FDP = 1;
- $E^c \cap \{p_1 = 0.21, p_2 = 1\}$ : in this case,  $p_{(1)} = 0.21 > \tau_1$  and  $p_{(2)} = 0.3 > \tau_2$  so  $H_1$  and  $H_2$  are not rejected and FDP = 0;
- $E^c \cap \{p_1 = 1, p_2 = 0.2\}$ : in this case,  $p_{(1)} = 0.2 \leq \tau_1$  and  $H_2$  will be (falsely) rejected and FDP = 1;
- $E^c \cap \{p_1 = 1, p_2 \neq 0.2\}$ : in this case,  $p_{(1)} = 0.29 > \tau_1$  and  $p_{(2)} = 0.3 > \tau_2$  so  $H_1$  and  $H_2$  are not rejected and FDP = 0;

Altogether, we obtain

$$\mathbb{E}(\text{FDP} \times \mathbf{1}_{\{E^c\}}) = (1 - \epsilon)(0.05 + 0.16 \times 0.29 + 0.79 \times 0.2) = (1 - \epsilon)0.2544.$$

On the other hand, let us focus on the event  $E = \{p_3 = 0\}$ . In this case,  $H_3$  is always rejected and the FDP of [Heyse] can be 1/2 if one null is rejected among  $H_1$  and  $H_2$ , and 2/3 if both  $H_1$  and  $H_2$  are rejected (it is 0 if both  $H_1$  and  $H_2$  are non rejected). We partition  $E$  into the following different events:

- $E \cap \{p_1 \neq 1, p_2 \neq 1\}$ : in this case,  $p_{(3)} \leq 0.29 = \tau_3$  and both  $H_1$  and  $H_2$  are rejected and FDP = 2/3;
- $E \cap \{p_1 \neq 1, p_2 = 1\}$ : in this case,  $p_{(2)} \leq 0.29 = \tau_2$  and  $p_{(3)} = 1 > \tau_3$  so  $H_1$  is rejected and not  $H_2$ . So FDP = 1/2;

- $E \cap \{p_1 = 1, p_2 \neq 1\}$ : in this case,  $p_{(2)} \leq 0.29 = \tau_2$  and  $p_{(3)} = 1 > \tau_3$  so  $H_2$  is rejected and not  $H_1$ . So FDP = 1/2;
- $E \cap \{p_1 = 1, p_2 = 1\}$ : in this case only  $H_3$  is rejected and FDP = 0.

Altogether, we obtain

$$\begin{aligned}\mathbb{E}(\text{FDP} \times \mathbb{1}_{\{E\}}) &= \epsilon((2/3) \times 0.21 \times 0.29 + (1/2) \times (0.21 \times 0.71 + 0.79 \times 0.29)) \\ &= \epsilon 0.2297.\end{aligned}$$

Finally, we get

$$\text{FDR} = \epsilon 0.2297 + (1 - \epsilon)0.2544 = 0.25193 > \alpha,$$

by choosing  $\epsilon = 0.1$ .

### 3.B.2 Proofs for lemmas comparing procedures

The lemmas presented here rely on the fact that, there is almost surely no  $p$ -value in  $[0, 1] \setminus \mathcal{A}$  (both in the continuous and discrete cases). All symbols “=” or “ $\subset$ ” are intended to be valid almost surely in this section.

A result which will be extensively used in the proofs of this section is the following one : for  $p$ -values valued in the set  $\mathcal{A}$ , then the step-up procedure with critical values  $\tau_k$ ,  $1 \leq k \leq m$ , has the same rejection set as the step-up procedure with critical values  $\xi_k = \max \{t \in \mathcal{A} : t \leq \tau_k\}$ ,  $1 \leq k \leq m$ . This fact comes from the simple following observation : for all  $k$ ,

$$\begin{aligned}\{1 \leq i \leq m : p_i \leq \tau_k\} &= \{1 \leq i \leq m : p_i \in \mathcal{A}, p_i \leq \tau_k\} \\ &= \{1 \leq i \leq m : p_i \in \mathcal{A}, p_i \leq \xi_k\} \\ &= \{1 \leq i \leq m : p_i \leq \xi_k\}.\end{aligned}$$

The  $\xi_k$ 's are called the “effective” critical values of  $\mathbf{SD}(\tau)$  or  $\mathbf{SU}(\tau)$  in the sequel.

#### 3.B.2.1 Proof of Lemma 3.3.1

The effective critical values of the BH procedure are given by the quantities  $\xi_k = \max \{t \in \mathcal{A} : t \leq \alpha k/m\}$ ,  $1 \leq k \leq m$ . If (3.2.1) holds, then  $\bar{F}(t) \leq t$  and each  $\xi_k$  is clearly smaller than the  $k$ -th critical values of [Heyse]. This implies that the rejection set of [Heyse] is larger than the one of [BH]. Conversely, under (3.2.3) and if  $F_i = F_j = \bar{F}$

for all  $i \neq j$ , we always have  $\bar{F}(t) = F_i(t) = t$  for  $t \in \mathcal{A}$ . This implies that the  $\xi_k$ 's are the critical values of [Heyse] and shows the reversed inclusion.

### 3.B.2.2 Proof of Lemmas 3.3.2 and 3.3.3

Let  $\tau_k$ ,  $1 \leq k \leq m$ , be the critical values of [HSU]. Let us consider

$$\xi_k = \max \left\{ t \in \mathcal{A} : t \leq \frac{\alpha}{1 + \alpha} \frac{k}{m} \right\},$$

the effective critical values of the [BH] procedure at level  $\alpha/(1+\alpha)$ . Now, for all  $t \in [0, 1]$ , we have by (3.2.1),

$$\begin{aligned} \bar{F}_{\text{SU}}(t) &= \frac{1}{m} \sum_{i=1}^m \frac{F_i(t)}{1 - F_i(\tau_m)} \leq \frac{t}{m} \sum_{i=1}^m \frac{1}{1 - F_i(\tau_m)} = t \cdot (1 + \bar{F}_{\text{SU}}(\tau_m)) \\ &\leq t \cdot (1 + \alpha), \end{aligned} \tag{3.B.1}$$

where the last inequality follows from the definition of  $\tau_m$ . Thus we have  $\bar{F}_{\text{SU}}(\xi_m) \leq \alpha$ , which in turn implies  $\xi_m \leq \tau_m$ . Additionally, the bound (3.B.1) yields for  $1 \leq k < m$

$$\begin{aligned} \tau_k &= \max \left\{ t \in \mathcal{A} : t \leq \tau_m, \bar{F}_{\text{SU}}(t) \leq \alpha k / m \right\} \\ &\geq \max \left\{ t \in \mathcal{A} : t \leq \tau_m, t(1 + \alpha) \leq \alpha k / m \right\} \\ &= \max \left\{ t \in \mathcal{A} : t(1 + \alpha) \leq \alpha k / m \right\} \\ &= \xi_k, \end{aligned}$$

where we used that  $\xi_m \leq \tau_m$ . This proves Lemma 3.3.2. The proof of Lemma 3.3.3 is analogue and is left to the reader.

### 3.B.2.3 Proof of Lemma 3.3.4

Let us first focus on the case (i) and denote by  $\tau_k$ ,  $1 \leq k \leq m$ , the critical values of [AHSU]. From (3.2.1), we have for  $1 \leq k \leq m-1$ ,

$$\begin{aligned} \tau_k &\geq \max \left\{ t \in \mathcal{A} : t \leq \tau_m, t \leq \alpha k (1 - \tau_m) / (m - k + 1) \right\} \\ &= \max \left\{ t \in \mathcal{A} : t \leq \left( (1 - \tau_m) \frac{\alpha k}{m - k + 1} \right) \wedge \tau_m \right\}, \end{aligned}$$

which correspond to the effective critical values of [BR- $\lambda$ ] with  $\lambda = \tau_m$ . Now consider the case (ii) and denote again by  $\tau_k$ ,  $1 \leq k \leq m$ , the critical values of [AHSD]. From

(3.2.1), we have for  $1 \leq k \leq m$ ,

$$\begin{aligned}\tau_k &\geq \max \{t \in \mathcal{A} : (m-k+1)t/(1-t) \leq \alpha k\} \\ &= \max \{t \in \mathcal{A} : t \leq \alpha k / (m-k(1-\alpha)+1)\}\end{aligned}$$

which correspond to the effective critical values of [GBS]. This implies the result.

### 3.B.3 Proofs of technical lemmas for step-down and step-up procedures

#### 3.B.3.1 Proof of Lemma 3.8.1

First note that for any step-up procedure

$$\hat{k} = \max \left\{ k \in \{0, 1, \dots, m\} : \sum_{i=1}^m \mathbb{1}_{\{p_i \leq \tau_k\}} \geq k \right\},$$

which is sometimes more handy, because this definition avoids to rely explicitly on the order statistics of the  $p$ -values.

Now, it is not difficult to check that  $\hat{k}^{\sharp, -i} \geq \hat{k} - 1$  always holds: this comes from the inequality

$$\hat{k} - 1 = \sum_{j=1}^m \mathbb{1}_{\{p_j \leq \tau_{\hat{k}}\}} - 1 \leq \sum_{j \neq i} \mathbb{1}_{\{p_j \leq \tau_{\hat{k}}\}} = \sum_{j \neq i} \mathbb{1}_{\{p_j \leq \tau_{\hat{k}-1}^{\sharp, -i}\}},$$

because  $\tau_{\ell-1}^{\sharp, -i} = \tau_\ell$  for  $\ell \in \{2, \dots, m\}$  (note that we can assume without loss of generality  $\hat{k} \geq 1$  here). This means that (i) implies (ii). Now, when  $p_i \leq \tau_{\hat{k}^{\sharp, -i}+1}$ , we have

$$\hat{k}^{\sharp, -i} = \sum_{j \neq i} \mathbb{1}_{\{p_j \leq \tau_{\hat{k}^{\sharp, -i}}^{\sharp, -i}\}} = \sum_{j \neq i} \mathbb{1}_{\{p_j \leq \tau_{\hat{k}^{\sharp, -i}+1}\}} = \sum_{j=1}^m \mathbb{1}_{\{p_j \leq \tau_{\hat{k}^{\sharp, -i}+1}\}} - 1,$$

which implies  $\hat{k}^{\sharp, -i} + 1 = \sum_{j=1}^m \mathbb{1}_{\{p_j \leq \tau_{\hat{k}^{\sharp, -i}+1}\}}$  and thus  $\hat{k}^{\sharp, -i} + 1 \leq \hat{k}$  (by using the definition of  $\hat{k}$ ). Since, again,  $\hat{k}^{\sharp, -i} \geq \hat{k} - 1$  always holds, we have  $\hat{k}^{\sharp, -i} + 1 = \hat{k}$ . Hence, (ii) implies (iii). Now, if  $\hat{k}^{\sharp, -i} + 1 = \hat{k}$ , we have

$$\begin{aligned}\mathbb{1}_{\{p_i \leq \tau_{\hat{k}}\}} &= \sum_{j=1}^m \mathbb{1}_{\{p_j \leq \tau_{\hat{k}}\}} - \sum_{j \neq i} \mathbb{1}_{\{p_j \leq \tau_{\hat{k}}\}} = \hat{k} - \sum_{j \neq i} \mathbb{1}_{\{p_j \leq \tau_{\hat{k}^{\sharp, -i}+1}\}} \\ &= \hat{k} - \sum_{j \neq i} \mathbb{1}_{\{p_j \leq \tau_{\hat{k}^{\sharp, -i}}^{\sharp, -i}\}} = \hat{k} - \hat{k}^{\sharp, -i} = 1,\end{aligned}$$

by definition of  $\tau^{\sharp, -i}$ , which gives that (iii) implies (i). Now, to prove the last statement, we first note that  $k^\sharp \geq \hat{k}^{\sharp, -i}$  always holds. Furthermore, if  $p_i > \tau_m$  let us prove  $k^\sharp \leq \hat{k}^{\sharp, -i}$ . First,  $k^\sharp = m$  is impossible because  $p_i$  is above  $\tau_m$  and thus  $p_i$  cannot be rejected by  $\mathbf{SU}^\sharp(\tau)$ . Hence,  $k^\sharp \leq m - 1$  and thus  $\tau_{k^\sharp}^{\sharp, -i}$  is well defined. Now, since  $p_i > \tau_m$ , we obtain

$$\sum_{j \neq i} \mathbb{1}_{\{p_j \leq \tau_{k^\sharp}^{\sharp, -i}\}} = \sum_{j \neq i} \mathbb{1}_{\{p_j \leq \tau_{k^\sharp}^{\sharp}\}} = \sum_{j=1}^m \mathbb{1}_{\{p_j \leq \tau_{k^\sharp}^{\sharp}\}} = k^\sharp,$$

which implies  $k^\sharp \leq \hat{k}^{\sharp, -i}$  by definition of  $\mathbf{SU}^{\sharp, -i}(\tau)$ .

### 3.B.3.2 Proof of Lemma 3.8.2

First note that for any step-down procedure

$$\tilde{k} = \max \left\{ k \in \{0, 1, \dots, m\} : \forall k' \leq k, \sum_{i=1}^m \mathbb{1}_{\{p_i \leq \tau_{k'}\}} \geq k' \right\}.$$

Now, we check that  $\tilde{k}^{\sharp, -i} + 1 \geq \tilde{k}$  always holds. Since  $\sum_{j \neq i} \mathbb{1}_{\{p_j \leq \tau_{\tilde{k}^{\sharp, -i}+1}^{\sharp, -i}\}} < \tilde{k}^{\sharp, -i} + 1$ , we have

$$\sum_{j=1}^m \mathbb{1}_{\{p_j \leq \tau_{\tilde{k}^{\sharp, -i}+2}\}} \leq 1 + \sum_{j \neq i} \mathbb{1}_{\{p_j \leq \tau_{\tilde{k}^{\sharp, -i}+1}^{\sharp, -i}\}} < \tilde{k}^{\sharp, -i} + 2,$$

which gives  $\tilde{k} < \tilde{k}^{\sharp, -i} + 2$  by definition of  $\tilde{k}$  and thus  $\tilde{k} \leq \tilde{k}^{\sharp, -i} + 1$ . Next, if  $p_i \leq \tau_{\tilde{k}}$ , we have

$$\sum_{j \neq i} \mathbb{1}_{\{p_j \leq \tau_{\tilde{k}}^{\sharp, -i}\}} = \sum_{j \neq i} \mathbb{1}_{\{p_j \leq \tau_{\tilde{k}+1}\}} = \sum_{j=1}^m \mathbb{1}_{\{p_j \leq \tau_{\tilde{k}+1}\}} - 1 < \tilde{k} + 1 - 1,$$

so that  $\tilde{k} > \tilde{k}^{\sharp, -i}$  and thus  $\tilde{k} \geq \tilde{k}^{\sharp, -i} + 1$ . This proves that (i) implies (iv). Next, if  $p_i > \tau_{\tilde{k}-i+1}$ , then

$$\sum_{j=1}^m \mathbb{1}_{\{p_j \leq \tau_{\tilde{k}-i+1}\}} = \sum_{j \neq i} \mathbb{1}_{\{p_j \leq \tau_{\tilde{k}-i+1}\}} = \sum_{j \neq i} \mathbb{1}_{\{p_j \leq \tau_{\tilde{k}-i+1}^{-i}\}} < \tilde{k}^{-i} + 1,$$

which entails  $\tilde{k} < \tilde{k}^{-i} + 1$  and thus  $\tilde{k} \leq \tilde{k}^{-i}$ . This proves  $\tilde{k} \neq \tilde{k}^{\sharp, -i} + 1$ . Hence, (iv) implies (iii). The fact that (iii) implies (ii) is obvious because  $\tilde{k} \geq \tilde{k}^{-i}$  always holds. Finally, we merely check that  $\tilde{k}$  is such that

$$\tilde{k} = \sum_{j=1}^m \mathbb{1}_{\{p_j \leq \tau_{\tilde{k}}\}} = \sum_{j=1}^m \mathbb{1}_{\{p_j \leq \tau_{\tilde{k}+1}\}},$$

which means that the set of  $p$ -values rejected at threshold  $\tau_{\tilde{k}}$  is the same as the set of  $p$ -values rejected at threshold  $\tau_{\tilde{k}+1}$ . This gives that (ii) implies (i). For the last assertion, it has been proved in the above reasoning while showing that (iv) implies (iii).

## Appendix 3.C Empirical analyses for randomized $p$ -values

In this section we follow the suggestion of one of the reviewers to investigate how using randomized  $p$ -values (see e.g. [Habiger, 2015](#)) compares to our procedures. We do this by reanalyzing the Pharmacovigilance and Arabidopsis methylation data from Section 3.5. To be more specific, we apply the BH and the Storey procedure (with  $\lambda = 1/2$ ) to randomized  $p$ -values and denote these procedures by [r-BH] and [r-Storey]. For each random set of randomized  $p$ -values this results in a random set of rejected hypotheses. We repeat this simulation 1000 times and for each simulation run determine the number of rejected hypotheses. The resulting distribution of the number of rejected hypotheses is summarized numerically in Table 3.2 and displayed visually in Figure 3.4.

Table 3.2 Numerical summaries of rejections by randomized procedures.

Data set	Procedure	Min	1st Qu.	Median	Mean	3rd Qu.	Max
Pharmacovigilance	[r-BH]	24	26	27	27.02	28	35
	[r-Storey]	23	25	26	26.58	28	33
Arabidopsis methylation	[r-BH]	2302	2324	2331	2332	2339	2379
	[r-Storey]	2820	2863	2873	2873	2884	2916

The discrete BH procedure [HSU] compares favorably with [r-BH]: For the pharmacovigilance data the number of rejections by [HSU] (=27, see Table 3.1) is just the median of the distribution of [r-BH] and for the arabidopsis methylation data the number of rejections by [HSU] (=2358, see Table 3.1) is in the very right tail of the distribution of [r-BH].

The pharmacovigilance data seems to contain very few signals, so there is no benefit in using (either randomized or non-randomized) adaptive procedures as compared to discrete procedures (in fact, [r-BH] is more powerful than [r-Storey]). This is also consistent with the findings in Sections 3.5 and 3.6. In contrast, the arabidopsis methylation data seems to contain a large portion of signals, so that adaptive procedures become effective. We see that [r-Storey] considerably outperforms the adaptive discrete procedures from Table 3.1 which are not based on a plug-in method. We think the reason for this phenomenon is that this seems to be a situation which is tailored to the strengths of the plug-in method (again this is consistent with the findings in Sections 3.5 and 3.6).

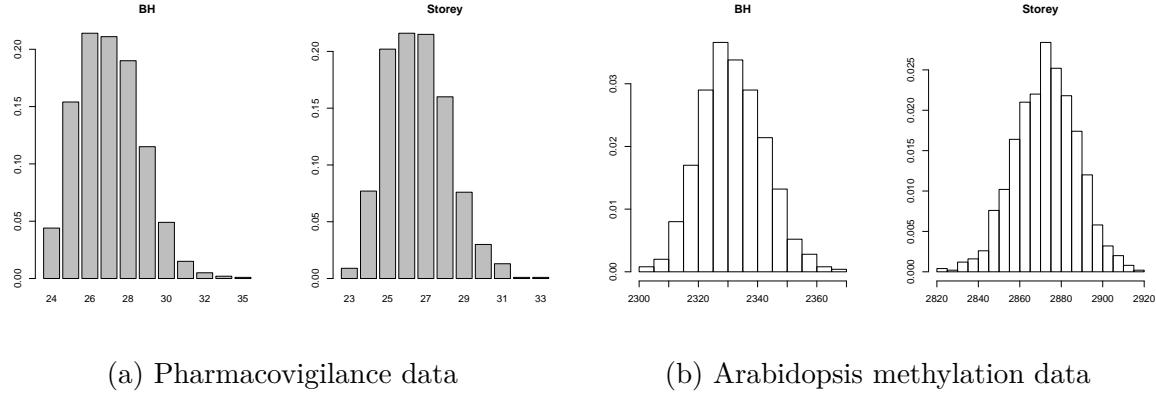


Fig. 3.4 Distribution of the number of rejected hypotheses when using randomized  $p$ -values.

Summarizing the findings from this section, it appears that the amount of power that is lost by avoiding randomization depends primarily on the proportion of alternatives. The Pharmacovigilance data set may serve as an example for a small proportion of alternatives. In this setting, no power is lost – on average – by using discreteness and avoiding randomization. When the proportion of alternatives is large however (the Arabidopsis methylation data may be considered a prototype example here) we think that the behavior of the randomized / discrete procedure is determined primarily by how the quantity of signal is estimated. To support this fact, we propose in Appendix 3.D a new procedure that combines our approach with the Storey estimator which rejects the same order of hypotheses as [r-Storey].

## Appendix 3.D A plug-in version of [HSU]

In this section, we sketch a discrete plug-in procedure in the spirit of [Storey et al. \(2004\)](#) for adapting to the unknown quantity of a discrete signal. To keep the exposition short, we describe this approach only for step-up procedures, however our ideas carry over directly to step-down procedures. As the proof of Theorem 3.4.1 shows, we have from (3.8.2) the following bound for FDR

$$\text{FDR}(\mathbf{SU}(\tau), P) \leq \max_{1 \leq k \leq m} \max_{\substack{A \subset \{1, \dots, m\} \\ |A|=m_0}} \left( \frac{1}{k} \sum_{i \in A} \frac{F_i(\tau_k)}{1 - F_i(\tau_m)} \right) \quad (3.D.1)$$

where  $m_0 = |\mathcal{H}_0|$  is the (unknown) number of true null hypotheses. Choosing critical value sequence  $\tau_1(m_0), \dots, \tau_m(m_0)$  that satisfy

$$\max_{\substack{A \subset \{1, \dots, m\} \\ |A|=m_0}} \sum_{i \in A} \frac{F_i(\tau_k(m_0))}{1 - F_i(\tau_m(m_0))} \leq k \cdot \alpha \quad (3.D.2)$$

yields a new HSU-type procedure which is adapted to the number of null hypotheses. In applications,  $m_0$  is an unknown quantity which has to be estimated appropriately, for more details on this issue, see e.g. [Blanchard and Roquain \(2009\)](#), [Storey et al. \(2004\)](#), [Liang and Nettleton \(2012\)](#), [Heesen and Janssen \(2016\)](#) and references therein. The plug-in method works as follows:

1. Given the data, determine an appropriate estimate  $\widehat{m}_0$  for  $m_0$ .
2. Apply the step-up procedure with critical values  $\tau_1(\widehat{m}_0), \dots, \tau_m(\widehat{m}_0)$ .

We emphasize that this approach is only a heuristic one and currently we do not have a proof for FDR control.

Depending on the amount of signals and discreteness of  $p$ -values this approach can lead to strongly enhanced rejection numbers. As an example, we revisit the analysis of the Arabidopsis methylation data (see section 3.5). Figure 3.5 depicts the number of rejections  $R$  as a function of  $\widehat{\pi}_0 = \widehat{m}_0/m$  for this data set. The estimator used by the [Storey] procedure in Table 3.1 yields  $\widehat{\pi}_0 = 0.6$  and thus the corresponding discrete plug-in procedure rejects  $R = 2659$  hypotheses. The randomized  $p$ -values that were used for evaluating [r-Storey] in Appendix 3.C result in an average  $\widehat{\pi}_0 = 0.468$ . Using this estimate, the discrete plug-in procedure rejects  $R = 2836$  hypotheses, which lies within the range of the rejection numbers for the completely randomized procedure [r-Storey].

## Appendix 3.E Tables for the simulations

Table 3.3 Average power in the simulation study (see Section 3.6).

$m$	$m_3$	$m_1$	$q$		[BH]	[Storey]	[Heyse]	[HSU]	[AHSU]
800	80	144	0.15		0.0000	0.0000	0.0004	0.0003	0.0003
		144	0.25		0.0004	0.0004	0.0197	0.0183	0.0183
		144	0.4		0.0803	0.0559	0.4425	0.4268	0.4268
		360	0.15		0.0000	0.0000	0.0007	0.0006	0.0006
		360	0.25		0.0004	0.0003	0.0244	0.0221	0.0221
		360	0.4		0.0803	0.0514	0.4529	0.4518	0.4518
		576	0.15		0.0000	0.0000	0.0009	0.0008	0.0008
		576	0.25		0.0004	0.0003	0.0343	0.0278	0.0278
		576	0.4		0.0803	0.0484	0.5367	0.4832	0.4832
		240	112	0.15	0.0000	0.0000	0.0003	0.0003	0.0003
		240	112	0.25	0.0005	0.0004	0.0276	0.0257	0.0257
		240	112	0.4	0.2148	0.1963	0.5365	0.5152	0.5152
640	640	280	0.15		0.0000	0.0000	0.0003	0.0003	0.0003
		280	0.25		0.0005	0.0004	0.0315	0.0282	0.0282
		280	0.4		0.2147	0.1883	0.5758	0.5596	0.5596
		448	0.15		0.0000	0.0000	0.0005	0.0004	0.0004
		448	0.25		0.0005	0.0003	0.0372	0.0323	0.0323
		448	0.4		0.2145	0.1793	0.5920	0.5844	0.5844
		32	0.15		0.0000	0.0000	0.0002	0.0002	0.0002
		32	0.25		0.0010	0.0016	0.0378	0.0352	0.0352
		32	0.4		0.4243	0.6519	0.6174	0.5983	0.6838
		80	0.15		0.0000	0.0000	0.0002	0.0002	0.0002
		80	0.25		0.0010	0.0014	0.0388	0.0359	0.0359
		80	0.4		0.4242	0.6370	0.6282	0.6146	0.6848
2000	200	128	0.15		0.0000	0.0000	0.0002	0.0002	0.0002
		128	0.25		0.0010	0.0013	0.0400	0.0368	0.0368
		128	0.4		0.4240	0.6276	0.6353	0.6271	0.6859
		360	0.15		0.0000	0.0000	0.0002	0.0002	0.0002
		360	0.25		0.0001	0.0001	0.0156	0.0145	0.0145
		360	0.4		0.0730	0.0499	0.4486	0.4334	0.4334
		900	0.15		0.0000	0.0000	0.0002	0.0002	0.0002
		900	0.25		0.0001	0.0001	0.0192	0.0170	0.0170
		900	0.4		0.0730	0.0439	0.4517	0.4517	0.4517
		1440	0.15		0.0000	0.0000	0.0003	0.0003	0.0003
		1440	0.25		0.0001	0.0001	0.0286	0.0218	0.0218
		1440	0.4		0.0730	0.0402	0.5402	0.4748	0.4748
1600	600	280	0.15		0.0000	0.0000	0.0002	0.0002	0.0002
		280	0.25		0.0001	0.0001	0.0239	0.0217	0.0217
		280	0.4		0.2058	0.1953	0.5350	0.5166	0.5166
		700	0.15		0.0000	0.0000	0.0002	0.0002	0.0002
		700	0.25		0.0001	0.0001	0.0290	0.0246	0.0246
		700	0.4		0.2058	0.1917	0.5750	0.5630	0.5630
		1120	0.15		0.0000	0.0000	0.0002	0.0002	0.0002
		1120	0.25		0.0001	0.0001	0.0350	0.0296	0.0296
		1120	0.4		0.2057	0.1832	0.5908	0.5853	0.5853
		80	0.15		0.0000	0.0000	0.0001	0.0001	0.0001
		80	0.25		0.0003	0.0007	0.0379	0.0352	0.0352
		80	0.4		0.4223	0.6498	0.6196	0.5942	0.6863
320	1600	200	0.15		0.0000	0.0000	0.0001	0.0001	0.0001
		200	0.25		0.0003	0.0006	0.0387	0.0361	0.0361
		200	0.4		0.4222	0.6352	0.6281	0.6157	0.6871
		320	0.15		0.0000	0.0000	0.0001	0.0001	0.0001
		320	0.25		0.0003	0.0005	0.0396	0.0369	0.0369
		320	0.4		0.4220	0.6282	0.6327	0.6279	0.6880

Table 3.4 Average FDR in the simulation study (see Section 3.6).

$m$	$m_3$	$m_1$	$q$	[BH]	[Storey]	[Heyse]	[HSU]	[AHSU]
800	80	144	0.15	0.000000	0.000000	0.000030	0.000021	0.000021
		144	0.25	0.000000	0.000000	0.000076	0.000066	0.000066
		144	0.4	0.000005	0.000002	0.001228	0.001154	0.001154
		360	0.15	0.000000	0.000000	0.000035	0.000030	0.000030
		360	0.25	0.000000	0.000000	0.000081	0.000067	0.000067
		360	0.4	0.000004	0.000001	0.000823	0.000797	0.000797
		576	0.15	0.000000	0.000000	0.000020	0.000017	0.000017
		576	0.25	0.000000	0.000000	0.000061	0.000042	0.000042
		576	0.4	0.000002	0.000001	0.001148	0.000915	0.000915
		240	112	0.15	0.000000	0.000000	0.000021	0.000021
240	240	112	0.25	0.000000	0.000000	0.000159	0.000139	0.000139
		112	0.4	0.000101	0.000062	0.004636	0.004540	0.004540
		280	0.15	0.000000	0.000000	0.000014	0.000013	0.000013
		280	0.25	0.000000	0.000000	0.000130	0.000106	0.000106
		280	0.4	0.000063	0.000032	0.003226	0.002962	0.002962
		448	0.15	0.000000	0.000000	0.000010	0.000007	0.000007
		448	0.25	0.000000	0.000000	0.000080	0.000060	0.000060
		448	0.4	0.000025	0.000012	0.002606	0.001583	0.001583
		640	32	0.15	0.000000	0.000000	0.000012	0.000012
		32	0.25	0.000000	0.000001	0.000308	0.000252	0.000252
640	640	32	0.4	0.001253	0.014708	0.014557	0.014527	0.015222
		80	0.15	0.000000	0.000000	0.000011	0.000011	0.000011
		80	0.25	0.000000	0.000000	0.000218	0.000176	0.000176
		80	0.4	0.000793	0.009106	0.009118	0.009111	0.009542
		128	0.15	0.000000	0.000000	0.000005	0.000005	0.000005
		128	0.25	0.000000	0.000000	0.000092	0.000071	0.000071
		128	0.4	0.000323	0.003566	0.003654	0.003653	0.003846
		2000	200	360	0.15	0.000000	0.000000	0.000011
		360	0.25	0.000000	0.000000	0.000043	0.000038	0.000038
		360	0.4	0.000003	0.000001	0.001251	0.001197	0.001197
2000	2000	900	0.15	0.000000	0.000000	0.000010	0.000008	0.000008
		900	0.25	0.000000	0.000000	0.000045	0.000035	0.000035
		900	0.4	0.000002	0.000001	0.000790	0.000790	0.000790
		1440	0.15	0.000000	0.000000	0.000005	0.000004	0.000004
		1440	0.25	0.000000	0.000000	0.000041	0.000025	0.000025
		1440	0.4	0.000001	0.000000	0.001160	0.000962	0.000962
		600	280	0.15	0.000000	0.000000	0.000011	0.000010
		280	0.25	0.000000	0.000000	0.000115	0.000093	0.000093
		280	0.4	0.000068	0.000056	0.004615	0.004571	0.004571
		700	0.15	0.000000	0.000000	0.000007	0.000007	0.000007
1600	1600	700	0.25	0.000000	0.000000	0.000105	0.000081	0.000081
		700	0.4	0.000041	0.000033	0.003076	0.002969	0.002969
		1120	0.15	0.000000	0.000000	0.000003	0.000003	0.000003
		1120	0.25	0.000000	0.000000	0.000057	0.000045	0.000045
		1120	0.4	0.000016	0.000012	0.002569	0.001592	0.001592
		80	0.15	0.000000	0.000000	0.000004	0.000004	0.000004
		80	0.25	0.000000	0.000001	0.000256	0.000229	0.000229
		80	0.4	0.001226	0.014589	0.014515	0.014499	0.015228
		200	0.15	0.000000	0.000000	0.000002	0.000002	0.000002
		200	0.25	0.000000	0.000000	0.000173	0.000152	0.000152
3200	3200	200	0.4	0.000768	0.009109	0.009108	0.009105	0.009563
		320	0.15	0.000000	0.000000	0.000001	0.000001	0.000001
		320	0.25	0.000000	0.000000	0.000073	0.000061	0.000061
		320	0.4	0.000305	0.003641	0.003646	0.003646	0.003830

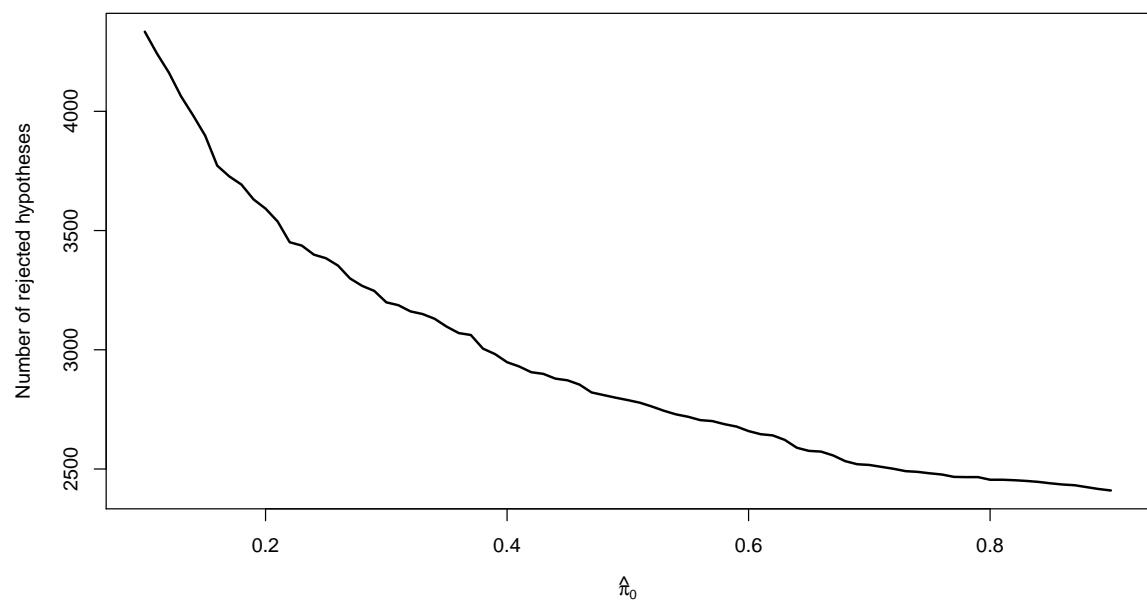


Fig. 3.5 Number of rejections of the discrete plug-in procedure for the arabidopsis methylation data.

# Chapter 4

## Improved post hoc bounds for localized signal

This chapter corresponds to the arXiv preprint ([Durand et al., 2018](#)), which is a joint work with Etienne Roquain, Pierre Neuvial and Gilles Blanchard. It has been slightly updated and some complementary results are provided in Appendix [B](#).

**Abstract** In a high dimensional multiple testing framework, we present new confidence bounds on the false positives contained in subsets  $S$  of selected null hypotheses. The coverage probability holds simultaneously over all subsets  $S$ , which means that the obtained confidence bounds are post hoc. Therefore,  $S$  can be chosen arbitrarily, possibly by using the data set several times. We focus in this paper specifically on the case where the null hypotheses are spatially structured. Our method is based on recent advances in post hoc inference and particularly on the general methodology of [Blanchard et al. \(2018b\)](#); we build confidence bounds for some pre-specified forest-structured subsets  $\{R_k, k \in \mathcal{K}\}$ , called the reference family, and then we deduce a bound for any subset  $S$  by interpolation. The proposed bounds are shown to improve substantially previous ones when the signal is locally structured. Our findings are supported both by theoretical results and numerical experiments. Moreover, we show that our bound can be obtained by a low-complexity algorithm, which makes our approach completely operational for a practical use. The proposed bounds are implemented in the open-source R package `sansSouci`<sup>1</sup>.

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<sup>1</sup>available from <https://github.com/pneuvial/sanssouci>.

## 4.1 Introduction

### 4.1.1 Background

Modern statistical data analysis often involves asking many questions of interest simultaneously, possibly using the data repeatedly, as long as the user feels that this could provide additional information. To avoid selection bias due to various forms of data snooping, specific strategies can be proposed to take into account the procedure as whole, and be investigated as to the statistical guarantees they provide. This problem is often referred to as selective inference, a long standing research field, with a recent renewal of interest. An historical reference is the work of Scheffé (1953) (see also Scheffé, 1959, p. 69), which is to our knowledge the earliest work proposing simultaneous selective inference. In the context of linear regression, Berk et al. (2013) proposed an improvement of this Scheffé protection by defining a less conservative correction term (the so-called PoSI constant), see also Bachoc et al. (2014, 2018) for recent developments on this issue.

Other strategies perform inference on the observed selection set only, either by a false coverage rate control (Benjamini and Yekutieli, 2005; Benjamini and Bogomolov, 2014) or by controlling a criterion conditional to a specific initial selection step, see the series of works Fithian et al. (2017); Taylor and Tibshirani (2015); Tibshirani et al. (2016); Choi et al. (2017); Taylor and Tibshirani (2018). In other studies, the selection step is based on sample splitting, see Cox (1975); Bühlmann and Mandozzi (2014); Dezeure et al. (2015), which is another way to tackle selective inference by explicitly avoiding data reuse.

We follow in this paper the aim of establishing confidence bounds on the number of false positives in a multiple testing framework, simultaneously over all possible set of selected hypotheses. If we observe a random variable  $X \sim P$ ,  $P$  belonging to some model  $\mathcal{P}$ , for which  $m$  null hypotheses  $H_{0,i} \subset \mathcal{P}$ ,  $i \in \mathbb{N}_m = \{1, \dots, m\}$  are under investigation for  $P$ , the aim is to build a function  $V(X, \cdot) : S \subset \mathbb{N}_m \mapsto V(X, S)$  (denoted by  $V(S)$  for short) satisfying

$$\forall P \in \mathcal{P}, \quad \mathbb{P}_{X \sim P} \left( \forall S \subset \mathbb{N}_m, |S \cap \mathcal{H}_0(P)| \leq V(S) \right) \geq 1 - \alpha, \quad (4.1.1)$$

where  $\mathcal{H}_0(P) = \{i \in \mathbb{N}_m : P \text{ satisfies } H_{0,i}\}$  is the set of true null hypotheses. The bound  $V(\cdot)$  will be referred to as a post hoc bound throughout this manuscript.

The problem of constructing post hoc bounds has been first tackled specifically in the case where the selection sets  $S$  are of the form of  $p$ -value level sets:  $\{i : p_i(X) \leq t\}$ ,  $t \in [0, 1]$ , where each  $p_i(X)$  is a  $p$ -value for the null hypothesis  $H_{0,i}$ ,  $1 \leq i \leq m$ .

The resulting bounds are often referred to as confidence envelopes, see Genovese and Wasserman (2004); Meinshausen (2006). Later, Genovese and Wasserman (2006) and Goeman and Solari (2011) proposed to extend this approach to arbitrary subsets  $S$ , by using a methodology based on performing  $2^m - 1$  local tests (one for each intersection hypothesis), with a possible complexity reduction by using shortcuts. In particular, the approach of Goeman and Solari (2011) extensively relies on the closed testing principle, which was introduced by Marcus et al. (1976). This approach has been further extended in Meijer and Goeman (2015); Meijer et al. (2015) by using the sequential rejection principle of Goeman and Solari (2010). This allows to incorporate structural informations into the post hoc bound. In particular, the method in Meijer et al. (2015), whose goal inspired the present work, deals with geometrically structured null hypotheses, along space or time and shows that incorporating such an external information can substantially improve the detection of signal and thus can increase the accuracy of the resulting post hoc bound.

More recently, Blanchard et al. (2018b) (BNR below) have proposed a flexible methodology that adjusts the complexity of the bound by way of a reference family: the post hoc bound is based on a family  $\mathfrak{R} = ((R_k(X), \zeta_k(X))_{k \in \mathcal{K}}$  ( $R_k, \zeta_k$  for short), with  $R_k \subset \mathbb{N}_m$  (and  $R_k \neq R_{k'}$  if  $k \neq k'$ ),  $\zeta_k \in \mathbb{N}$ , that satisfies the following joint error rate (JER) control:

$$\forall P \in \mathcal{P}, \quad \mathbb{P}_{X \sim P} \left( \forall k \in \mathcal{K}, |R_k \cap \mathcal{H}_0(P)| \leq \zeta_k \right) \geq 1 - \alpha, \quad (4.1.2)$$

An important difference between (4.1.1) and (4.1.2) is that  $S$  in (4.1.1) is let arbitrary and typically chosen by the user, whereas  $R_k, \zeta_k$  in (4.1.2) is part of the methodology and is chosen by the statistician to make (4.1.2) hold. Once the reference family is fixed, a post hoc bound is obtained from (4.1.2) simply by interpolation, by exploiting the constraints that the event in (4.1.2) imposes to the unknown set  $\mathcal{H}_0(P)$ , namely that it is a subset  $A$  with the property " $\forall k \in \mathcal{K}, |R_k \cap A| \leq \zeta_k$ ":

$$V_{\mathfrak{R}}^*(S) = \max \left\{ |S \cap A|, A \subset \mathbb{N}_m, \forall k \in \mathcal{K}, |R_k \cap A| \leq \zeta_k \right\}, \quad S \subset \mathbb{N}_m. \quad (4.1.3)$$

Hence, if (4.1.2) holds, then  $V = V_{\mathfrak{R}}^*$  satisfies (4.1.1). This post-hoc bound will be referred to as the *optimal bound* (relative to a given reference family).

### 4.1.2 Contributions of the paper

In this paper, we propose new post hoc bounds that incorporate the specific spatial structure of the null hypotheses. While this aim is similar in spirit to [Meijer et al. \(2015\)](#), our method is markedly different, as it relies on the general strategy laid down by BNR, with a specifically structured reference family  $R_k, k \in \mathcal{K}$  (see Section 4.6.1 for a comparison between our approach and the one of [Meijer et al., 2015](#)). In addition, the way the method is built here is different than the one proposed in Section 3-6 of BNR: the main focus in BNR is the case of (random) reference sets  $R_k = R_k(X)$  that are designed in order to satisfy (4.1.2) with  $\zeta_k = k - 1$  (thus corresponding to a “joint  $k$ -family-wise error rate”). By contrast, in the present work the reference sets  $R_k$  are fixed in advance, and the (random) bounds on the number false positives  $\zeta_k = \zeta_k(X)$  are designed to satisfy the constraint (4.1.2). The rationale behind this approach is that the reference sets  $R_k$  can be chosen arbitrarily by the statistician, so that it can accommodate any pre-specified structure (reflecting some prior knowledge on the considered problem). Since we are interested in structured signal, we focus on a reference family enjoying a forest structure, meaning that two reference sets are either disjoint or nested.

The second ingredient of our method is the local bounds  $\zeta_k(X)$ , that should estimate  $|R_k \cap \mathcal{H}_0(P)|$  with a suitable deviation term. While any deviation inequality can be used, we have chosen to focus on the DKW inequality ([Dvoretzky et al., 1956](#)), that has the advantage to be sub-Gaussian. Hence, the uniformity over the range  $k \in \mathcal{K}$  can be obtained by a simple union bound without being too conservative.

Let us mention that using the DKW inequality to obtain a confidence bound for the proportion of null hypotheses is not new, see [Genovese and Wasserman \(2004\)](#) (Equation (16) therein), [Meinshausen \(2006\)](#), and [Farcomeni and Pacillo \(2011\)](#). While our bound is a uniform improvement of the existing version (see Remark 4.4.2 below for more details), our main innovation is to use the DKW bound in a local manner and to appropriately combine these local bounds to derive an overall post hoc bound. The improvement can be substantial, as illustrated in our numerical experiments.

The paper is organized as follows: precise setup and notation are introduced in Section 4.2. For any reference family with a forest structure, the optimal post hoc bound is computed in Section 4.3. The calibration of the local bounds  $\zeta_k$  and of the overall reference family is done in Section 4.4. This section also includes a theoretical comparison with previous methods, which quantifies formally the amplitude of the improvement induced by the new method. The latter is supported by numerical experiments in Section 4.5, where a hybrid approach is also introduced to mimic the best between the new approach and the existing Simes bound (the latter being defined in (4.2.4) below). A

discussion is given in Section 4.6 and the proofs are provided in Section 4.7. Additional technical details are postponed to Appendices 4.A and 4.B.

## 4.2 Preliminaries

### 4.2.1 Assumptions

We focus on the common situation where a test statistic  $T_i(X)$  is available for each null hypothesis  $H_{0,i}$ . For  $i \in \mathbb{N}_m$ , each statistic  $T_i(X)$  is transformed into a  $p$ -value  $p_i(X)$ , satisfying the following assumptions:

$$\forall i \in \mathcal{H}_0, \quad \forall t \in [0, 1], \quad \mathbb{P}(p_i(X) \leq t) \leq t; \quad (\text{Superunif})$$

$$\{p_i(X)\}_{i \in \mathcal{H}_0} \text{ is a family of independent } p\text{-values and is independent of } \{p_i(X)\}_{i \in \mathcal{H}_1}. \quad (\text{Indep})$$

Extending our results to the case where (Indep) fails is possible, see the discussion in Section 4.6.

### 4.2.2 Classical post hoc bounds

As argued in BNR, computing the optimal post hoc bound (4.1.3) relative to a given reference family  $(R_k, \zeta_k)_{k \in \mathcal{K}}$  can be NP-hard, and simpler, more conservative versions can be provided, that is, bounds  $V$  such that for all  $S \subset \mathbb{N}_m$ ,  $V_{\mathfrak{R}}^*(R) \leq V(R)$ . A simple upper-bound for  $V_{\mathfrak{R}}^*$  is given by

$$\bar{V}_{\mathfrak{R}}(S) = |S| \wedge \min_{k \in \mathcal{K}} \{\zeta_k + |S \setminus R_k|\}, \quad S \subset \mathbb{N}_m. \quad (4.2.1)$$

It is straightforward to check that

$$V_{\mathfrak{R}}^*(S) \leq \bar{V}_{\mathfrak{R}}(S), \quad S \subset \mathbb{N}_m. \quad (4.2.2)$$

While this inequality is strict in general, BNR established that it is an equality if the reference family is nested, that is,

$$\mathcal{K} = \{1, \dots, K\} \text{ and } R_k \subset R_{k+1} \text{ for } 1 \leq k \leq K-1. \quad (\text{Nested})$$

Condition (Nested) is mild when the sequence  $\zeta_k$  is nondecreasing, e.g.,  $\zeta_k = k - 1$ .

A consequence of (4.2.2) is that  $\bar{V}_{\mathfrak{R}}$  is a post hoc bound in the sense of (4.1.1) as soon as the reference family  $\mathfrak{R}$  is such that (4.1.2) holds. A simple union bound under (Superunif) yields that (4.1.2) holds with  $\mathfrak{R} = \{(R_1, \zeta_1)\}$ ,  $R_1 = \{i \in \mathbb{N}_m : p_i \leq \alpha/m\}$ ,  $\zeta_1 = 0$ . This leads to the Bonferroni post hoc bound

$$V_{\text{Bonf}}(S) = \sum_{i \in S} \mathbf{1}_{\{p_i(X) > \alpha/m\}}, \quad S \subset \mathbb{N}_m. \quad (4.2.3)$$

The more subtle Simes inequality (Simes, 1986), valid under (Superunif)–(Indep), ensures that (4.1.2) holds with  $\mathfrak{R} = \{(R_k, \zeta_k), 1 \leq k \leq m\}$ ,  $R_k = \{i \in \mathbb{N}_m : p_i \leq \alpha k/m\}$ ,  $\zeta_k = k - 1$ . This leads to the Simes post hoc bound

$$V_{\text{Simes}}(S) = \min_{1 \leq k \leq m} \left\{ \sum_{i \in S} \mathbf{1}_{\{p_i(X) > \alpha k/m\}} + k - 1 \right\}, \quad S \subset \mathbb{N}_m. \quad (4.2.4)$$

As noted in BNR, this bound is identical to the post hoc bound of Goeman and Solari (2011), which will be used as a benchmark in this paper.

### 4.2.3 Improved interpolation bound

When the sequence  $\zeta_k$  is not nondecreasing, inequality (4.2.2) can be far too conservative. We introduce the following extension: for a reference family  $\mathfrak{R} = (R_k(X), \zeta_k(X))_{k \in \mathcal{K}}$  of cardinal  $K = |\mathcal{K}|$ ,

$$\tilde{V}_{\mathfrak{R}}^q(S) = \min_{Q \subset \mathcal{K}, |Q| \leq q} \left( \sum_{k \in Q} \zeta_k \wedge |S \cap R_k| + \left| S \setminus \bigcup_{k \in Q} R_k \right| \right), \quad 1 \leq q \leq K, \quad S \subset \mathbb{N}_m; \quad (4.2.5)$$

$$\tilde{V}_{\mathfrak{R}}(S) = \tilde{V}_{\mathfrak{R}}^K(S), \quad S \subset \mathbb{N}_m. \quad (4.2.6)$$

Obviously, we have  $\tilde{V}_{\mathfrak{R}}^1 = \bar{V}_{\mathfrak{R}}$  and  $\tilde{V}_{\mathfrak{R}}^q$  is non-increasing in  $q$ . The following result shows that these bounds are all conservative versions of  $V_{\mathfrak{R}}^*$ .

**Lemma 4.2.1.** *For any reference family  $\mathfrak{R}$ , we have*

$$V_{\mathfrak{R}}^*(S) \leq \tilde{V}_{\mathfrak{R}}(S) \leq \tilde{V}_{\mathfrak{R}}^q(S) \leq \bar{V}_{\mathfrak{R}}(S), \quad 1 \leq q \leq K, \quad S \subset \mathbb{N}_m. \quad (4.2.7)$$

*In particular, if  $\mathfrak{R}$  is such that (4.1.2) holds, then  $\tilde{V}_{\mathfrak{R}}$  is a post hoc bound in the sense of (4.1.1).*

Lemma 4.2.1 is proved in Section 4.7.1. The inequality  $V_{\mathfrak{R}}^*(S) \leq \tilde{V}_{\mathfrak{R}}(S)$  in (4.2.7) is strict in general, see Example 4.2.1. As we will show in the next section, this relation

is nevertheless an equality when  $\mathfrak{R}$  has a specific forest structure, which makes  $\tilde{V}_{\mathfrak{R}}$  a particularly interesting bound.

*Example 4.2.1.* Let  $m = 4$ ,  $K = 3$ ,  $R_1 = \{1, 2, 4\}$ ,  $R_2 = \{2, 3, 4\}$ ,  $R_3 = \{1, 3, 4\}$ . Consider the event where  $\zeta_1(X) = \zeta_2(X) = \zeta_3(X) = 1$ . For  $S = \mathbb{N}_4$ , we easily check that  $V_{\mathfrak{R}}^*(S) = 1$  and  $\tilde{V}_{\mathfrak{R}}(S) = 2$ .

## 4.3 Post hoc bound for forest structured reference family

### 4.3.1 Forest structure

**Definition 4.3.1.** A reference family  $\mathfrak{R} = (R_k, \zeta_k)_{k \in \mathcal{K}}$  is said to have a forest structure if following property is satisfied:

$$\forall k, k' \in \mathcal{K}, \quad R_k \cap R_{k'} \in \{R_k, R_{k'}, \emptyset\}, \quad (\text{Forest})$$

that is, two elements of  $\{R_k\}_{k \in \mathcal{K}}$  are either disjoint or nested.

The forest structure is general enough to cover a wide range of different situations, as for instance the disjoint case

$$\forall k, k' \in \mathcal{K}, \quad k \neq k' \Rightarrow R_k \cap R_{k'} = \emptyset. \quad (\text{Disjoint})$$

and the nested case ([Nested](#)). In general, if each  $R_k$  is considered as a node and if an oriented edge  $R_k \leftarrow R_{k'}$  is depicted between two different sets  $R_k$  and  $R_{k'}$  if and only if  $R_k \subset R_{k'}$  and there is no  $R_{k''}$  such that  $R_k \subsetneq R_{k''} \subsetneq R_{k'}$ ; the obtained graph correspond to a (directed) forest in the classical graph theory sense, see e.g. [Kolaczyk \(2009\)](#). An illustration is given in Figure 4.1. The positions of the nodes in this picture rely on the depth of  $\mathfrak{R}$ , which can be defined as the function

$$\phi : \begin{cases} \mathcal{K} & \rightarrow \mathbb{N}^* \\ k & \mapsto 1 + |\{k' \in \mathcal{K} : R_{k'} \supsetneq R_k\}|. \end{cases} \quad (4.3.1)$$

For instance, under ([Disjoint](#)),  $\phi(k) = 1$  for all  $k \in \mathcal{K}$ , while under ([Nested](#)),  $\phi(k) = K + 1 - k$  for all  $1 \leq k \leq K$ .

*Example 4.3.1.* Let  $m = 25$ ,  $R_1 = \{1, \dots, 20\}$ ,  $R_2 = \{1, 2\}$ ,  $R_3 = \{3, \dots, 10\}$ ,  $R_4 = \{11, \dots, 20\}$ ,  $R_5 = \{5, \dots, 10\}$ ,  $R_6 = \{11, \dots, 16\}$ ,  $R_7 = \{17, \dots, 20\}$ ,  $R_8 = \{21, 22\}$ ,

$R_9 = \{22\}$ . Then the corresponding reference family  $\mathfrak{R} = (R_k, \zeta_k)_{1 \leq k \leq 9}$  satisfies (Forest). The sets  $R_1, R_8$  are of depth 1; the sets  $R_2, R_3, R_4, R_9$  are of depth 2; the sets  $R_5, R_6, R_7$  are of depth 3.

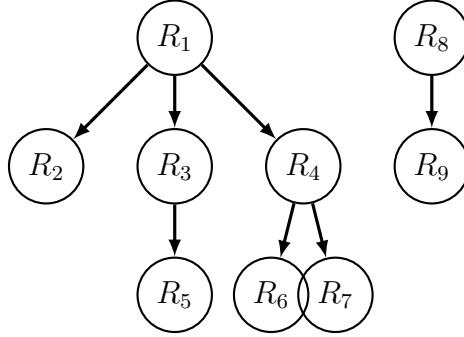


Fig. 4.1 Graph corresponding to the reference family given in Example 4.3.1.

A useful characterization of a forest-structure reference family is given in the next lemma.

**Lemma 4.3.1.** *For any reference family  $\mathfrak{R} = (R_k, \zeta_k)_{k \in \mathcal{K}}$  having the structure (Forest), there exists a partition  $(P_n)_{1 \leq n \leq N}$  of  $\mathbb{N}_m$  such that for each  $k \in \mathcal{K}$ , there exists some  $(i, j)$  with  $1 \leq i \leq j \leq N$  and  $R_k = P_{i:j}$ , where we denote*

$$P_{i:j} = \bigcup_{i \leq n \leq j} P_n, \quad 1 \leq i \leq j \leq N. \quad (4.3.2)$$

Conversely, for some partition  $(P_n)_{1 \leq n \leq N}$  of  $\mathbb{N}_m$ , consider any reference family of the form  $\mathfrak{R} = (P_{i:j}, \zeta_{i,j})_{(i,j) \in \mathcal{C}}$  with  $\mathcal{C} \subset \{(i, j) \in \mathbb{N}_N^2 : i \leq j\}$  such that for  $(i, j), (i', j') \in \mathcal{C}$ , we have

$$[i, j] \cap [i', j'] = \emptyset; \text{ or } [i, j] \subset [i', j']; \text{ or } [i', j'] \subset [i, j],$$

where  $[i, j]$  denotes the set of all integers between  $i$  and  $j$ . Then  $\mathfrak{R}$  has the structure (Forest).

For the ease of notation, the set  $\mathcal{C}$  will be identified to  $\mathcal{K}$  throughout the paper, which leads to the following slight abuse: denoting indifferently  $k \in \mathcal{K}$  or  $(i, j) \in \mathcal{K}$ , and

$$\mathfrak{R} = (R_k, \zeta_k)_{k \in \mathcal{K}} \quad \text{or} \quad \mathfrak{R} = (P_{i:j}, \zeta_{i,j})_{(i,j) \in \mathcal{K}}. \quad (4.3.3)$$

We call ‘‘atoms’’ the elements of the underlying partition  $(P_n)_{1 \leq n \leq N}$  because they have the thinnest granularity in the structure and because any subset  $R_k$  of the family

can be expressed as a combination of these atoms. Note however that this partition is not unique. A simple algorithm to compute  $(P_n)_n$  and the proof of Lemma 4.3.1 are provided in Appendix 4.B. An example of such a partition is given in Example 4.3.2 and Figure 4.2.

*Example 4.3.2.* For the reference family given in Example 4.3.1, a partition as in Lemma 4.3.1 is given by  $P_1 = R_2$ ,  $P_2 = R_3 \setminus R_5$ ,  $P_3 = R_5$ ,  $P_4 = R_6$ ,  $P_5 = R_7$ ,  $P_6 = R_8 \setminus R_9$ ,  $P_7 = R_9$ ,  $P_8 = \mathbb{N}_m \setminus \{R_1 \cup R_8\}$ .

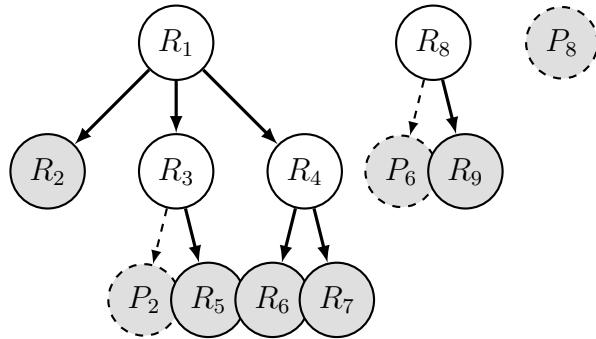


Fig. 4.2 Graph corresponding to the reference family given by Example 4.3.1, with the associated partition (atoms)  $\{P_n, 1 \leq n \leq N\}$ , displayed by light gray nodes and given in Example 4.3.2. The nodes that correspond to atoms that are not in the reference family are depicted with a dashed circle.

An important particular case in our analysis is the case where the forest structure includes all atoms, that is

$$\forall n \in \{1, \dots, N\}, \quad P_n \in \{R_k, k \in \mathcal{K}\}. \quad (\text{All-atoms})$$

When (All-atoms) does not hold (as in Example 4.3.2), we can impose this condition by adding them to the structure, building in this way the completed reference family:

**Definition 4.3.2.** Consider any reference family  $\mathfrak{R} = (P_{i:j}, \zeta_{i,j})_{(i,j) \in \mathcal{K}}$  satisfying (Forest) and associated to atoms  $(P_n)_{1 \leq n \leq N}$  by (4.3.3). Let  $\mathcal{K}^+ = \{(i, i), 1 \leq i \leq N : (i, i) \notin \mathcal{K}\}$ ,  $\zeta_{i,i} = |P_{i:i}| = |P_i|$  for all  $(i, i) \in \mathcal{K}^+$ , and  $\mathcal{K}^\oplus = \mathcal{K} \cup \mathcal{K}^+$ . Then the completed version of  $\mathfrak{R}$  is given by  $\mathfrak{R}^\oplus = (P_{i:j}, \zeta_{i,j})_{(i,j) \in \mathcal{K}^\oplus}$ .

For the reference family  $\mathfrak{R}$  given by Example 4.3.1, the completed version  $\mathfrak{R}^\oplus$  is depicted in Figure 4.3.

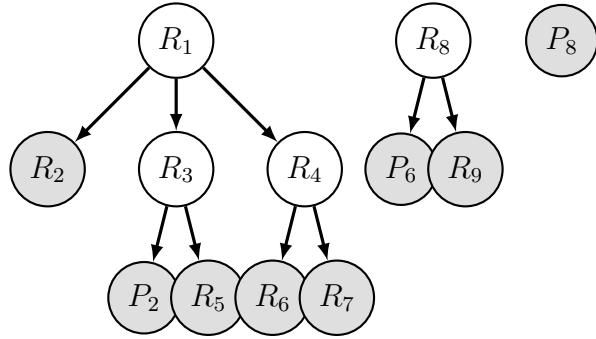


Fig. 4.3 Graph corresponding to the completed version  $\mathfrak{R}^\oplus$  of the reference family  $\mathfrak{R}$  given by Example 4.3.1 with the atoms given in Example 4.3.2.

### 4.3.2 Deriving the optimal post hoc bound

The next result shows that the expression of the optimal post hoc bound  $V_{\mathfrak{R}}^*$  can be simplified when  $\mathfrak{R}$  satisfies (Forest).

**Theorem 4.3.1.** *Let  $\mathfrak{R}$  be a reference family having the structure (Forest). Then the optimal bound  $V_{\mathfrak{R}}^*$  (4.1.3) can be derived from the bounds  $\tilde{V}_{\mathfrak{R}}^q$  (4.2.5) and  $\tilde{V}_{\mathfrak{R}}$  (4.2.6) in the following way:*

$$V_{\mathfrak{R}}^*(S) = \tilde{V}_{\mathfrak{R}}(S), \quad S \subset \mathbb{N}_m; \quad (4.3.4)$$

$$V_{\mathfrak{R}}^*(S) = \tilde{V}_{\mathfrak{R}}^d(S), \quad S \subset \mathbb{N}_m, \quad (4.3.5)$$

where  $d$  is the maximum number of disjoint sets that can be found in the reference family, that is,

$$d = \max\{|Q|, Q \subset \mathcal{K} : \forall k, k' \in Q, \ k \neq k' \Rightarrow R_k \cap R_{k'} = \emptyset\}.$$

A byproduct of Theorem 4.3.1 is that, if (Nested) holds,  $V_{\mathfrak{R}}^* = \tilde{V}_{\mathfrak{R}}^1(S) = \bar{V}_{\mathfrak{R}}$  and we recover Proposition 2.5 of BNR. Another interesting case is the structure (Disjoint), where  $\tilde{V}_{\mathfrak{R}}$  has a simpler form. This is summarized in the following result.

**Corollary 4.3.1.** *Let  $\mathfrak{R}$  be a reference family.*

(i) *if  $\mathfrak{R}$  satisfies (Nested), then  $V_{\mathfrak{R}}^* = \bar{V}_{\mathfrak{R}}$ .*

(ii) *if  $\mathfrak{R}$  satisfies (Disjoint), then  $V_{\mathfrak{R}}^*(S) = \sum_{k=1}^K \zeta_k \wedge |S \cap R_k| + |S \setminus \bigcup_{k=1}^K R_k|$ ,  $S \subset \mathbb{N}_m$ .*

Theorem 4.3.1 and Corollary 4.3.1 are respectively proved in Section 4.7.2 and Section 4.7.3.

The proof of Theorem 4.3.1 being constructive, it provides an algorithm to compute easily  $V_{\mathfrak{R}}^*(S)$ , that we now describe. Let us first introduce an additional piece of notation. For some reference family  $\mathfrak{R} = (P_{i:j}, \zeta_{i,j})_{(i,j) \in \mathcal{K}}$  of depth function  $\phi$  (see (4.3.1)), we denote

$$\mathcal{K}^h = \{(i, j) \in \mathcal{K} : \phi(i, j) = h \text{ or } (i = j \text{ and } \phi(i, i) \leq h)\}, \quad h \geq 1.$$

Hence, each  $\mathcal{K}^h$  contains the indexes of the sets of depth  $h$  and also the atoms with an inferior depth. Figure 4.4 displays some  $\mathcal{K}^h$  for the reference family of Example 4.3.1.

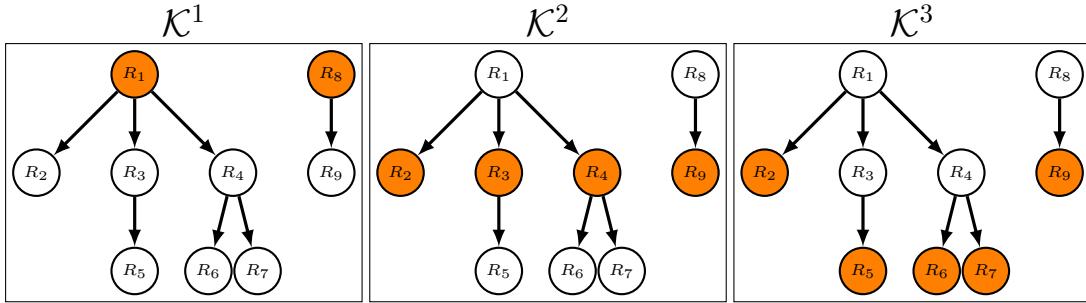


Fig. 4.4 Display of the nodes corresponding to  $\mathcal{K}^1$ ,  $\mathcal{K}^2$ ,  $\mathcal{K}^3$  (in orange) for the reference family given in Example 4.3.1.

Algorithm 1 below gives the steps to compute  $V_{\mathfrak{R}}^*(S)$ : first, complete the family  $\mathfrak{R}$  by adding all the members of the partition, as explained in Definition 4.3.2, in order to get  $\mathfrak{R}^\oplus$ . By Lemma 4.A.4, we have  $V_{\mathfrak{R}^\oplus}^*(S) = V_{\mathfrak{R}}^*(S)$ , so that this operation does not change the targeted quantity. In particular, (All-atoms) holds after this step. Second, the algorithm uses a reverse loop, which successively updates a vector  $V$  whose components correspond to active nodes; the current value of the bound is equal to the sum of the components of  $V$ . Each step of the loop will update the value of  $V$  to make the bound possibly smaller, to obtain at the end  $V_{\mathfrak{R}}^*(S)$ . The time complexity of the Algorithm 1 for a given  $S$  is  $O(Hm)$ , where  $H = \max_{k \in \mathcal{K}} \phi(k)$  is the maximal depth of the reference family, where  $\phi$  is the depth function defined by (4.3.1).

Let us describe the loop in more detail by using the particular situation of Figure 4.5. Initialization:  $H = 3$  and  $\mathcal{K}^H = \mathcal{K}^3$ , which corresponds to the active nodes in the rightmost graph. Hence,  $V$  is equal to the vector of values  $\zeta_k \wedge |S \cap R_k|$  among these nodes. First step:  $h = 2$  hence  $\mathcal{K}^h = \mathcal{K}^2$ , for which the active nodes are displayed in the middle graph. Each of these nodes  $k \in \mathcal{K}^2$ , gives a bound  $\zeta_k \wedge |S \cap R_k|$  that should be compared with the one of the previous step, that is,  $\sum_{k' \in \text{Succ}_k} V_{k'}$ , where  $\text{Succ}_k$  denotes the offspring of  $R_k$ . The vector  $V$  is defined by the best choice among these two. Second (and final) step:  $h = 1$  hence  $\mathcal{K}^h = \mathcal{K}^1$  (leftmost graph) which only contains the roots

of the forest and where  $V$  is updated following the same process. The algorithm then returns  $V_{\mathfrak{R}}^*(S) = \sum_{k \in \mathcal{K}^1} V_k$ .

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**Algorithm 1:** Computation of  $V_{\mathfrak{R}}^*(S)$ 


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**Data:**  $\mathfrak{R} = (P_{i;j}, \zeta_{i;j})_{(i;j) \in \mathcal{K}}$  and  $S \subset \mathbb{N}_m$ .  
**Result:**  $V_{\mathfrak{R}}^*(S)$ .

- 1  $\mathfrak{R} \leftarrow \mathfrak{R}^\oplus; \mathcal{K} \leftarrow \mathcal{K}^\oplus$  (completion, see Definition 4.3.2);
- 2  $H \leftarrow \max_{k \in \mathcal{K}} \phi(k)$ , see (4.3.1);
- 3  $V \leftarrow (\zeta_k \wedge |S \cap R_k|)_{k \in \mathcal{K}^H}$ ;
- 4 **for**  $h \in \{H-1, \dots, 1\}$  **do**
- 5      $newV \leftarrow (0)_{k \in \mathcal{K}^h}$ ;
- 6     **for**  $k \in \mathcal{K}^h$  **do**
- 7          $Succ_k \leftarrow \{k' \in \mathcal{K}^{h+1} : R_{k'} \subset R_k\}$ ;
- 8          $newV_k \leftarrow \min(\zeta_k \wedge |S \cap R_k|, \sum_{k' \in Succ_k} V_{k'})$ ;
- 9     **end**
- 10      $V \leftarrow newV$ ;
- 11 **end**
- 12 **return**  $\sum_{k \in \mathcal{K}^1} V_k$ .

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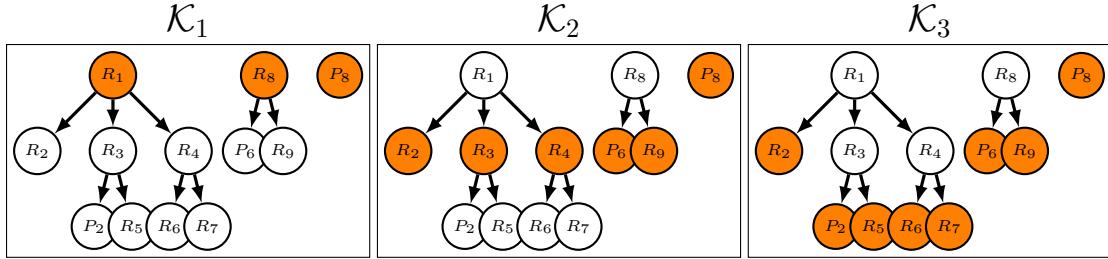


Fig. 4.5 Same as Figure 4.4 but for the completed version.

## 4.4 Local calibration of the reference family

In this section, we explain how to build a reference family  $\mathfrak{R}$  such that (4.1.2) holds. The results presented in this section hold for any deterministic  $(R_k)_k$  and the calibration concerns only  $(\zeta_k)_k$  here.

### 4.4.1 Calibration of $\zeta_k$ by DKW inequality

In this section, we estimate  $|S \cap \mathcal{H}_0|$  by using an approach close in spirit to the so-called Storey estimator (Storey, 2002). The latter depends on a parameter, denoted by  $t$  here,

that has to be chosen appropriately (see [Blanchard and Roquain, 2009](#) for a discussion on this issue). To avoid this caveat while improving accuracy, we can derive an estimator uniform on  $t$  by using the DKW inequality ([Dvoretzky et al., 1956](#)), with the optimal constant of [Massart \(1990\)](#).

For any deterministic subsets  $R_k \subset \mathbb{N}_m$ ,  $k \in \mathcal{K}$ ,  $K = |\mathcal{K}|$ , let

$$\zeta_k(X) = |R_k| \wedge \min_{t \in [0,1]} \left[ \left( \frac{C}{2(1-t)} + \left( \frac{C^2}{4(1-t)^2} + \frac{\sum_{i \in R_k} \mathbf{1}\{p_i(X) > t\}}{1-t} \right)^{1/2} \right)^2 \right], \quad k \in \mathcal{K}, \quad (4.4.1)$$

where  $C = \sqrt{\frac{1}{2} \log \left( \frac{K}{\alpha} \right)}$  and  $\lfloor x \rfloor$  denotes the largest integer smaller than or equal to  $x$ .

**Proposition 4.4.1.** *Consider any deterministic (different) subsets  $R_k \subset \mathbb{N}_m$ ,  $k \in \mathcal{K}$  ( $K = |\mathcal{K}|$ ) and assume  $\alpha/K < 1/2$ . Assume that for all  $k \in \mathcal{K}$ , the p-value family  $\{p_i(X), i \in R_k\}$  satisfies [\(Superunif\)](#) and [\(Indep\)](#). Then the JER control (4.1.2) holds for the reference family  $\mathfrak{R} = (R_k, \zeta_k(X))_{k \in \mathcal{K}}$ , for which the local bounds  $\zeta_k$  are given by (4.4.1).*

Combining Proposition 4.4.1 with Lemma 4.2.1, we obtain that, under the assumptions of Proposition 4.4.1, the bound

$$V_{\text{DKW}} = \tilde{V}_{\mathfrak{R}} \text{ given by (4.2.6) with } \mathfrak{R} = (R_k, \zeta_k(X))_{k \in \mathcal{K}} \text{ and } \zeta_k(X) \text{ given by (4.4.1)}, \quad (4.4.2)$$

satisfies (4.1.1) and thus is a valid post hoc bound.

Proposition 4.4.1 is proved in Section 4.7.4. Note that  $\zeta_k(X) \geq \lfloor \log(K/\alpha)/2 \rfloor \geq 1$  as soon as  $\alpha \leq e^{-2}K$ . Hence, this contrasts with previous approaches ([Blanchard et al., 2018b](#); [Goeman and Solari, 2011](#)), for which  $\zeta_k = 0$  was included in the reference family. This means that using this reference family induces a minimum cost. In the next section, we will see that this cost is generally compensated by the accuracy of the joint estimation of  $|R_k \cap \mathcal{H}_0|$ ,  $k \in \mathcal{K}$ .

*Remark 4.4.1.* In practice,  $\zeta_k(X)$  in (4.4.1) can be computed as

$$\zeta_k(X) = s \wedge \min_{0 \leq \ell \leq s} \left( \left| \frac{C}{2(1-p_{(\ell)})} + \left( \frac{C^2}{4(1-p_{(\ell)})^2} + \frac{s-\ell}{1-p_{(\ell)}} \right)^{1/2} \right|^2 \right),$$

where  $s = |R_k|$  and  $0 = p_{(0)} \leq p_{(1)} \leq \dots \leq p_{(s)}$  are the ordered p-values of  $\{p_i(X), i \in R_k\}$ .

*Remark 4.4.2.* With our notation, the previous  $(1 - \alpha)$ -confidence bound of Genovese and Wasserman (2004) (Equation (16) therein) corresponds to take

$$\zeta_k^{GW}(X) = |R_k| \wedge \min_{t \in [0,1]} \left\lfloor \frac{\sum_{i \in R_k} \mathbf{1}\{p_i(X) > t\} + |R_k|^{1/2}C}{1-t} \right\rfloor.$$

By using (4.A.1) in Lemma 4.A.1 with  $a = 1 - t$ ,  $b = C$ ,  $c = \sum_{i \in R_k} \mathbf{1}\{p_i(X) > t\}$ , and  $d = |R_k|$ , we can see that the quantity  $\zeta_k^{GW}(X)$  is always larger than the  $\zeta_k(X)$  given by (4.4.1). Hence our result is a uniform improvement of Genovese and Wasserman (2004).

*Remark 4.4.3.* The local bounds  $\zeta_k$  in (4.4.1) depend on the target level  $\alpha$  only through  $C$ , where  $2C^2 = \log(K/\alpha)$ . Therefore, the post hoc bounds derived from Proposition 4.4.1 are expected to depend only weakly on  $\alpha$ . This important point is illustrated in our numerical experiments (Section 4.5), where this property is used to propose a hybrid post hoc bound taking the best of both the Simes and the DKW-based bounds.

#### 4.4.2 Comparison to existing post hoc bounds

To explore the benefit of the new reference family when the signal is localized, let us consider a stylized model where the signal is localized according to a regular partition

$$R_k = \{1 + (k-1)s, \dots, ks\}, \quad 1 \leq k \leq K, \tag{4.4.3}$$

composed of  $K$  regions of equal size  $s$ . In particular, this reference family satisfies (Disjoint). Among the regions  $R_k$ , only  $R_1$  contains false nulls, and  $r \in (0, 1)$  denotes the proportion of signal in  $R_1$ , that is

$$r = |R_1 \cap \mathcal{H}_1| / |R_1|. \tag{4.4.4}$$

The remaining regions contain no signal, that is  $|R_k \cap \mathcal{H}_1| = 0$ , for  $k \geq 2$ .

In addition, we consider an independent Gaussian one-sided setting where the false nulls have mean  $\mu > 0$ , that is, we assume that  $X_i \sim \mathcal{N}(0, 1)$  if  $i \in \mathcal{H}_0$  and  $X_i \sim \mathcal{N}(\mu, 1)$  if  $i \in \mathcal{H}_1$ , and the  $p$ -values are derived as  $p_i(X) = \bar{\Phi}(X_i)$ ,  $i \in \mathbb{N}_m$ , where  $\bar{\Phi}$  denotes the upper-tail of the standard normal distribution.

**Proposition 4.4.2.** *Let us consider the post hoc bounds  $V_{Bonf}$  (4.2.3);  $V_{Simes}$  (4.2.4) and the new post hoc bound  $V_{DKW}$  given by (4.4.2) and associated to the reference regions  $R_k$*

defined above. In the setting defined above, we have

$$\frac{\mathbb{E}(V_{DKW}(R_1))}{|R_1|} \leq 1 \wedge \left(1 - r + 2r \bar{\Phi}(\mu) + \frac{4C}{\sqrt{s}} \left(1 + \frac{C}{\sqrt{s}}\right)\right) \quad (4.4.5)$$

$$\frac{\mathbb{E}(V_{Simes}(R_1))}{|R_1|} \geq (1 - r)(1 - \alpha s/m) + r \bar{\Phi}(\mu - \bar{\Phi}^{-1}(\alpha s/m)); \quad (4.4.6)$$

$$\frac{\mathbb{E}(V_{Bonf}(R_1))}{|R_1|} = (1 - r)(1 - \alpha/m) + r \bar{\Phi}(\mu - \bar{\Phi}^{-1}(\alpha/m)). \quad (4.4.7)$$

This proposition is proved in Section 4.7.5. In particular, combining (4.4.5) and (4.4.6) yields

$$\frac{\mathbb{E}(V_{DKW}(R_1))}{\mathbb{E}(V_{Simes}(R_1))} \leq \frac{1 \wedge \left(1 - r + 2r \bar{\Phi}(\mu) + \frac{4C}{\sqrt{s}} \left(1 + \frac{C}{\sqrt{s}}\right)\right)}{(1 - r)(1 - \alpha s/m) + r \bar{\Phi}(\mu - \bar{\Phi}^{-1}(\alpha s/m))}. \quad (4.4.8)$$

This ratio is displayed in Figure 4.6 for a choice of model parameters. The new bound can substantially improve the Simes bound over a wide range of effect sizes.

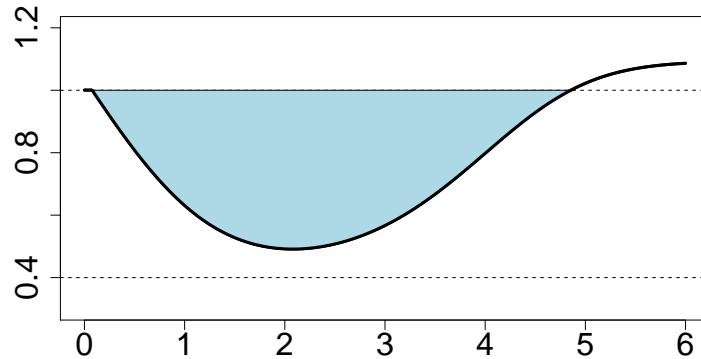


Fig. 4.6 Y-axis: upper bound of the ratio between the new bound and the Simes bound, see (4.4.8). X-axis: effect size  $\mu$ .  $m = 10^7$ ,  $s = m^{2/3}$ ,  $K = m/s$ ,  $r = 3/5$ ,  $\alpha = 0.1$ .

This improvement can also be put forward by an asymptotic approach.

**Corollary 4.4.1.** *Let us consider the framework of Proposition 4.4.2. In the asymptotic setting in  $m$  where  $s$  tends to infinity with  $s \gg \log K$  and  $\mu$  tends to infinity with  $\mu - \bar{\Phi}^{-1}(\alpha/m) \rightarrow -\infty$ , we have*

$$\limsup_m \left\{ \frac{\mathbb{E}(V_{DKW}(R_1))}{|R_1|} \right\} \leq 1 - r, \quad \text{and} \quad \limsup_m \left\{ \frac{\mathbb{E}(V_{Bonf}(R_1))}{|R_1|} \right\} = 1.$$

If moreover  $s \ll m$  (i.e.,  $K \rightarrow \infty$ ) and  $\mu - \bar{\Phi}^{-1}(\alpha s/m) \rightarrow -\infty$ , we have

$$\limsup_m \left\{ \frac{\mathbb{E}(V_{DKW}(R_1))}{|R_1|} \right\} \leq 1 - r, \quad \text{and} \quad \limsup_m \left\{ \frac{\mathbb{E}(V_{Simes}(R_1))}{|R_1|} \right\} = 1.$$

In particular, this corollary establishes that the order of the new bound can improve the Simes bound by a factor  $1 - r$ .

## 4.5 Numerical experiments

### 4.5.1 Setting

In this section we perform numerical experiments to compare our new post hoc bound  $V_{DKW}$  (4.4.2) with Simes post hoc bound (4.2.4). Let  $q$  be some fixed integer, say larger than 1. We consider two versions of our new bound:

- The first version of our post hoc bound, denoted  $V_{\text{part}}$ , is defined by (4.4.2) in which the reference family  $\mathfrak{R}^{\text{part}}$  is the regular partition of  $\mathbb{N}_m$  given by (4.4.3) for  $K^{\text{part}} = 2^q$  ( $s = m/2^q$  being assumed to be an integer).
- The second version of our post hoc bound, denoted  $V_{\text{tree}}$ , is defined similarly by (4.4.2), but the reference family  $\mathfrak{R}^{\text{tree}}$  is given this time by the perfect binary tree whose leaves are the elements of  $\mathfrak{R}^{\text{part}}$ . Hence, by using the notation of Lemma 4.3.1, this means  $P_k = \{1 + (k-1)s, \dots, ks\}$ ,  $1 \leq k \leq 2^q$ . The cardinal of the reference family is thus  $K^{\text{tree}} = 2^{q+1} - 1$ .

The true/false null hypothesis configuration is as follows: the false null hypotheses are contained in  $P_k$  for  $1 \leq k \leq K_1$ , for some fixed value of  $K_1$ . The quantity  $r$  is defined similarly as in (4.4.4), as the fraction of false null hypotheses in those  $P_k$ , and is set to  $r \in \{0.5, 0.75, 0.9, 1\}$ . All of the other partition pieces only contain true null hypotheses. Finally, the true null  $p$ -values are distributed as i.i.d.  $\mathcal{N}(0, 1)$ , and false null  $p$ -values are distributed as i.i.d.  $\mathcal{N}(\bar{\mu}, 1)$ , where  $\bar{\mu}$  is a fixed value in  $\{2, 3, 4\}$ . This construction is illustrated in Figure 4.7 for  $q = 3$  (leading to  $K^{\text{part}} = 8$  and  $K^{\text{tree}} = 15$ ) and  $K_1 = 2$ . In our experiments, we have chosen  $q = 7$  and  $s = 100$  (corresponding to  $K^{\text{part}} = 128$  and  $K^{\text{tree}} = 255$  and  $m = 12800$ ), and  $K_1 = 8$ .

We also performed numerical experiments with  $s \in \{10, 20, 50\}$  and  $K_1 \in \{1, 4, 16\}$ , and with Poisson- and Gaussian-distributed  $\bar{\mu}$ . Because the results are qualitatively similar, we only report the above-described setting.

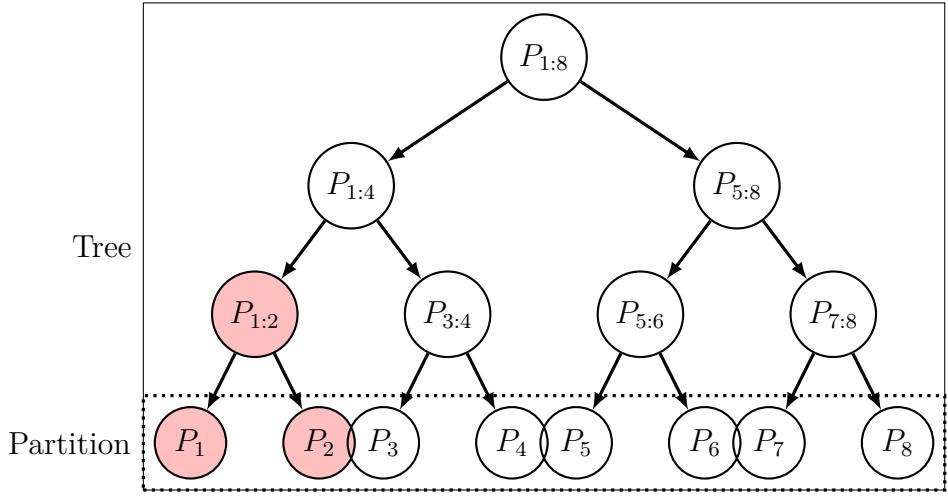


Fig. 4.7 Partition and perfect binary tree structures used in simulations, here with  $q = 3$  and  $K_1 = 2$  ( $K^{\text{part}} = 8$  and  $K^{\text{tree}} = 15$ ). The pink nodes are those containing some signal.

#### 4.5.2 Comparing confidence envelopes

One possible way to evaluate the performance of post hoc bounds is to consider the associated confidence envelopes on the number of true discoveries among the most significant hypotheses. Formally, for  $k = 1, \dots, m$ , we let  $S_k = \{i_1, \dots, i_k\}$ , where  $i_j$  is the index of the  $j^{\text{th}}$  smallest  $p$ -value. Note that focusing on such sets is *a priori* favorable to the Simes bound, for which the reference family are among the  $S_k$ . In Figure 4.8, each panel corresponds to a particular choice of the model parameters  $r$  (in rows) and  $\bar{\mu}$  (in columns). Each panel compares the actual number of true positives ( $k - |\mathcal{H}_0 \cap S_k|$ ),  $k = 1, \dots, m$  (labelled ‘‘Oracle’’) to post hoc bounds of the form  $(k - V(S_k))$ ,  $k = 1, \dots, m$ , where  $V$  is  $V_{\text{Simes}}$ ,  $V_{\text{part}}$ , or  $V_{\text{tree}}$ . In this figure, the confidence level is set to  $1 - \alpha = 95\%$ .

The chosen model parameters span a wide range of situations between very low and very high signal. For very low signal ( $\bar{\mu} = 2, r = 0.75$ , top-left panel), all the bounds are trivial, i.e. provide  $V(S_k)$  close to  $|S_k| (= k)$ . As expected, all the bounds get sharper as the signal to noise ratio increases, that is, as  $\bar{\mu}$  or  $r$  increase, and for very high signal ( $\bar{\mu} = 4, r = 1$ , bottom-right panel), all the bounds are very close to the actual number of true positives. The tree-based bound dominates the partition-based bound, which is expected because in this particular experiment, the regions  $P_k$  containing signal are adjacent (see Figure 4.7), and the multiscale nature of the tree-based bound allows it to take advantage of large-scale clusters. When the signal regions are not adjacent, these

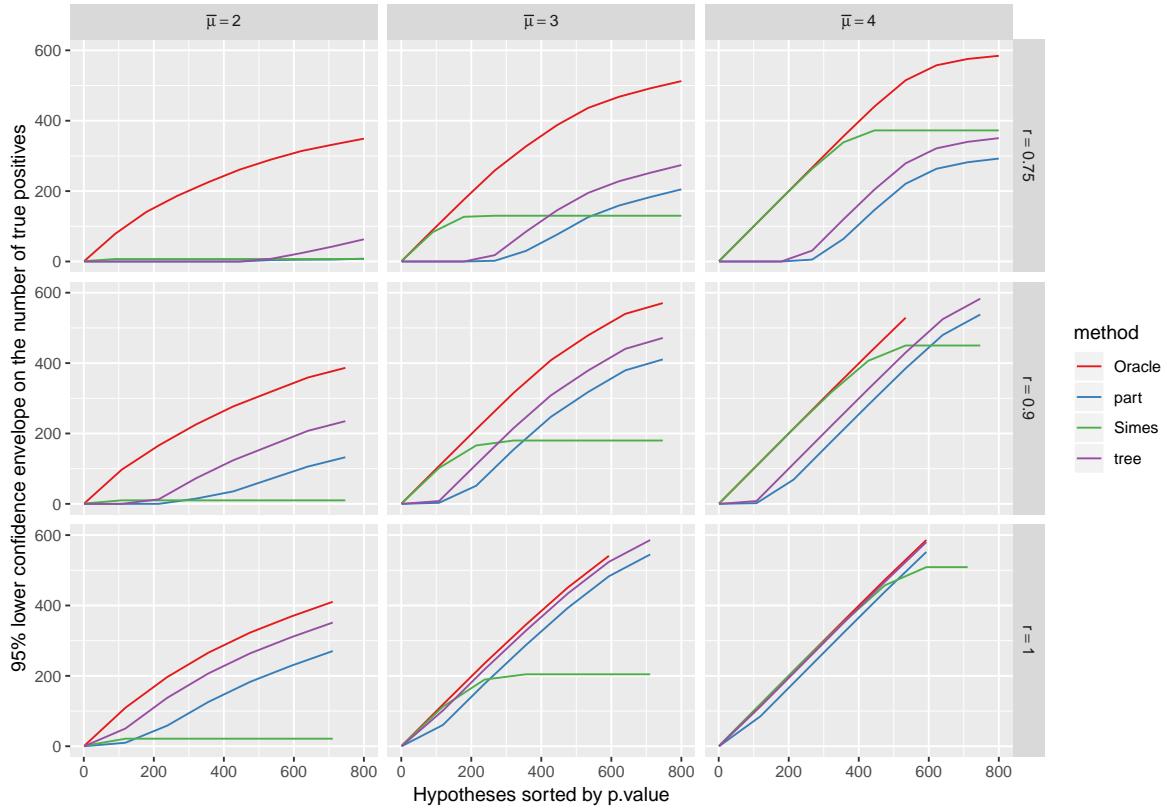


Fig. 4.8 95% lower confidence envelopes on the number of true positives obtained from Simes inequality and from the proposed methods are compared to the actual (Oracle) number of true positives.

two bounds are very close (additional numerical experiments not shown). Our proposed bounds are more sensitive to the proportion of signal in each active region, while the Simes bound is more sensitive to the strength of the signal in those regions. As a result, none of the Simes and the “tree” bound is uniformly better than the other one. The Simes bound is typically sharper than the “tree” bound for small values of  $k$ , but becomes more conservative for larger values of  $k$ . This is expected, because the “tree” bound is based on *estimating the proportion of non-null items*, while the Simes bound is based on *pinpointing non-null items*.

#### 4.5.3 Hybrid approach

An interesting question raised in Section 4.4.1 (Remark 4.4.3) is how these bounds are influenced by the target confidence level, which is fixed to  $1 - \alpha = 95\%$  in Figure 4.8. In Figure 4.9 we compare the bounds obtained across values of  $\alpha$  (corresponding to different line types) for  $\bar{\mu} \in \{3, 4\}$  and  $r \in \{0.75, 0.9\}$ . The influence of  $\alpha$  on the Simes bound is

quite substantial. This is consistent with the shape of the bound (4.2.4), the  $p$ -values are directly compared to  $\alpha$ . The influence of  $\alpha$  on the bounds derived from (4.4.1) is much weaker, as expected from Remark 4.4.3. In particular, the envelopes derived from the “tree” method are very close to each other when  $\alpha$  varies from 0.001 to 0.05. These

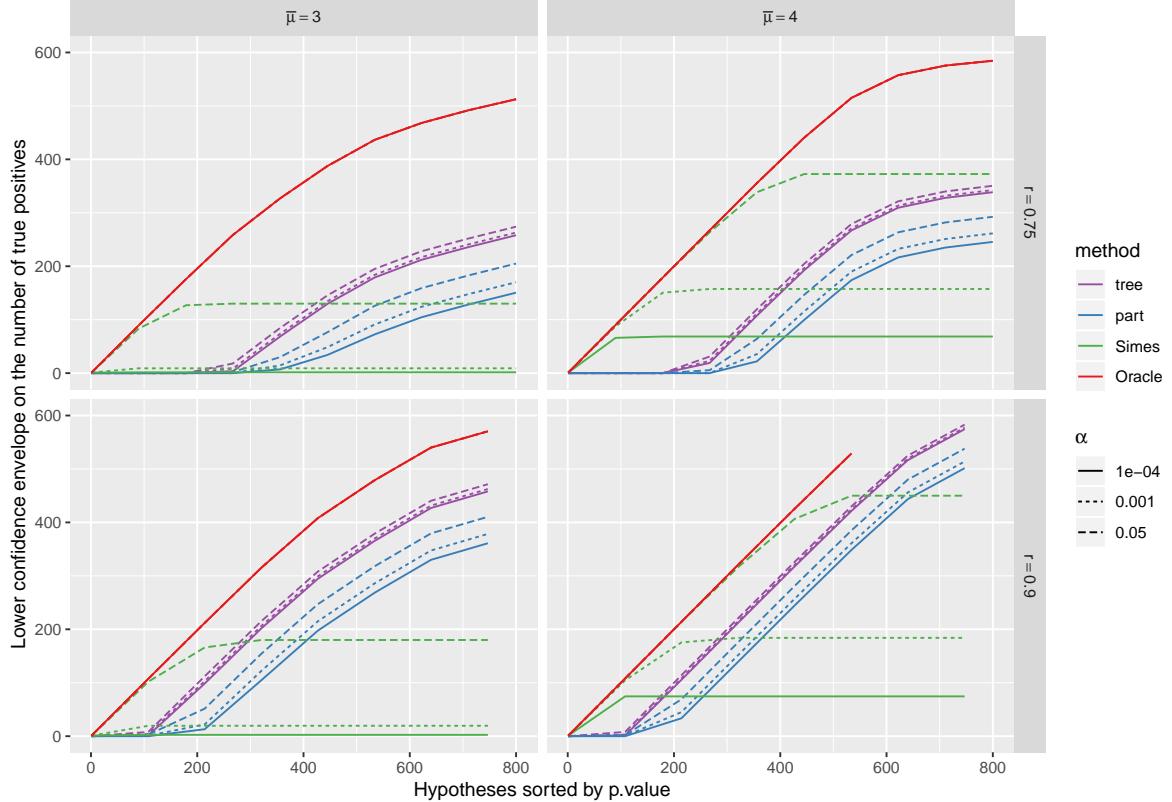


Fig. 4.9 Influence of the target level parameter  $\alpha$  on upper confidence envelopes on the number of true positives.

striking differences suggest to introduce hybrid confidence envelopes that could take advantage of the superiority of the Simes bound on sets  $S_k$  for small  $k$  with that of the DKW-tree-based bound on sets  $S_k$  for larger  $k$ . For a fixed  $\gamma \in [0, 1]$ , let us define the bound  $V_{\text{hybrid}}^\gamma$  as follows. For  $S \subset \mathbb{N}_m$ ,

$$V_{\text{hybrid}}^\gamma(\alpha, S) = \min(V_{\text{Simes}}((1 - \gamma)\alpha, S), V_{\text{tree}}(\gamma\alpha, S)), \quad (4.5.1)$$

where the notation in the bounds explicitly acknowledges the dependence of the bounds in the target level  $\alpha$ . By an union bound,  $V_{\text{hybrid}}^\gamma(\alpha, \cdot)$  is a  $(1 - \alpha)$ -level post hoc bound. Figure 4.10 gives an illustration with  $\alpha = 0.05$  and  $\gamma = 0.02$ . In this case, the hybrid envelope is the minimum of the Simes envelope at level  $(1 - \gamma)\alpha = 0.049$  and the DKW-

tree-based envelope at level 0.001. Because  $(1 - \gamma)\alpha$  is very close to  $\alpha$ , the confidence envelope  $V_{\text{hybrid}}^{0.02}$  is essentially equivalent to the Simes-based confidence envelope for small  $k$ ; for larger values of  $k$ ,  $V_{\text{hybrid}}^{0.02}$  is only slightly worse than the DKW-tree-based confidence envelope at level  $\gamma\alpha = 0.001$ .

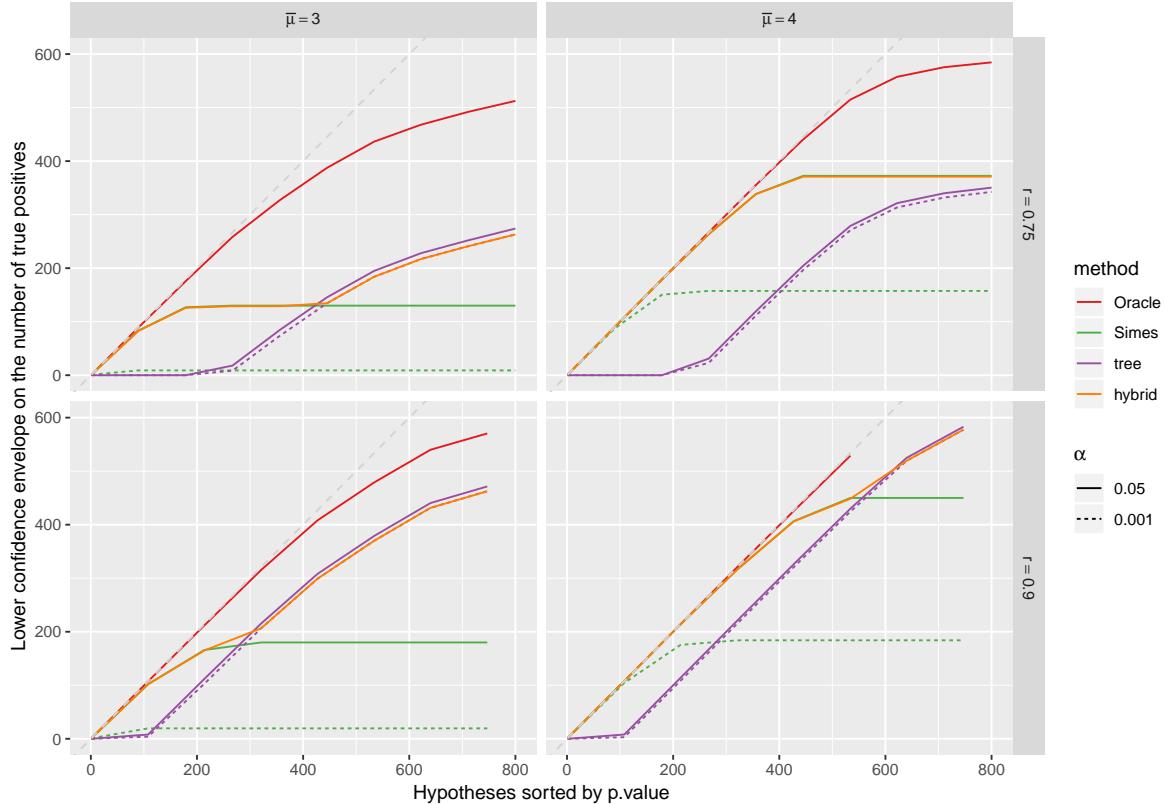


Fig. 4.10 Combining Simes and tree-based confidence envelopes on the number of true positives into a hybrid confidence envelope.

## 4.6 Discussion

### 4.6.1 Comparison to Meijer et al. (2015)

Since our aim is similar to the one of [Meijer et al. \(2015\)](#) (denoted MKG below for short), let us make a short qualitative comparison between MKG and our study. First, while both approaches are based on graph-structured subsets  $\{R_k, k \in \mathcal{K}\}$ , the geometrical shapes of the nodes  $R_k$  are different: the nodes in MKG correspond to all possible consecutive intervals, possibly overlapping, while our regions are based on partitioned regions at different resolutions. Our approach avoids redundancies of the tests but is suitable when

the signal is structured according to the pre-specified partition structure, and may lead to a less accurate bound otherwise. This in turn impacts the way the local pieces of information are combined. The MKG approach uses a sequential, top-down algorithm, with an  $\alpha$ -recycling method (that allows, for instance, to spend the same nominal level  $\alpha$  both for a parent and its child). By contrast, our approach uses a bottom-up algorithm, with an overall nominal level adjusted by a simple overall union bound, which is generally conservative but seems fair here as the nodes are disjoint (at each resolution).

Second, the criteria used are different: MKG focus on simultaneous FWER control of local tests of intersections of null hypotheses  $\cap_{i \in R_k} H_{0,i}$ ,  $k \in \mathcal{K}$ , while our statistical criterion ensures with high probability  $|\mathcal{H}_0 \cap R_k| \leq \zeta_k$ , for all  $k \in \mathcal{K}$ , for some bounds  $\zeta_k$ . As already noted in BNR (see the supplementary file therein), the two approaches coincide when  $\zeta_k = |R_k| - 1$ , because  $|\mathcal{H}_0 \cap R_k| > |R_k| - 1$  is equivalent to the fact that  $\cap_{i \in R_k} H_{0,i}$  is true. Hence, a family  $\{R_k, k \in \mathcal{K}\}$  violating  $|\mathcal{H}_0 \cap R_k| > |R_k| - 1$  for some  $k$  will also wrongly reject  $\cap_{i \in R_k} H_{0,i}$  for some  $k$ . However, when using another type of  $\zeta_k$ , such as the DKWM device used here, such a connection is not valid anymore and the two criteria does not incorporate the local structure of the nodes in the same way. Here, using  $\zeta_k$ 's based on classical estimators will in principle lead to better post hoc bounds.

Third, within each node, the local statistics used are not of the same nature: in MKG, the local tests are based on a multivariate  $\chi^2$ -type test, see [Goeman et al. \(2004\)](#). Here, we use an estimator relying on individual  $p$ -values that exploits the independence structure. This means that the assumptions made in MKG are much weaker, since it is valid under arbitrary dependence. Our approach can in principle also accommodate such a distributional setting, but this needs additional investigations, see the discussion in Section 4.6.2.

Finally, let us mention a setting for which the two methods can be fairly compared. First take the MKG method with Bonferroni local tests. As proved in MKG, the resulting FWER controlling procedure (reject the  $H_{0,i}$  for which  $V(\{i\}) = 0$ ) then reduces to the Holm procedure [Holm \(1979\)](#). By contrast, if we consider  $\zeta_k$  equals to the number of accepted null hypotheses by the Holm procedure restricted to  $R_k$  (satisfying ([Disjoint](#))), our methodology induces another overall FWER controlling procedure: simply the one rejecting all the null hypotheses rejected by the local Holm procedures. Both FWER controlling procedures are valid under arbitrary dependence. Interestingly, if the signal is sparse but localized in one of the pre-specified  $R_k$ , the new procedure will dominate the Holm procedure (this is supported by a numerical experiment and a theoretical study, not reported here for short). This illustrates, once again, that our methodology can improve the state of the art, even in a very elementary framework.

### 4.6.2 Extension to general local confidence bounds

In this work, the local bounds  $\zeta_k$  have been designed by using the DKW inequality. This can be straightforwardly extended to the case where the bound (4.4.1) is replaced by  $\zeta_k(X) = L_k(\alpha/K)$ , for which the function  $L_k(\cdot)$  is a local bound satisfying the condition

$$\forall \lambda \in (0, 1), \quad \forall k \in \mathcal{K}, \quad \forall P \in \mathcal{P}, \quad \mathbb{P}_{X \sim P}(|R_k \cap \mathcal{H}_0(P)| \leq L_k(\lambda)) \leq \lambda. \quad (4.6.1)$$

The properties of the final post hoc bound will obviously depend on the choice of  $L_k$ . For instance, the validity of our post hoc bounds relies on (Indep), which is a strong assumption. The latter is only used to make the DKW inequality valid. If this assumption is violated, we should use another local bound  $L_k$ , that satisfies condition (4.6.1) under the specific dependence setting of the data. For instance, when the dependence is known or satisfies a randomization hypothesis (see Hemerik and Goeman, 2018), such a local bound can be easily constructed by applying the  $\lambda$ -calibration methodology of BNR (e.g., the one corresponding to the balanced template therein). However, the computational complexity of the final post hoc bound will substantially increase, which will make such an approach difficult to use in practice. Solving this problem seems challenging and is left for future work.

## 4.7 Proofs

### 4.7.1 Proof of Lemma 4.2.1

The second and third inequalities in (4.2.7) are straightforward from the fact that  $\tilde{V}_{\mathfrak{R}}^q$  is non-increasing in  $q$  and  $\tilde{V}_{\mathfrak{R}}^1 = \bar{V}_{\mathfrak{R}}$ . For the first inequality, let  $S \subset \mathbb{N}_m$  and consider  $A \subset \mathbb{N}_m$  such that  $\forall k \in \mathcal{K}, |R_k \cap A| \leq \zeta_k$ . For any  $Q \subset \mathcal{K}$ , we get

$$\begin{aligned} |S \cap A| &\leq \sum_{k \in Q} |S \cap A \cap R_k| + \left| S \cap A \cap \left( \bigcup_{k \in Q} R_k \right)^c \right| \\ &\leq \sum_{k \in Q} \zeta_k \wedge |S \cap R_k| + \left| S \setminus \bigcup_{k \in Q} R_k \right|, \end{aligned}$$

which implies the result.

### 4.7.2 Proof of Theorem 4.3.1

In this proof, we fix  $S \subset \mathbb{N}_m$ . Also, we let

$$\mathcal{A}(\mathfrak{R}) = \{A \subset \mathbb{N}_m : \forall k \in \mathcal{K}, |R_k \cap A| \leq \zeta_k\}, \quad (4.7.1)$$

so that  $V_{\mathfrak{R}}^*(S) = \max_{A \in \mathcal{A}(\mathfrak{R})} |S \cap A|$ . Also note that (4.2.5)–(4.2.6) can be rewritten as

$$\tilde{V}_{\mathfrak{R}}(S) = \min_{\mathcal{K}' \subset \mathcal{K}} \left( \sum_{k \in \mathcal{K}'} \zeta_k \wedge |S \cap R_k| + \left| S \setminus \bigcup_{k \in \mathcal{K}'} R_k \right| \right). \quad (4.7.2)$$

#### 4.7.2.1 Proof of (4.3.4)

First, by Lemma 4.A.4, it is sufficient to prove (4.3.4) for  $\mathfrak{R}^\oplus$ . Hence, we can focus without loss of generality on the case where (All-atoms) holds. Recall that this means that  $(i, i) \in \mathcal{K}$  for all  $1 \leq i \leq N$ . Now, to prove that  $\tilde{V}_{\mathfrak{R}}(S) = V_{\mathfrak{R}}^*(S)$ , it suffices to build  $A \subset S$  such that  $A \in \mathcal{A}(\mathfrak{R})$  and  $|A| = \tilde{V}_{\mathfrak{R}}(S)$ . The key point is that for any  $h$ ,  $A$  is the disjoint union of the  $A \cap R_k$ ,  $k \in \mathcal{K}^h$ , because the  $R_k$ ,  $k \in \mathcal{K}^h$ , form a partition of  $\mathbb{N}_m$  (by Lemma 4.A.2). Let  $H = \max_{k \in \mathcal{K}} \phi(k)$  be the greater depth of the Forest structure, we will construct  $A$  with a decreasing recursion over  $h \in \{1, \dots, H\}$ . To this end, we need some additional notation: first, for any  $k \in \mathcal{K}$ , let  $\mathcal{K}_k = \{k' \in \mathcal{K} : R_{k'} \subset R_k\}$  be the set of indexes of elements that are subsets of  $R_k$ . Then, for any  $h$ , let  $\mathcal{K}^{\geq h} = \bigcup_{h' \leq h' \leq H} \mathcal{K}^{h'}$ . Note that  $\mathcal{K}^{\geq 1} = \mathcal{K}$ . Finally let

$$\mathfrak{P}^h = \{\mathcal{P} \subset \mathcal{K}^{\geq h} : \text{the } R_k, k \in \mathcal{P}, \text{ form a partition of } \mathbb{N}_m\},$$

and note that the result of Lemma 4.A.3 (that is, equation (4.A.2)) can be rewritten in

$$\tilde{V}_{\mathfrak{R}}(S) = \min_{\mathcal{P} \in \mathfrak{P}^1} \sum_{k \in \mathcal{P}} \zeta_k \wedge |S \cap R_k|. \quad (4.7.3)$$

The decreasing recursion starts like this: noting that  $\mathcal{K}^H$  is the set of all the  $(i, i)$ 's,  $1 \leq i \leq N$ , we define  $A^H$  by choosing (arbitrarily)  $\zeta_{i,i} \wedge |S \cap P_{i:i}|$  distinct elements of  $S \cap P_{i:i}$  for each  $1 \leq i \leq N$ . Note that we have both

$$\forall k \in \mathcal{K}^{\geq H}, \quad |A^H \cap R_k| \leq \zeta_k,$$

and

$$|A^H| = \sum_{k \in \mathcal{K}^H} \zeta_k \wedge |S \cap R_k| = \min_{\mathcal{P} \in \mathfrak{P}^H} \sum_{k \in \mathcal{P}} \zeta_k \wedge |S \cap R_k|,$$

since  $\mathfrak{P}^H = \{\mathcal{K}^H\}$ .

Now let  $h$  be given and assume we have constructed an  $A^{h+1} \subset S$  such that both

$$\forall k \in \mathcal{K}^{\geq h+1}, \quad |A^{h+1} \cap R_k| \leq \zeta_k,$$

and

$$\begin{aligned} |A^{h+1}| &= \min_{\mathcal{P} \in \mathfrak{P}^{h+1}} \sum_{k \in \mathcal{P}} \zeta_k \wedge |S \cap R_k| \\ &= \sum_{k \in \mathcal{P}^{h+1}} \zeta_k \wedge |S \cap R_k|, \end{aligned} \quad (4.7.4)$$

for a given  $\mathcal{P}^{h+1} \in \mathfrak{P}^{h+1}$ . Using that  $|A^{h+1}| = \sum_{k \in \mathcal{P}^{h+1}} |A^{h+1} \cap R_k|$  and that  $|A^{h+1} \cap R_k| \leq \zeta_k \wedge |S \cap R_k|$  for all  $k \in \mathcal{P}^{h+1}$ , we deduce that  $|A^{h+1} \cap R_k| = \zeta_k \wedge |S \cap R_k|$  for all  $k \in \mathcal{P}^{h+1}$ .

Now we want to construct  $A^h$  by defining all the  $A^h \cap R_k$ ,  $k \in \mathcal{K}^h$ . By writing that  $R_k = \bigcup_{k' \in \mathcal{P}^{h+1} \cap \mathcal{K}_k} R_{k'}$ , the union being disjoint, we have first that, for all  $k \in \mathcal{K}^h$ ,

$$\begin{aligned} |A^{h+1} \cap R_k| &= \sum_{k' \in \mathcal{P}^{h+1} \cap \mathcal{K}_k} |A^{h+1} \cap R_{k'}| \\ &= \sum_{k' \in \mathcal{P}^{h+1} \cap \mathcal{K}_k} \zeta_{k'} \wedge |S \cap R_{k'}|. \end{aligned}$$

Second, we have that:

$$\min_{\mathcal{P} \in \mathfrak{P}^h} \sum_{k \in \mathcal{P}} \zeta_k \wedge |S \cap R_k| = \sum_{k \in \mathcal{K}^h} \min_{\mathcal{P} \in \mathfrak{P}^h} \left( \sum_{k' \in \mathcal{P} \cap \mathcal{K}_k} \zeta_{k'} \wedge |S \cap R_{k'}| \right) \quad (4.7.5)$$

$$= \sum_{k \in \mathcal{K}^h} \min \left( \zeta_k \wedge |S \cap R_k|, \min_{\mathcal{P} \in \mathfrak{P}^{h+1}} \left( \sum_{k' \in \mathcal{P} \cap \mathcal{K}_k} \zeta_{k'} \wedge |S \cap R_{k'}| \right) \right) \quad (4.7.6)$$

$$\begin{aligned} &= \sum_{k \in \mathcal{K}^h} \min \left( \zeta_k \wedge |S \cap R_k|, \sum_{k' \in \mathcal{P}^{h+1} \cap \mathcal{K}_k} \zeta_{k'} \wedge |S \cap R_{k'}| \right) \quad (4.7.7) \\ &= \sum_{k \in \mathcal{K}^h} \min \left( \zeta_k \wedge |S \cap R_k|, |A^{h+1} \cap R_k| \right). \end{aligned}$$

In the above, (4.7.5) holds by additivity and because for every  $\mathcal{P} \in \mathfrak{P}^h$ , any element of  $\mathcal{P}$  is also an element of one of the  $\mathcal{P} \cap \mathcal{K}_k$ ,  $k \in \mathcal{K}^h$ . Moreover, for every  $\mathcal{P} \in \mathfrak{P}^h$  and  $k \in \mathcal{K}^h$ ,  $\mathcal{P} \cap \mathcal{K}_k$  is either  $\{k\}$ , either a set of elements of depth  $\geq h + 1$ , hence (4.7.6). Finally, (4.7.7) holds because all the minima in (4.7.6) are realized in  $\mathcal{P}^{h+1}$ , otherwise the minimality of  $\mathcal{P}^{h+1}$  in (4.7.4) would be contradicted.

We finally construct all the  $A^h \cap R_k$ ,  $k \in \mathcal{K}^h$ , in the following way: if  $|A^{h+1} \cap R_k| \leq \zeta_k \wedge |S \cap R_k|$ , we let  $A^h \cap R_k = A^{h+1} \cap R_k$ , else we let  $A^h \cap R_k$  be a subset of  $\zeta_k \wedge |S \cap R_k|$  distinct elements of  $A^{h+1} \cap R_k$ . This both ensures that

$$|A^h| = \min_{\mathcal{P} \in \mathfrak{P}^h} \sum_{k \in \mathcal{P}} \zeta_k \wedge |S \cap R_k|,$$

and that

$$\forall k \in \mathcal{K}^{\geq h}, \quad |A^h \cap R_k| \leq \zeta_k,$$

because  $\mathcal{K}^{\geq h} = \mathcal{K}^h \cup \mathcal{K}^{\geq h+1}$  and  $A^h \subset A^{h+1}$ , which ends the recursion.

Now letting  $A = A^1$ , we have found an  $A \subset S$  such that  $A \in \mathcal{A}(\mathfrak{R})$  and  $|A| = \tilde{V}_{\mathfrak{R}}(S)$  (by (4.7.3)).

#### 4.7.2.2 Proof of (4.3.5)

By (4.3.4) and Lemmas 4.A.3 and 4.A.4, we have

$$V_{\mathfrak{R}}^*(S) = V_{\mathfrak{R}^\oplus}^*(S) = \tilde{V}_{\mathfrak{R}^\oplus}(S) = \sum_{k \in \bar{\mathcal{K}}} \zeta_k \wedge |S \cap R_k|,$$

for some  $\bar{\mathcal{K}} \subset \mathcal{K}^\oplus$  such that the  $R_k$ ,  $k \in \bar{\mathcal{K}}$ , form a partition of  $\mathbb{N}_m$ . Hence,

$$\begin{aligned} V_{\mathfrak{R}}^*(S) &= \sum_{k \in \mathcal{K} \cap \bar{\mathcal{K}}} \zeta_k \wedge |S \cap R_k| + \sum_{k \in \bar{\mathcal{K}} \setminus \mathcal{K}} \zeta_k \wedge |S \cap R_k| \\ &= \sum_{k \in \mathcal{K} \cap \bar{\mathcal{K}}} \zeta_k \wedge |S \cap R_k| + \sum_{k \in \bar{\mathcal{K}} \setminus \mathcal{K}} |S \cap R_k| \\ &= \sum_{k \in \mathcal{K} \cap \bar{\mathcal{K}}} \zeta_k \wedge |S \cap R_k| + \left| S \setminus \bigcup_{k \in \mathcal{K} \cap \bar{\mathcal{K}}} R_k \right|, \end{aligned}$$

because the  $R_k$ ,  $k \in \bar{\mathcal{K}} \setminus \mathcal{K}$  are all disjoint. Now,  $|\mathcal{K} \cap \bar{\mathcal{K}}| \leq d$  by definition of  $d$ , which means that the latter display is larger than or equal to  $\tilde{V}_{\mathfrak{R}}^d(S)$ , which proves the result.

#### 4.7.3 Proof of Corollary 4.3.1

**Proof of (i)** This is a direct byproduct of Theorem 4.3.1, because if (Nested) holds, then  $d = 1$  and thus  $V_{\mathfrak{R}}^* = \tilde{V}_{\mathfrak{R}}^d = \tilde{V}_{\mathfrak{R}}^1 = \bar{V}_{\mathfrak{R}}$ .

**Proof of (ii)** By Theorem 4.3.1,  $V_{\mathfrak{R}}^* = \tilde{V}_{\mathfrak{R}} = \tilde{V}_{\mathfrak{R}}^K$  defined by (4.2.5)–(4.2.6). Now, for any  $S \subset \mathbb{N}_m$ , for any  $Q \subset \mathcal{K}$  with  $|Q| \leq K - 1$ , by denoting  $k_0$  any element not in  $Q$ , we

have

$$R_{k_0} \cap \left( \bigcup_{k \in Q} R_k \right) = \emptyset,$$

by (Disjoint), and

$$\begin{aligned} \sum_{k \in Q} \zeta_k \wedge |S \cap R_k| + \left| S \setminus \bigcup_{k \in Q} R_k \right| &= |S \cap R_{k_0}| + \sum_{k \in Q} \zeta_k \wedge |S \cap R_k| + \left| S \setminus \left( \bigcup_{k \in Q} R_k \cup R_{k_0} \right) \right| \\ &\geq \zeta_{k_0} \wedge |S \cap R_{k_0}| + \sum_{k \in Q} \zeta_k \wedge |S \cap R_k| + \left| S \setminus \left( \bigcup_{k \in Q} R_k \cup R_{k_0} \right) \right| \\ &= \sum_{k \in Q \cup \{k_0\}} \zeta_k \wedge |S \cap R_k| + \left| S \setminus \bigcup_{k \in Q \cup \{k_0\}} R_k \right|. \end{aligned}$$

Hence, the minimum in (4.2.5) within the  $\tilde{V}_{\mathfrak{R}}^K$  expression is attained for  $Q = \mathcal{K}$  and the result is proved.

#### 4.7.4 Proof of Proposition 4.4.1

Let us show that for all  $\lambda \in (0, 1/2)$ , for any  $S \subset \mathbb{N}_m$  with cardinal  $s = |S|$ , we have with probability at least  $1 - \lambda$  that

$$|S \cap \mathcal{H}_0| \leq \min_{t \in [0, 1)} \left( \frac{\sqrt{\log(1/\lambda)/2}}{2(1-t)} + \left\{ \frac{\log(1/\lambda)/2}{4(1-t)^2} + \frac{N_t(S)}{1-t} \right\}^{1/2} \right)^2, \quad (4.7.8)$$

for  $N_t(S) = \sum_{i \in S} \mathbf{1}\{p_i(X) > t\}$ . Let  $v = |S \cap \mathcal{H}_0|$  (assumed to be positive without loss of generality) and  $U_1, \dots, U_v$  being  $v$  i.i.d. uniform random variables. The DKW inequality (with the optimal constant of Massart, 1990) ensures that, with probability at least  $1 - \lambda$ , for all  $t \in [0, 1]$ , we have

$$v^{-1} \sum_{i=1}^v \mathbf{1}\{U_i > t\} - (1-t) \geq -\sqrt{\log(1/\lambda)/(2v)}.$$

Now using Lemma 4.A.1 with  $x = v^{1/2}$ ,  $a = 1-t$ ,  $b = \sqrt{\log(1/\lambda)/2}$  and  $c = \sum_{i=1}^v \mathbf{1}\{U_i > t\}$  provides (4.7.8) but with  $N_t(S)$  replaced by  $c$ . Since  $p_i(X)$  stochastically dominates  $U_i$ , by independence  $N_t(S)$  also dominates  $c$ , which yields

$$\forall k \in \mathcal{K}, \mathbb{P}(|R_k \cap \mathcal{H}_0| > \zeta_k(X)) \leq \frac{\alpha}{K},$$

by choosing  $\lambda = \frac{\alpha}{K}$ . Then (4.1.2) follows by a classical union bound argument.

#### 4.7.5 Proof of Proposition 4.4.2

We have for any  $t \in [0, 1)$ ,

$$\begin{aligned} \frac{\mathbb{E}(V_{\text{Bonf}}(R_1))}{|R_1|} &= s^{-1} \sum_{i \in R_1 \cap \mathcal{H}_0} \mathbb{P}(p_i(X) > \alpha/m) + s^{-1} \sum_{i \in R_1 \cap \mathcal{H}_1} \mathbb{P}(p_i(X) > \alpha/m) \\ &= (1 - r)(1 - \alpha/m) + r \left(1 - \bar{\Phi}(\bar{\Phi}^{-1}(\alpha/m) - \mu)\right), \end{aligned}$$

which gives (4.4.7). Next,

$$\begin{aligned} V_{\text{Simes}}(R_1) &= \min_{1 \leq k \leq s} \left\{ \sum_{i \in R_1} \mathbb{1}_{\{p_i(X) > \alpha k/m\}} + k - 1 \right\} \\ &\geq \sum_{i \in R_1} \mathbb{1}_{\{p_i(X) > \alpha s/m\}}, \end{aligned}$$

which gives (4.4.6). Finally, for all  $t \in [0, 1)$ , by denoting  $N = \sum_{i \in R_1} \mathbb{1}\{p_i(X) > t\}$ , we have

$$\begin{aligned} \mathbb{E}(V_{\text{DKW}}(R_1)) &\leq \mathbb{E} \left[ \left( \frac{C}{2(1-t)} + \left\{ \frac{C^2}{4(1-t)^2} + \frac{N}{1-t} \right\}^{1/2} \right)^2 \right] \\ &\leq \mathbb{E} \left[ \left( \frac{C}{1-t} + \left\{ \frac{N}{1-t} \right\}^{1/2} \right)^2 \right] \\ &\leq \frac{C^2}{(1-t)^2} + \frac{\mathbb{E}N}{1-t} + \frac{2C}{(1-t)^{3/2}} \mathbb{E}[N^{1/2}] \\ &\leq \frac{C^2}{(1-t)^2} + \frac{\mathbb{E}N}{1-t} + \frac{2C}{1-t} \left( \frac{\mathbb{E}N}{1-t} \right)^{1/2}, \end{aligned}$$

where we used  $\sqrt{x+y} \leq \sqrt{x} + \sqrt{y}$  for all  $x, y \geq 0$  and that  $x \mapsto x^{1/2}$  is concave. Since

$$\mathbb{E}[N/|R_1|] = (1 - r)(1 - t) + r \left(1 - \bar{\Phi}(\bar{\Phi}^{-1}(t) - \mu)\right),$$

and  $\mathbb{E}[N] \leq s(1 - t)$ , this provides

$$\frac{\mathbb{E}(V_{\text{DKW}}(R_1))}{|R_1|} \leq \min_t \left\{ s^{-1} \frac{C^2}{(1-t)^2} + 1 - r + r \frac{\bar{\Phi}(\mu - \bar{\Phi}^{-1}(t))}{1-t} + s^{-1/2} \frac{2C}{1-t} \right\}.$$

Taking  $t = 1/2$  gives (4.4.5).

## Appendix 4.A Auxiliary lemmas

The following lemma holds.

**Lemma 4.A.1.** *For all  $a > 0$  and  $b, c, x \geq 0$ , the two following assertions are equivalent*

- (i)  $c - ax^2 \geq -bx$ ;
- (ii)  $x \leq \frac{b}{2a} + \sqrt{\frac{b^2}{4a^2} + \frac{c}{a}}$ .

In particular, we have for all  $d \geq 0$ ,

$$d \wedge \left( \frac{b}{2a} + \sqrt{\frac{b^2}{4a^2} + \frac{c}{a}} \right)^2 \leq d \wedge \left( \frac{c + d^{1/2}b}{a} \right). \quad (4.A.1)$$

*Proof.* The equivalence between (i) and (ii) is obvious. For  $d \geq 0$ , if we have the inequality  $\left( b/(2a) + \sqrt{b^2/(4a^2) + c/a} \right)^2 \geq d$ , then (ii) is satisfied with  $x = d^{1/2}$ , which entails  $c - ad \geq -bd^{1/2}$  and gives  $d \leq (c + d^{1/2}b)/a$ . If, on the contrary,  $\left( b/(2a) + \sqrt{b^2/(4a^2) + c/a} \right)^2 \leq d$ , then

$$\begin{aligned} \left( \frac{b}{2a} + \sqrt{\frac{b^2}{4a^2} + \frac{c}{a}} \right)^2 &= \frac{b^2}{2a^2} + \frac{c}{a} + \frac{b}{a} \sqrt{b^2/(4a^2) + c/a} \\ &= \frac{c}{a} + \frac{b}{a} \left( b/(2a) + \sqrt{b^2/(4a^2) + c/a} \right) \leq \frac{c}{a} + \frac{b}{a} d^{1/2}. \end{aligned}$$

This entails the result.  $\square$

The two following lemmas are used in the proof of Theorem 4.3.1, in the case where condition (All-atoms) holds.

**Lemma 4.A.2.** *For a reference family that has a Forest structure, if (All-atoms) holds, then for any  $h \geq 1$ , the  $P_{i:j}$ ,  $(i, j) \in \mathcal{K}^h$ , form a partition of  $\mathbb{N}_m$ .*

*Proof.* Let  $h \geq 1$ . Let  $(i, j), (i', j') \in \mathcal{K}^h$  such that  $(i, j) \neq (i', j')$ . By (Forest), either  $P_{i:j}$  and  $P_{i':j'}$  are disjoint, or, without loss of generality,  $P_{i:j} \subset P_{i':j'}$ . If  $\phi(i', j') = h$  then the latter is not possible because that would mean that  $\phi(i, j) \geq h + 1$ . If  $i' = j'$ , then  $P_{i:j} \subset P_{i':j'}$  would imply that  $P_i \cup \dots \cup P_j \subset P_{i'}$  which in turn implies  $i = j = i' = j'$  which is also impossible. So  $P_{i:j}$  and  $P_{i':j'}$  are disjoint.

Now take any  $e \in \mathbb{N}_m$ .  $(P_n)_{1 \leq n \leq N}$  is a partition so there exists some  $n \leq N$  such that  $e \in P_n$ . If  $\phi(n, n) \leq h$  then  $(n, n) \in \mathcal{K}^h$ . If  $\phi(n, n) > h$ , then  $\{k \in \mathcal{K} : P_n \subsetneq R_k\}$  has at least  $h$  elements. Furthermore those elements are nested by (Forest), so there exists  $k \in \mathcal{K}$  such that  $P_n \subsetneq R_k$  and  $\phi(k) = h$ , hence  $e \in R_k$  with  $k \in \mathcal{K}^h$ . Finally in both cases  $e \in \bigcup_{k \in \mathcal{K}^h} R_k$  so  $\mathbb{N}_m = \bigcup_{k \in \mathcal{K}^h} R_k$ , which concludes the proof.  $\square$

**Lemma 4.A.3.** *For a reference family that satisfies (Forest) and (All-atoms), we have*

$$\tilde{V}_{\mathfrak{R}}(S) = \min_{\substack{\bar{\mathcal{K}} \subset \mathcal{K} \\ \text{the } R_k, k \in \bar{\mathcal{K}}, \\ \text{form a partition of } \mathbb{N}_m}} \sum_{k \in \bar{\mathcal{K}}} \zeta_k \wedge |S \cap R_k|. \quad (4.A.2)$$

that is, the minimum in (4.7.2) is always achieved on a partition of  $\mathbb{N}_m$ .

*Proof.* Let any  $\mathcal{K}' \subset \mathcal{K}$ . Because property (Forest) is true, there exists  $\mathcal{K}'_1 \subset \mathcal{K}'$  such that the  $R_k$ ,  $k \in \mathcal{K}'_1$ , are pairwise disjoint, and

$$\forall k \in \mathcal{K}', \exists k' \in \mathcal{K}'_1, R_k \subset R_{k'}.$$

Note that this implies that  $\bigcup_{k \in \mathcal{K}'_1} R_k = \bigcup_{k \in \mathcal{K}'} R_k$ . Likewise, because  $\mathcal{K}$  includes all the  $(i, i)$ ,  $1 \leq i \leq N$ , there exists  $\mathcal{K}'_2 \subset \mathcal{K}$  such that the  $R_k$ ,  $k \in \mathcal{K}'_2$ , are pairwise disjoint, and

$$\mathbb{N}_m \setminus \bigcup_{k \in \mathcal{K}'_1} R_k = \bigcup_{k \in \mathcal{K}'_2} R_k.$$

Let  $\bar{\mathcal{K}} = \mathcal{K}'_1 \cup \mathcal{K}'_2$  and note that the  $R_k$ ,  $k \in \bar{\mathcal{K}}$ , form a partition of  $\mathbb{N}_m$ . To conclude the proof of (4.A.2), we write that

$$\begin{aligned} & \sum_{k \in \mathcal{K}'} \zeta_k \wedge |S \cap R_k| + \left| S \setminus \bigcup_{k \in \mathcal{K}'} R_k \right| = \\ & \sum_{k \in \mathcal{K}'} \zeta_k \wedge |S \cap R_k| + \left| S \cap \left( \mathbb{N}_m \setminus \bigcup_{k \in \mathcal{K}'_1} R_k \right) \right| \geq \\ & \sum_{k \in \mathcal{K}'_1} \zeta_k \wedge |S \cap R_k| + \sum_{k \in \mathcal{K}'_2} |S \cap R_k| \geq \\ & \sum_{k \in \mathcal{K}'_1} \zeta_k \wedge |S \cap R_k| + \sum_{k \in \mathcal{K}'_2} \zeta_k \wedge |S \cap R_k| = \sum_{k \in \bar{\mathcal{K}}} \zeta_k \wedge |S \cap R_k|. \end{aligned} \quad \square$$

The last lemma is useful for the general case where (All-atoms) no longer holds, by making use of the completed Forest structure introduced in Definition 4.3.2.

**Lemma 4.A.4.** *For a reference family  $\mathfrak{R} = (R_k, \zeta_k)_{k \in \mathcal{K}}$  that has a Forest structure, and  $\mathcal{K}^+, \mathcal{K}^\oplus, \mathfrak{R}^\oplus$  as in Definition 4.3.2, we have for all  $S \subset \mathbb{N}_m$ :*

$$V_{\mathfrak{R}^\oplus}^*(S) = V_{\mathfrak{R}}^*(S),$$

$$\tilde{V}_{\mathfrak{R}^\oplus}(S) = \tilde{V}_{\mathfrak{R}}(S).$$

*Proof.* It is trivial that  $\mathcal{A}(\mathfrak{R}) = \mathcal{A}(\mathfrak{R}^\oplus)$  (see (4.7.1)) because  $\zeta_k = |R_k|$  for  $k \in \mathcal{K}^+$ , hence  $V_{\mathfrak{R}^\oplus}^*(S) = V_{\mathfrak{R}}^*(S)$ . It is also obvious that  $\tilde{V}_{\mathfrak{R}}(S) \geq \tilde{V}_{\mathfrak{R}^\oplus}(S)$  by (4.7.2) and since  $\mathcal{K} \subset \mathcal{K}^\oplus$ . Now let any  $\mathcal{K}' \subset \mathcal{K}^\oplus$ . Let  $\mathcal{K}'_1 = \mathcal{K}' \cap \mathcal{K}$  and  $\mathcal{K}'_2 = \mathcal{K}' \cap \mathcal{K}^+$ . Note that  $\mathcal{K}'$  is the disjoint union of  $\mathcal{K}'_1$  and  $\mathcal{K}'_2$ . Then,

$$\begin{aligned} \sum_{k \in \mathcal{K}'} \zeta_k \wedge |S \cap R_k| + \left| S \setminus \bigcup_{k \in \mathcal{K}'} R_k \right| &= \sum_{k \in \mathcal{K}'_1} \zeta_k \wedge |S \cap R_k| + \sum_{k \in \mathcal{K}'_2} |S \cap R_k| + \left| S \setminus \bigcup_{k \in \mathcal{K}'} R_k \right| \\ &\geq \sum_{k \in \mathcal{K}'_1} \zeta_k \wedge |S \cap R_k| + \left| S \setminus \bigcup_{k \in \mathcal{K}'_1} R_k \right| \\ &\geq \tilde{V}_{\mathfrak{R}}(S), \end{aligned}$$

because  $\zeta_k = |R_k|$  for  $k \in \mathcal{K}'_2$ . Hence  $\tilde{V}_{\mathfrak{R}^\oplus}(S) \geq \tilde{V}_{\mathfrak{R}}(S)$ , which concludes the proof.  $\square$

## Appendix 4.B Material for Lemma 4.3.1

Algorithm 2 below builds  $(P_n)$  and follows directly from the proof. It may be useful for the reader to start by looking the algorithm, in order to get a sense of what the formal proof does.

*Proof of Lemma 4.3.1.* Let  $H = \max_{k \in \mathcal{K}} \phi(k)$ , where  $\phi$  is the depth function defined by (4.3.1). We use a recursion to build, for each  $1 \leq h \leq H$ , an integer  $N^h \geq 1$  and a partition  $P^h = (P_n^h)_{1 \leq n \leq N^h}$  which satisfy the following three properties:

$$P^h \text{ is a partition of } \mathbb{N}_m, \tag{\mathscr{P}_1^h}$$

$$\forall k \in \mathcal{K} \text{ such that } \phi(k) < h, \exists (i, j) \in \{1, \dots, N^h\}^2 : R_k = \bigcup_{i \leq n \leq j} P_n^h, \tag{\mathscr{P}_2^h}$$

$$\forall k \in \mathcal{K} \text{ such that } \phi(k) = h, \exists n \in \{1, \dots, N^h\} : R_k = P_n^h. \tag{\mathscr{P}_3^h}$$

We start the recursion with  $h = 1$ . Let  $Succ_1 = \{k \in \mathcal{K} : \phi(k) = 1\}$ ,

$$New_1 = \{R_k : k \in Succ_1\} \cup \left\{ \mathbb{N}_m \setminus \bigcup_{k \in Succ_1} R_k \right\} \setminus \{\emptyset\},$$

and  $N^1 = |New_1|$ . We let  $P^1$  be the family of elements of  $New_1$ .  $(\mathcal{P}_1^1)$  is true because, by (Forest), for  $k, k' \in Succ_1$ ,  $k \neq k'$ ,  $R_k$  and  $R_{k'}$  are disjoint (otherwise they can't have same depth).  $(\mathcal{P}_2^1)$  and  $(\mathcal{P}_3^1)$  are trivially true.

Now let  $h \in \{2, \dots, H\}$  and assume that there exists  $N^{h-1}$  and  $P^{h-1}$  satisfying  $(\mathcal{P}_1^{h-1})$ ,  $(\mathcal{P}_2^{h-1})$  and  $(\mathcal{P}_3^{h-1})$ . For all  $n \in \{1, \dots, N^{h-1}\}$ , let

$$Succ_{h,n} = \left\{ k \in \mathcal{K} : \phi(k) = h \text{ and } R_k \subset P_n^{h-1} \right\},$$

$$New_{h,n} = \{R_k : k \in Succ_{h,n}\} \cup \left\{ P_n^{h-1} \setminus \bigcup_{k \in Succ_{h,n}} R_k \right\} \setminus \{\emptyset\},$$

$\mathbb{S}_n^h = \sum_{n'=0}^n |New_{h,n'}|$  (with  $|New_{h,0}| = 0$  by convention), and  $(P_{\mathbb{S}_{n-1}^h+1}^h, \dots, P_{\mathbb{S}_n^h}^h)$  be the family of the elements of  $New_{h,n}$ . Then let  $N^h = \mathbb{S}_{N^{h-1}}^h$  and  $P^h = (P_1^h, \dots, P_{N^h}^h)$ . Note that for each  $1 \leq n \leq N^{h-1}$ ,  $P_n^{h-1}$  is the disjoint union of  $P_{\mathbb{S}_{n-1}^h+1}^h, \dots, P_{\mathbb{S}_n^h}^h$ , because by (Forest), for  $k, k' \in Succ_{h,n}$ ,  $k \neq k'$ ,  $R_k$  and  $R_{k'}$  are disjoint (otherwise they can't have same depth). This and  $(\mathcal{P}_1^{h-1})$  imply  $(\mathcal{P}_1^h)$ . Let  $k \in \mathcal{K}$  such that  $\phi(k) < h$ , then  $(\mathcal{P}_2^{h-1})$  and  $(\mathcal{P}_3^{h-1})$  imply that there exists  $(i, j) \in \{1, \dots, N^{h-1}\}^2$  such that  $R_k = \bigcup_{i \leq n \leq j} P_n^{h-1}$ . Hence

$$R_k = \bigcup_{\mathbb{S}_{i-1}^{h-1}+1 \leq n \leq \mathbb{S}_j^h} P_n^h,$$

and we get  $(\mathcal{P}_2^h)$ . Finally let  $k \in \mathcal{K}$  such that  $\phi(k) = h$ . Let  $k'$  be the unique element of  $\mathcal{K}$  such that  $\phi(k') = h - 1$  and  $R_k \subsetneq R_{k'}$ . By  $(\mathcal{P}_3^{h-1})$ , there exists  $n \in \{1, \dots, N^{h-1}\}$  such that  $R_{k'} = P_n^{h-1}$ . Hence  $k \in Succ_{h,n}$  and  $R_k$  is equal to one of the elements of  $New_{h,n}$ , which gives us  $(\mathcal{P}_3^h)$ .

Now that the recursion has ended, properties  $(\mathcal{P}_1^H)$ ,  $(\mathcal{P}_2^H)$  and  $(\mathcal{P}_3^H)$  imply the existence of the desired partition. The proof of the converse statement is straightforward from (4.3.2).  $\square$

For the purpose of Algorithm 2, we let **len** and **con** be the concatenation and length functions such that, for all  $S_1, \dots, S_n, S_{n+1} \subset \mathbb{N}_m$  and  $S = (S_1, \dots, S_n)$ ,  $\text{len}(S) = n$ ,  $\text{con}(S, S_{n+1}) = (S_1, \dots, S_n, S_{n+1})$  if  $S_{n+1} \neq \emptyset$  and  $\text{con}(S, \emptyset) = S$ .

---

**Algorithm 2:** Computation of  $(P_n)_{1 \leq n \leq N}$ 

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**Data:**  $\mathfrak{R} = (R_k, \zeta_k)_{k \in \mathcal{K}}$  satisfying (Forest).

**Result:**  $P = (P_n)_{1 \leq n \leq N}$  such that for each  $k \in \mathcal{K}$ , there exists some  $(i, j)$  such that  $R_k = \bigcup_{i \leq n \leq j} P_n$ .

```

1   $P \leftarrow (\mathbb{N}_m);$ 
2   $N \leftarrow 1;$ 
3   $H \leftarrow \max_{k \in \mathcal{K}} \phi(k);$ 
4  for  $h \in (1, \dots, H)$  do
5     $newP \leftarrow ();$ 
6    for  $n \in \{1, \dots, N\}$  do
7       $Succ_{h,n} \leftarrow \{k \in \mathcal{K} : R_k \subset P_n, \phi(k) = h\};$ 
8      for  $k \in Succ_{h,n}$  do
9         $| newP \leftarrow \text{con}(newP, R_k);$ 
10       end
11        $newP \leftarrow \text{con}\left(P_n \setminus \bigcup_{k \in Succ_{h,n}} R_k, newP\right);$ 
12     end
13      $P \leftarrow newP;$ 
14      $N \leftarrow \text{len}(P);$ 
15   end
16 return  $P$ 

```

---

# Conclusion and outlook

The results of this manuscript support the fact that heterogeneity can be handled in a way that allows for more true discoveries and a better post hoc selection. These results open new perspectives, as follow-up research or as filling the gaps that still remain.

**Multiple testing** First, the main results of Chapters 2 and 3 rely on an independence assumption or on the relaxed weak dependence assumption (see [Storey et al., 2004](#)). As real datasets are likely to manifest many dependence patterns, it is desirable to extend our results to more general dependence settings such as the already studied PRDS one. To my knowledge, the few works addressing this concern relied on quite conservative procedures, see [Roquain and Van De Wiel \(2008\)](#) in the weighting framework and [Döhler \(2016\)](#) in the discrete framework. Since a connection between discrete testing and weighting has been made in Section 3.4.2, any advance in one of these areas is likely to be applicable to the other.

Additionally, results of Chapter 2 are only asymptotic, which may be problematic in practical applications where a moderate number of tests are performed. Let us mention two types of finite sample results that would be particularly interesting. The first type is to derive finite sample FDR control and power results at the price of a slightly conservative modification of the procedure. This has been done in the case of deterministic weights ([Roquain and van de Wiel, 2009](#), under independence) and, recently, an FDR control with data driven weights has been obtained; see [Ignatiadis and Huber \(2017, Theorems 2 and 3\)](#) which uses the censoring technology brought by [Li and Barber \(2016\)](#) (under independence and with specific estimators of  $\pi_{g,0}$ ). However, they did not get any result about power, so there is a room for improvement. The second type of results, perhaps more difficult to achieve, would be to quantify the convergence rate of the quantities of interest. Obtaining such rates should also allow to quantify the overfitting of optimized weighting procedures like IHW and ADDOW. However, this would require to use much more involved proofs, with an accurate study of derivatives of some complex functionals.

Finally, the optimality result of Theorem 2.5.2 has several restrictions: first, it holds for a limited class of weighted procedures, which depends on the accuracy of the  $\pi_{g,0}$  estimators that have been chosen at first place to run ADDOW. This is rather restrictive and it would be much more satisfying, but maybe also much more challenging, to get an optimality result among all the weighted procedures that control the FDR at the desired level (asymptotically). Certainly this requires to use some form of optimal  $\pi_{g,0}$  estimators in ADDOW. Second, the optimality result extensively relies on assumption (ME). When this condition is violated, it is even not clear that the ADDOW procedure has a larger power than the BH procedure (while it does more rejections, see Figure 2.6). Related to this, a critical issue is to quantify how rejection maximization differs from power maximization when assumption (ME) is not met.

On a side note, the procedures of Chapter 3 seem to be compatible with the approach of Tarone (1990) and Gilbert (2005), so the study of an hybridization of both could be of interest.

**Selective inference** While the new bounds developed in Chapter 4 behave mostly as expected in a localized context, simulations of Section 4.5 have suggested that neither  $V_{\text{DKW}}$  nor  $V_{\text{Simes}}$  is strictly better than the other, hence a first hybrid bound has been proposed, see Equation (4.5.1). Another possibility, not yet studied but that we see as a possible future development, is to combine the “deterministic region” approach with the “joint FWER” approach by applying the methods of Blanchard et al. (2018b) inside a family of fixed regions  $R_k$ . This would give rise to a reference family of the form

$$\mathfrak{R} = (R_{k,i_k}, \zeta_{k,i_k})_{\substack{k \in \mathcal{K} \\ 1 \leq i_k \leq |R_k|}}, \quad (4.2.1)$$

where the different  $\zeta_{k,i_k}$  are computed by applying Blanchard et al. (2018b) procedures to  $R_k$ . Note that the “joint FWER” approach and the computation of the corresponding bound can be quite computationally challenging. To circumvent the issue of the bound computation, a solution could start from the following remark: if the  $R_k$  are disjoint, the  $\mathfrak{R}$  family defined in (4.2.1) will follow the (Forest) structure. This means that Theorem 4.3.1 can be applied to  $\mathfrak{R}$  and thus a devoted algorithm is possible. While the details of this approach are still to be explored, this would also conveniently not rely on the independence hypothesis which was necessary to validate  $V_{\text{DKW}}$  (see Proposition 4.4.1).

A future application of Chapter 4 could be to GWAS data, for which the genome provides a natural one-dimensional local structure, that can be suitably combined with our (Forest) condition.

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# Appendix A

## Technical comments on key references

This appendix presents some comments on papers of the literature that were at the basis of my thesis. It includes some corrections that could be of interest for future investigations. The first note comes from a discussion with Gilles Blanchard.

### A.1 Note on the closed testing shortcuts of [Goeman and Solari \(2011\)](#)

In [Goeman and Solari \(2011\)](#), the authors present a way to use closed testing to derive post-hoc bounds on the number of true or false positives for any rejection set. Due to the large number of local tests to perform closed testing, which is  $2^n - 1$  for  $n$  tests, some shortcuts are needed to compute the bounds  $t_\alpha(R)$  and  $f_\alpha(R)$  as soon as  $n$  exceeds 30 (we refer to the original paper for all the notation). Two types of shortcut have been detailed in the paper. The first shortcut concerns exchangeable local tests that satisfy a monotonicity assumption

$$\delta(\{p_1, \dots, p_k\}) \geq \delta(\{q_1, \dots, q_k\}) \quad (9)$$

whenever  $p_1 \leq q_1, \dots, p_k \leq q_k$ , and an union assumption

$$\delta(q \cup P) \geq \delta(P) \quad (10)$$

whenever  $q \leq \min(p \in P)$ . The other shortcut concerns Simes type local tests, that is tests based on nondecreasing critical values.

In the present note, we focus on the first shortcut, detailed in appendix A of the original paper and therefore named shortcut A in the following. In their Section 4.1, the authors claim that Fisher's combination method allows its use; and in their Section 4.2, they claim that Simes type local tests satisfying assumption

$$c_i^l \leq c_i^m \quad \text{whenever} \quad l \geq m \quad (6)$$

also allow it. In Sections A.1.1 and A.1.2, with simple counterexamples we show that both statements do not hold in general, because in both settings assumption (10) may not be verified. The local test proposed in their Section 4.3 for the independent case (with the  $\sqrt{\#I}$  component) also seems to fail assumption (10), because of the square root. However, we show in Section A.1.3 that Simes type local tests with assumption

$$c_i^m \geq c_{i-w}^{m-w} \quad \text{for every} \quad 1 \leq w < i \quad (8)$$

(as corrected in [Goeman and Solari, 2013](#)) still allow this shortcut because assumption (8) implies assumption (10).

From the aforementioned, assumption (10) appears to be problematic and rarely met, so we propose in Section A.1.4 a new shortcut, based on shortcut A but without requiring assumption (10). While being more computationally expensive than shortcut A, this new shortcut is exact and still requires less than  $n^2$  tests to be performed.

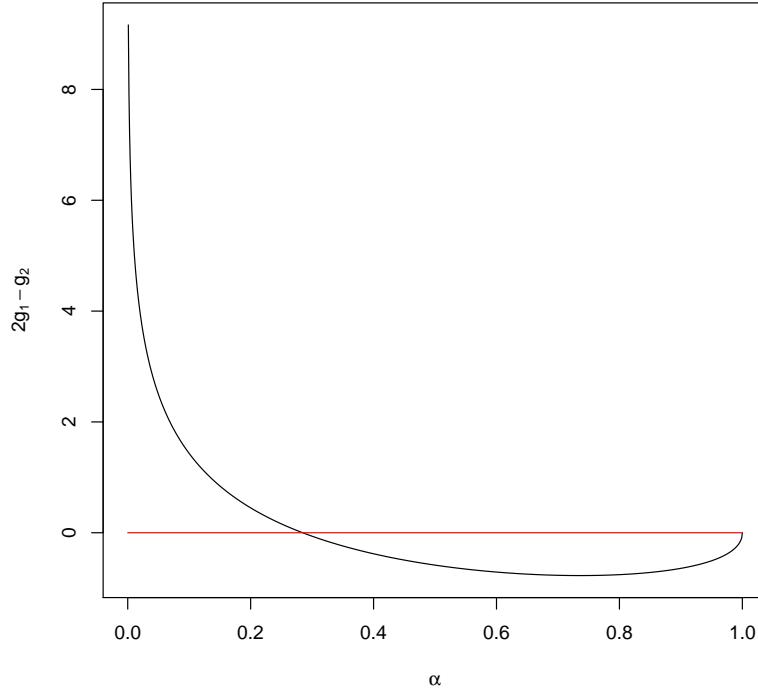
### A.1.1 Fisher's combination method does not imply assumption (10)

We use reductio ad absurdum and assume that Fisher's combination method implies assumption (10). Here, the function  $\delta$  which maps a set of  $p$ -values  $P_I = \{p_i, i \in I\}$  to rejection, is given by:

$$\delta(P_I) = \mathbb{1}_{\{-2 \sum_{i \in I} \log p_i \geq g_{\#I}\}},$$

where  $g_k$  is the  $(1 - \alpha)$ -quantile of a  $\chi^2$ -distribution with  $2k$  degrees of freedom.

Let  $p = e^{-\frac{g_1}{2}}$  so that  $-2 \log p = g_1$  and  $\delta(\{p\}) = 1$ . Let  $q_\epsilon = p - \epsilon$  for some  $\epsilon > 0$ . By (10), then  $\delta(\{q_\epsilon\} \cup \{p_1\}) = 1$  which implies that  $2g_1 \geq g_2$  by making  $\epsilon$  tend to 0. Figure A.1 shows that this is false for a large set of values of  $\alpha$ , hence a contradiction. Figure A.1 also suggests that there may exist a value  $\alpha_0$  such that assumption (10) holds for any  $\alpha \leq \alpha_0$ , but it seems difficult to prove.

Fig. A.1  $2g_1 - g_2$  against  $\alpha$ 

### A.1.2 Assumption (6) does not imply assumption (10)

We show that the Bonferroni critical values  $c_i^m = \frac{\alpha}{m}$  do not fulfill assumption (10) while they obviously satisfy assumption (6). Here

$$\delta(P_I) = \mathbb{1}_{\left\{ \exists i \in I : p_{(i)}^I \leq \frac{\alpha}{\#I} \right\}} = \mathbb{1}_{\left\{ p_{(1)}^I \leq \frac{\alpha}{\#I} \right\}},$$

where  $p_{(i)}^I$  denotes the  $i$ th smallest  $p$ -value of  $P_I$ . The last equality above holds because  $c_i^m$  does not depend on  $i$  in Bonferroni case.

$\delta(\{\alpha\}) = \mathbb{1}_{\{\alpha \leq \frac{\alpha}{1}\}} = 1$  but  $\delta(\{\frac{2}{3}\alpha, \alpha\}) = \mathbb{1}_{\{\frac{2}{3}\alpha \leq \frac{\alpha}{2}\}} = 0$  so assumption (10) is not satisfied.

### A.1.3 Assumption (8) allows using shortcut A

It is clear that assumption (9) is fulfilled because if  $p_i \leq q_i$  for all  $i \in I$  then the ordered  $p$ -values also satisfy  $p_{(i)} \leq q_{(i)}$  for all  $1 \leq i \leq \#I$ . We only need to show that assumption

(10) is satisfied. Let  $P_I = \{p_i, i \in I\}$  such that  $\delta(P_I) = 1$ , let  $q \leq \min_{i \in I} p_i$  and let us show that  $\delta(\{q\} \cup P_I) = 1$  using assumption (8).

Denote  $i_0 \in \{1, \dots, \#I\}$  an index such that  $p_{(i_0)}^I \leq c_{i_0}^{\#I}$  where the  $p_{(i)}^I$ ,  $1 \leq i \leq \#I$ , are the ordered  $p$ -values of  $P_I$ . Denote also  $p_{(i)}^n$ ,  $1 \leq i \leq \#I + 1$ , the ordered  $p$ -values of  $\{q\} \cup P_I$ . Because  $q \leq \min_{i \in I} p_i$ ,  $p_{(1)}^n = q$  and  $p_{(i+1)}^n = p_{(i)}^I$  for all  $1 \leq i \leq \#I$ . Now assumption (8) yields

$$p_{(i_0+1)}^n = p_{(i_0)}^I \leq c_{i_0}^{\#I} \leq c_{i_0+1}^{\#I+1},$$

so  $\delta(\{q\} \cup P_I) = 1$ .

#### A.1.4 New exact shortcut without assumption (10)

We start by making a statement analogous to the final statement of the proof in the original Appendix A: given an  $s < \#R$ ,

$$t_\alpha(R) \leq s \iff \forall J \subseteq \{1, \dots, n\} \text{ such that } |J \cap R| \geq s + 1, \delta(P_J) = 1. \quad (\text{A.1.1})$$

*Proof.*

$$\begin{aligned} t_\alpha(R) \leq s &\iff \forall I \subseteq R \text{ such that } |I| \geq s + 1, I \in \mathcal{X} \\ &\iff \forall I \subseteq R \text{ such that } |I| \geq s + 1, \text{ and } \forall J \supseteq I, \delta(P_J) = 1 \\ &\iff \forall J \text{ such that } |J \cap R| \geq s + 1, \delta(P_J) = 1. \end{aligned} \quad \square$$

This statement takes the form of a necessary and sufficient condition (NSC). Goeman and Solari wrote their own statement only as a sufficient condition (SC) whereas it was also an equivalence. It is important to highlight the NCS nature of the statement, because that is what allows to compute the exact value of  $t_\alpha(R)$ , by applying the shortcut to the successive values  $s = \#R - 1, s = \#R - 2, \dots$ , as long as  $t_\alpha(R) \leq s$ . A simple SC would only provide an upper bound.

This shortcut only requires assumption (9), so is applicable to Fisher's combination method and any Simes type local tests (even without assumptions (6) or (8), see our Section A.1.3). The shortcut is the following:  $t_\alpha(R) \leq s$  if and only if

$$\delta(Q_{s'}^R \cup \bar{Q}_j^R) = 1, \forall s' \in \{s + 1, \dots, \#R\}, \forall j \in \{0, \dots, \#\bar{R}\}, \quad (\text{A.1.2})$$

where, as in [Goeman and Solari \(2011\)](#),  $Q_{s'}^R$  is the set of the  $s'$  largest  $p$ -values indexed by  $R$  and  $\bar{Q}_j^R$  the set of the  $j$  largest  $p$ -values indexed by  $\bar{R}$ . The validity of the shortcut

comes from the clear equivalence between (A.1.2) and the right side of (A.1.1) (write any  $J$  as the disjointed union of  $J \cap R$  and  $J \cap \bar{R}$  and then apply assumption (9)).

It is also straightforward that (A.1.2) induces more test computations than shortcut A (see equation (11) of Goeman and Solari, 2011), and that is because we don't use assumption (10). However, the exact value of  $t_\alpha(R)$  is obtained by computing all the  $\delta(Q_{s'}^R \cup \bar{Q}_j^R)$ ,  $s' \in \{t_\alpha(R), \dots, \#R\}$ ,  $j \in \{0, \dots, \#\bar{R}\}$  which is less than or equal to  $(\#R + 1) \times (n - \#R + 1) \leq (n + \frac{1}{2})^2$  tests performed. Furthermore, for small  $R$ , the number of tests performed can be much smaller than  $(n + \frac{1}{2})^2$ , that is, linear in  $n$  instead of quadratic.

## A.2 Note on Roquain and van de Wiel (2009)

In Roquain and van de Wiel (2009), the authors presented an important contribution to the  $p$ -value weighting literature, introducing for the first time (to our knowledge) the concept of multi-weighting, and using this new notion to derive optimal weights maximizing the power while controlling the False Discovery Rate (FDR). In the following we refer to the original paper for the notation and the numerotation.

The novelty of their approach can be summarized as follows: instead of assigning to each  $p$ -value  $p_i$ ,  $1 \leq i \leq m$  a weight  $w_i$ , assign a function  $W_i : u \mapsto W_i(u)$  depending on a rejection threshold  $u \in [0, 1]$ . This provides a new multiple testing class of procedures they call *multi-weighted step-up procedures*, denoted  $\mathbf{SU}(\mathbf{W})$  (where  $\mathbf{W} = (W_i)_i$ ), which consists in rejecting all  $p_i \leq \alpha \hat{u} W_i(\hat{u})$  where

$$\begin{aligned}\hat{u} &= \mathcal{I}(\hat{\mathbb{G}}_{\mathbf{W}}) \\ &= \max \left\{ u \in [0, 1] \mid \hat{\mathbb{G}}_{\mathbf{W}}(u) \geq u \right\}\end{aligned}$$

and

$$\hat{\mathbb{G}}_{\mathbf{W}}(u) = m^{-1} \sum_{i=1}^m \mathbf{1}\{p_i \leq \alpha u W_i(u)\}.$$

They then define the optimal weight function  $\mathbf{W}^*$  by maximizing the power at each rejection threshold  $u$ :

$$\mathbf{W}^*(u) \in \arg \max_{\{\mathbf{w} \mid \sum_{i=1}^m w_i = m\}} \text{Pow}_u(\mathbf{w})$$

where  $\text{Pow}_u(\mathbf{w}) = \text{Pow}(\{i \mid p_i \leq \alpha u w_i\})$ . Of course, maximizing the power requires the knowledge of the distribution of the  $p$ -values under the alternative hypothesis, that is, the c.d.f.  $F_i$ .

The two main theorems of the paper give statements about the power optimality of the resulting procedure  $\mathbf{SU}(\mathbf{W}^*)$  for finite sample (Theorem 4.2), and asymptotically (Theorem 4.3). However, the proof of these two theorems rely on a technical result, Proposition 8.3, and there is an error in the proof of the statement (*i*) of this proposition. In this correction note, we suggest to state a weaker statement than (*i*) which still allows to prove Theorems 4.2 and 4.3, up to a slightly modification of Theorem 4.3: in equation (16), the lim should be replaced by a lim sup.

**The error** Take the proof of statement (*i*), page 702, in the second block of equations, when the authors go from

$$\mathbb{E} \left[ \pi_1 m^{-1} \sum_{i=1}^m F_i \circ \Delta_i(\phi(\hat{u}'_{-i})) - (1 - \alpha\pi_0)\bar{u} \right]$$

to

$$\pi_1 \mathbb{P}(\Omega_1^c) + G_{\mathbf{W}}(\bar{u} + \lambda) - \alpha\pi_0(\bar{u} + \lambda) - (1 - \alpha\pi_0)\bar{u}.$$

The  $(1 - \alpha\pi_0)\bar{u}$  can be ignored because it does not change between the two lines. The upper-bounding made by the authors consists in writing

$$\begin{aligned} \mathbb{E} \left[ \pi_1 m^{-1} \sum_{i=1}^m F_i \circ \Delta_i(\phi(\hat{u}'_{-i})) \right] &= \pi_1 \mathbb{E} \left[ m^{-1} \sum_{i=1}^m F_i \circ \Delta_i(\phi(\hat{u}'_{-i})) (\mathbb{1}_{\Omega_1^c} + \mathbb{1}_{\Omega_1}) \right] \\ &\leq \pi_1 \mathbb{P}(\Omega_1^c) + \pi_1 m^{-1} \sum_{i=1}^m F_i \circ \Delta_i(\bar{u} + \lambda), \end{aligned}$$

and then using that

$$\pi_1 m^{-1} \sum_{i=1}^m F_i \circ \Delta_i(\bar{u} + \lambda) = G_{\mathbf{W}}(\bar{u} + \lambda) - \alpha\pi_0(\bar{u} + \lambda). \quad (\text{E})$$

But (E) is not generally true because the c.d.f. of a uniform distribution over  $[0, 1]$  is  $t \geq 0 \mapsto t \wedge 1$ , not  $t \mapsto t$ , which means that:

$$\pi_1 m^{-1} \sum_{i=1}^m F_i \circ \Delta_i(u) = G_{\mathbf{W}}(u) - \pi_0 m^{-1} \sum_{i=1}^m (\Delta_i(u) \wedge 1), \quad \forall u \in [0, 1]. \quad (\text{Pw})$$

Since  $\Delta_i(\bar{u} + \lambda)$  can be  $> 1$  in general, (E) fails and the proof cannot be completed.

Note that this does not impact the proof of statement (*ii*) because we still have

$$\pi_1 m^{-1} \sum_{i=1}^m F_i \circ \Delta_i(u) \geq G_{\mathbf{W}}(u) - \alpha\pi_0 u, \quad \forall u \in [0, 1].$$

**Weaker statement** We propose to replace previous statement (i) of Proposition 8.3 by:

$$\text{Pow } \mathbf{SU}(\mathbf{W}) - (1 - \alpha\pi_0)u^* \leq \pi_1 m^2 \exp\{-2m(\mathcal{I}_\lambda^+(G_{\mathbf{W}}) - m^{-1})_+^2\} + \lambda(1 - \alpha\pi_0). \quad (\text{WeakState})$$

Two distinct changes have been made. The less notable one is that we dropped the “ $-\mathcal{I}_\lambda^+(G_{\mathbf{W}})$ ” which turns out to be useless in the rest of the paper (the authors dropped it too as soon as they used the statement in their proofs of each theorem). The second change is that we switched  $\bar{u}$  for  $u^*$ .

It is easy to see that these changes do not modify at all the proof of Theorem 4.2, see the bottom of page 701 where the statement is used. The proof was already using that  $u^* \geq u_{\mathbf{w}}$  to switch  $u_{\mathbf{w}}$  for  $u^*$ . Nevertheless the original statement was necessary to show equation (29) page 704, inside the proof of Theorem 4.3. Now, to prove Theorem 4.3, we have to first show (28) as in the original paper, then use (15) for a fixed  $\mathbf{w}$ , making  $m \rightarrow \infty$  and then  $\lambda \rightarrow 0$ . This explains why the  $\lim_m \text{Pow}(\mathbf{LSU}(\mathbf{w}))$  should be replaced by a  $\limsup$ .

**Proof of (WeakState)** First note that (Pw) is also the equation of  $\text{Pow}_u(\mathbf{W}(u))$  for all  $u \in [0, 1]$ . Note also that for  $\mathbf{W}^*$  instead of a general  $\mathbf{W}$ , equation (E) is valid because  $\Delta_i^*(u) \leq 1$  for all  $u$  (easy to see on the closed formula given by Proposition 3.2). So we start by proceeding as in the original paper until we get (26). Then we write:

$$\begin{aligned} \text{Pow}(\mathbf{SU}(\mathbf{W})) - (1 - \alpha\pi_0)u^* &\leq \mathbb{E} \left[ \pi_1 m^{-1} \sum_{i=1}^m F_i \circ \Delta_i(\phi(\hat{u}'_{-i})) \right] - (1 - \alpha\pi_0)u^* \\ &\leq \pi_1 \mathbb{P}(\Omega_1^c) + \pi_1 m^{-1} \sum_{i=1}^m F_i \circ \Delta_i(\bar{u} + \lambda) - (1 - \alpha\pi_0)u^* \\ &\leq \pi_1 \mathbb{P}(\Omega_1^c) + \text{Pow}_{\bar{u} + \lambda}(\mathbf{W}(\bar{u} + \lambda)) - (1 - \alpha\pi_0)u^* \\ &\leq \pi_1 \mathbb{P}(\Omega_1^c) + \text{Pow}_{u^* + \lambda}(\mathbf{W}(\bar{u} + \lambda)) - (1 - \alpha\pi_0)u^* \quad (\text{a}) \\ &\leq \pi_1 \mathbb{P}(\Omega_1^c) + \text{Pow}_{u^* + \lambda}(\mathbf{W}^*(u^* + \lambda)) - (1 - \alpha\pi_0)u^* \quad (\text{b}) \\ &\leq \pi_1 \mathbb{P}(\Omega_1^c) + G_{\mathbf{W}^*}(u^* + \lambda) - \alpha\pi_0(u^* + \lambda) - (1 - \alpha\pi_0)u^* \\ &\quad (\text{c}) \\ &\leq \pi_1 \mathbb{P}(\Omega_1^c) + G_{\mathbf{W}^*}(u^* + \lambda) - (u^* + \lambda) + \lambda(1 - \alpha\pi_0) \\ &\leq \pi_1 \mathbb{P}(\Omega_1^c) + \lambda(1 - \alpha\pi_0). \quad (\text{d}) \end{aligned}$$

Above, we used that  $u^* \geq \bar{u}$  along with that  $F_i$  is nondecreasing in (a) and the definition of  $\mathbf{W}^*$  as an arg max in (b). (E) applied to  $\Delta^*$  provides (c), and (d) comes from

$G_{\mathbf{W}^*}(u^* + \lambda) \leq u^* + \lambda$ . The end of the proof, that is the upper-bounding of  $\mathbb{P}(\Omega_1^c)$ , is the same as in the original paper.

### A.3 Note on Gontscharuk and Finner (2013)

In Gontscharuk and Finner (2013), the authors construct a sequence of  $p$ -values under weak dependence (see their Definition 2.1) to get a counterexample about asymptotic FDR control. Their sequence is constructed in Example 3.1 and the statement that it satisfies Definition 2.1 is in Lemma 3.2. But the proof of Lemma 3.2 makes use of the Glivenko-Cantelli theorem, which cannot be used here because the distribution of the  $p_i^{(n)}$  depends on  $n$ . Here we propose another proof, but we have to add an assumption about  $n_0 = |I_{n,0}|$ . Instead of just assuming that  $n_0 \xrightarrow{n \rightarrow \infty} \infty$ , we assume that  $\frac{n_0}{n} \xrightarrow{n \rightarrow \infty} \pi_0$  for some  $\pi_0 \leq 1$ .  $k$  is chosen as in the original paper, and we consider  $n$  large enough so that (4) is fulfilled. Note that the new assumption implies that  $\pi_0 \alpha \sum_{j=1}^k \frac{1}{j} \leq 1$ .

**The conditional proof** Let  $j$  such that  $1 \leq j \leq k+1$  and, if  $j \leq k$ ,  $J \in \mathcal{A}_j = \{J \subseteq I_{n,0}, |J| = j\}$ . We work conditionally to the event  $E = \{N = j \text{ and } Z_j = J\}$  if  $j \leq k$ , or  $E = \{N = k+1\}$  if  $j = k+1$ . So, if  $j \leq k$ , for  $i \in J$ ,  $p_i^{(n)} \sim U[\alpha(j-1)/n, \alpha j/n]$  and for  $i \in I_{n,0} \setminus J$ ,  $p_i^{(n)} \sim U[\alpha k/n, 1]$ . And if  $j = k+1$ , for  $i \in I_{n,0}$ ,  $p_i^{(n)} \sim U[\alpha k/n, 1]$ . Furthermore, recall that conditionally to  $E$ , the  $p$ -values are independent. We will use that, as noted by the authors, at least  $n_0 - k$  true nulls have a  $p$ -value following  $U[\alpha k/n, 1]$ .

**Notation** Let  $F_n$  be the cumulative distribution function (c.d.f.) of  $U[\alpha k/n, 1]$ . As noted by the authors,  $\sup_{t \in [0,1]} |F_n(t) - t| \rightarrow 0$  because  $k/n \rightarrow 0$ . As in the original paper,  $\hat{F}_{n,0}$  is the empirical c.d.f. of the  $p_i^{(n)}$ 's,  $i \in I_{n,0}$ . So

$$\begin{aligned}\hat{F}_{n,0}(t) &= \frac{1}{n_0} \sum_{i \in I_{n,0}} \mathbb{1}_{\{p_i^{(n)} \leq t\}} \\ &= \frac{n_0 - k}{n_0} \frac{1}{n_0 - k} \sum_{i \in I_{n_0-k}} \mathbb{1}_{\{p_i^{(n)} \leq t\}} + \frac{1}{n_0} \sum_{i \in I_{n,0} \setminus I_{n_0-k}} \mathbb{1}_{\{p_i^{(n)} \leq t\}}\end{aligned}$$

where  $I_{n_0-k}$  is a set such that  $|I_{n_0-k}| = n_0 - k$  and  $p_i^{(n)} \sim U[\alpha k/n, 1]$  for all  $i \in I_{n_0-k}$ .  $k$  is fixed so  $\mathbb{P} \left( \sup_{t \in [0,1]} \left| \frac{1}{n_0} \sum_{i \in I_{n,0} \setminus I_{n_0-k}} \mathbb{1}_{\{p_i^{(n)} \leq t\}} \right| \rightarrow 0 \middle| E \right) = 1$ . Let  $\hat{F}_{n_0-k}(t) =$

$\frac{1}{n_0-k} \sum_{i \in I_{n_0-k}} \mathbb{1}_{\{p_i^{(n)} \leq t\}}$ . Now we only have to show that

$$\mathbb{P} \left( \sup_{t \in [0,1]} |\hat{F}_{n_0-k}(t) - F_n(t)| \rightarrow 0 \middle| E \right) = 1,$$

to conclude that  $\mathbb{P} \left( \sup_{t \in [0,1]} |\hat{F}_{n,0}(t) - t| \rightarrow 0 \middle| E \right) = 1$  and end the proof by removing the conditioning.

**Concentration inequality** We apply the DKWM inequality (Massart, 1990) thanks to the independence: let any  $\epsilon > 0$ , then

$$\mathbb{P} \left( \sup_{t \in [0,1]} |\hat{F}_{n_0-k}(t) - F_n(t)| > \epsilon \middle| E \right) \leq 2e^{-2(n_0-k)\epsilon^2}$$

The series  $2e^{-2(n_0-k)\epsilon^2}$  converges because  $n_0 \underset{n \rightarrow \infty}{\sim} \pi_0 n$  by our added assumption. Note that this assumption was added only to get the convergence of the series so it could be weakened. So, conditionally to  $E$ ,  $\sup_{t \in [0,1]} |\hat{F}_{n_0-k}(t) - F_n(t)|$  converges almost completely to 0, which implies its almost sure convergence to 0, hence  $\mathbb{P} \left( \sup_{t \in [0,1]} |\hat{F}_{n_0-k}(t) - F_n(t)| \rightarrow 0 \middle| E \right) = 1$  as desired.



# Appendix B

## Supplement for Chapter 4

This appendix presents some minor results I obtained when working on what would become the Chapter 4 of this manuscript. Notation is strictly the same.

### B.1 Other calibration

Proposition 4.4.1 holds only with the assumption that (Indep) is satisfied, because the construction of (4.4.1) relies on the DKWM inequality. It is desirable to have other constructions of  $\zeta_k$  that do not need independence, as stated in Section 4.6 (see in particular Equation (4.6.1)). Here we propose another calibration based on local (i.e., in each subset  $R_k$ ) familywise error rate (FWER) control. As in Section 4.4, the  $R_k$ 's are deterministic.

Assume that for each  $k$  we have at hand a local method  $\phi_k : [0, 1] \times \mathcal{P}(\mathbb{N}_m) \rightarrow \mathcal{P}(\mathbb{N}_m)$  (the dependence on  $X$  is not written) such that  $\phi_k(\lambda, R)$  is the set of rejected hypotheses when applying  $\phi_k$  to  $R$  and such that the method provides FWER-control at level  $\lambda$ :

$$\forall R \subset \mathbb{N}_m, \text{FWER}(\phi_k(\lambda, R)) = \mathbb{P}(|\phi_k(\lambda, R) \cap \mathcal{H}_0| > 0) \leq \lambda.$$

Assume also that the rejection sets are nondecreasing in  $\lambda$ :  $\phi_k(\lambda_1, R) \subset \phi_k(\lambda_2, R)$  for all  $R$  and  $\lambda_1 \leq \lambda_2$ , which is a natural and frequently met assumption. For any  $\lambda$ , let  $\hat{\ell}_\lambda(R) = |\phi_k(\lambda, R)|$ , and let

$$\zeta_k^{\text{rg}}(X) = |R_k| - \hat{\ell}_{\frac{\alpha}{K}}(R_k) = \left| R_k \setminus \phi_k \left( \frac{\alpha}{K}, R \right) \right| \quad (\text{B.1.1})$$

The reference family  $\mathfrak{R}^{\text{rg}}$  given by  $(R_k, \zeta_k^{\text{rg}}(X))_{k \in \mathcal{K}}$  hence satisfies (4.1.2), see Theorem B.2.1 below.

An example of such local method is the Holm-Bonferroni (HB) procedure defined by

$$\forall k \in \mathcal{K}, \phi_k(\lambda, R) = \phi_{HB}(\lambda, R) = \left\{ i \in R : p_i \leq \frac{\lambda}{|R| - \hat{\ell}_\lambda(R) + 1} \right\}, \quad (\text{B.1.2})$$

where

$$\hat{\ell}_\lambda(R) = \max \left\{ \ell \in \{0, 1, \dots, |R|\} : \forall \ell' \leq \ell, p_{(\ell':R)} \leq \frac{\lambda}{|R| - \ell' + 1} \right\},$$

and the  $p_{(\ell:R)}$ 's are the ordered  $p$ -values of  $R$ :  $p_{(1:R)} \leq \dots \leq p_{(|R|:R)}$ . The FWER control of the HB method relies only on ([Superunif](#)) and not on ([Indep](#)), hence providing ([4.1.2](#)) without independence.

Finally, note that only independence inside the  $R_k$ 's is needed for Proposition [4.4.1](#), so different types of calibration can be used for different subsets, as in the following example.

*Example B.1.1.* Let  $\mathcal{K} = \{1, \dots, K\}$ . We can use calibration [\(4.4.1\)](#) for  $R_1$  if we know that the  $p$ -values  $p_i, i \in R_1$ , are independent, and calibration [\(B.1.1\)](#) for the  $R_k, k > 1$ .

## B.2 Step-down refinement

If the signal is so localized that some regions contain only pure signal, we can define a sequential refinement of the previous calibration, in the spirit of the HB procedure, the step-down algorithm of [Blanchard et al. \(2018b\)](#) and the sequential rejection principle of [Goeman and Solari \(2010\)](#).

Let  $\mathcal{K}_{>0} = \{k \in \mathcal{K} : |R_k \cap \mathcal{H}_0| > 0\}$  and  $K_{>0} = |\mathcal{K}_{>0}|$ . Then, by denoting  $\zeta_k^{>0} = |R_k| - \hat{\ell}_{\frac{\alpha}{K_{>0}}}(R_k)$  and  $\mathfrak{R}^{>0} = \left( (R_k, \zeta_k^{>0}) \right)_k$ , we have:

$$\mathbb{P} \left( \exists k : |R_k \cap \mathcal{H}_0| > \zeta_k^{>0} \right) \leq \mathbb{P} \left( \exists k : \left| \phi_k \left( \frac{\alpha}{K_{>0}}, R_k \right) \cap \mathcal{H}_0 \right| > 0 \right) \quad (\text{B.2.1})$$

$$\begin{aligned} &\leq \sum_{k \in \mathcal{K}_{>0}} \mathbb{P} \left( k : \left| \phi_k \left( \frac{\alpha}{K_{>0}}, R_k \right) \cap \mathcal{H}_0 \right| > 0 \right) \\ &\leq \sum_{k \in \mathcal{K}_{>0}} \text{FWER} \left( \phi_k \left( \frac{\alpha}{K_{>0}}, R_k \right) \right) \leq \sum_{k \in \mathcal{K}_{>0}} \frac{\alpha}{K_{>0}} \leq \alpha, \end{aligned} \quad (\text{B.2.2})$$

that is,  $\mathfrak{R}^{>0}$  satisfies [\(4.1.2\)](#). So, if  $K_{>0} < K$  (meaning that some regions contain only signal), we still have the desired joint error rate control at level  $\alpha$  but with a less

conservative correction. In the above, (B.2.1) comes from:

$$|R_k \cap \mathcal{H}_0| > \zeta_k^{>0} \implies \left| \phi_k \left( \frac{\alpha}{K_{>0}}, R_k \right) \right| > |R_k \cap \mathcal{H}_1| \implies \left| \phi_k \left( \frac{\alpha}{K_{>0}}, R_k \right) \cap \mathcal{H}_0 \right| > 0. \quad (\text{B.2.3})$$

Now we can try to estimate  $K_{>0}$  with the following sequential algorithm: first let  $\mathcal{K}_1 = \mathcal{K}$  and  $K_1 = K$ . We apply the procedure of previous section with  $\lambda = \frac{\alpha}{K_1}$ , define  $\zeta_k^1(X) = |R_k| - \hat{\ell}_{\frac{\alpha}{K_1}}(R_k)$ , then remove the regions where only signal was detected, that is we let  $\mathcal{K}_2 = \mathcal{K}_1 \setminus \{k : \zeta_k^1(X) = 0\}$  and  $K_2 = |\mathcal{K}_2|$ . Similarly, at step  $\tau$ , apply the procedure with  $\lambda = \frac{\alpha}{K_\tau}$ , let  $\zeta_k^\tau(X) = |R_k| - \hat{\ell}_{\frac{\alpha}{K_\tau}}(R_k)$ ,  $\mathcal{K}_{\tau+1} = \mathcal{K}_\tau \setminus \{k : \zeta_k^\tau(X) = 0\}$ , and  $K_{\tau+1} = |\mathcal{K}_{\tau+1}|$ . For all  $\tau$ , let  $\mathfrak{R}^\tau = ((R_k, \zeta_k^\tau))_k$ . The algorithm eventually stops, meaning that at a given step  $\hat{\tau}$  we have  $\mathcal{K}_{\hat{\tau}+1} = \mathcal{K}_{\hat{\tau}}$ . Note that  $\zeta_k^1 = \zeta_k^{\text{rg}}$  and  $\mathfrak{R}^1 = \mathfrak{R}^{\text{rg}}$ .

The refined family  $\mathfrak{R}^{\text{r-rg}}$  is then defined as  $\mathfrak{R}^{\hat{\tau}}$ , and its joint error rate is also controlled at level  $\alpha$ .

**Theorem B.2.1.** *Let  $\phi_k$ ,  $k \in \mathcal{K}$ , be a procedure:  $[0, 1] \times \mathcal{P}(\mathbb{N}_m) \rightarrow \mathcal{P}(\mathbb{N}_m)$  which provides FWER-control at level  $\lambda$  and is nondecreasing in  $\lambda$  for each  $R \subset \mathbb{N}_m$ , as described in Section B.1. Then for the previous construction we have:*

$$\mathbb{P} \left( \mathcal{H}_0 \in \bigcap_{\tau \geq 1} \mathcal{A}(\mathfrak{R}^\tau) \right) \geq 1 - \alpha, \quad (\text{B.2.4})$$

where  $\mathcal{A}(\cdot)$  is defined in Equation (4.7.1). In particular,  $\mathbb{P}(\mathcal{H}_0 \in \mathcal{A}(\mathfrak{R}^1)) \geq 1 - \alpha$  and  $\mathbb{P}(\mathcal{H}_0 \in \mathcal{A}(\mathfrak{R}^{\hat{\tau}})) \geq 1 - \alpha$  which means that the joint error control (4.1.2) holds for  $\mathfrak{R}^{\text{rg}}$  and  $\mathfrak{R}^{\text{r-rg}}$ .

*Proof.* We show the following stronger result:

$$\mathbb{P} \left( \forall \tau, \forall k : \left| \phi_k \left( \frac{\alpha}{K_\tau}, R_k \right) \cap \mathcal{H}_0 \right| = 0 \right) \geq 1 - \alpha, \quad (\text{B.2.5})$$

which in turn implies (B.2.4) by implications similar to (B.2.3).

Assume that for all  $k \in \mathcal{K}$ ,  $\left| \phi_k \left( \frac{\alpha}{K_{>0}}, R_k \right) \cap \mathcal{H}_0 \right| = 0$ , which happens with probability at least  $1 - \alpha$  by (B.2.2). We show with a recursion that for all  $\tau \geq 1$ ,  $\mathcal{K}_{>0} \subset \mathcal{K}_\tau$ . The latter implies that  $\frac{\alpha}{K_\tau} \leq \frac{\alpha}{K_{>0}}$ , then  $\phi_k \left( \frac{\alpha}{K_\tau}, R_k \right) \subset \phi_k \left( \frac{\alpha}{K_{>0}}, R_k \right)$ , hence  $\left| \phi_k \left( \frac{\alpha}{K_\tau}, R_k \right) \cap \mathcal{H}_0 \right| = 0$  and  $|R_k \cap \mathcal{H}_0| \leq \zeta_k^\tau$  for all  $k$  (still by the same implication as in (B.2.3)).

For  $\tau = 1$  this is straightforward because  $\mathcal{K}_{>0} \subset \mathcal{K} = \mathcal{K}_1$ . Now we assume that  $\mathcal{K}_{>0} \subset \mathcal{K}_\tau$ . We have, for all  $k$ ,  $|R_k \cap \mathcal{H}_0| \leq \zeta_k^\tau$  so  $\{k : \zeta_k^\tau = 0\} \subset \mathcal{K}_{>0}^c$  hence  $\mathcal{K}_{>0} \subset \mathcal{K}_{\tau+1}$ , which ends the recursion.  $\square$

Finally note that this refinement technique works for any calibration such that  $\zeta_k$  is a nonincreasing function of  $\alpha/K$ , and not only for calibrations based on local FWER control. Calibration (4.4.1) meets this criterion, but as we already noted, if  $\zeta_k$  is computed with (4.4.1), it cannot be equal to 0 for usual values of  $\alpha$ . Mixed calibrations as in Example B.1.1 also meet this criterion.

### B.3 Interpolation bounds and counterexamples

One may question the choice of using  $\tilde{V}_{\mathfrak{R}}^q$  as defined in (4.2.5), instead of the more straightforward bounds

$$V_{\mathfrak{R}}^q(S) = \min_{Q \subset \mathcal{K}, |Q|=q} \left( \sum_{k \in Q} \zeta_k \wedge |S \cap R_k| + \left| S \setminus \bigcup_{k \in Q} R_k \right| \right), \quad 1 \leq q \leq K, \quad S \subset \mathbb{N}_m, \quad (\text{B.3.1})$$

the difference with (4.2.5) being in the  $=$  sign instead of the  $\leq$  sign in the minimum (note that  $V_{\mathfrak{R}}^q$  is a valid post hoc bound by the same proof as Lemma 4.2.1). The answer is that, contrary to  $\tilde{V}_{\mathfrak{R}}^q$ ,  $V_{\mathfrak{R}}^q$  lacks many desirable properties. For instance, in general,  $V_{\mathfrak{R}}^q(S)$  is not nonincreasing in  $q$ , not  $\leq \bar{V}_{\mathfrak{R}}(S)$ , and the minimum is not achieved on a subset  $Q$  matching a pairwise disjoint sequence of  $R_k$ 's.

*Example B.3.1.* Let  $m = 6$ ,  $\mathcal{K} = \{1, 2, 3, 4\}$ ,  $R_1 = \{1, 2\}$ ,  $R_2 = \{2, 3\}$ ,  $R_3 = \{3, 4\}$  and  $R_4 = \{5, 6\}$ . The signal is localized in  $R_2$ :  $\mathcal{H}_1 = R_2$ , and our method to compute the  $\zeta_k$ 's recovers it exactly:  $\zeta_1 = \zeta_3 = 1$ ,  $\zeta_2 = 0$  and  $\zeta_4 = 2$ . Finally let  $S = R_2$ . We have  $V_{\mathfrak{R}}^1(S) = 0$  and  $V_{\mathfrak{R}}^2(S) = 0$  by respectively realizing the minimum in  $Q = \{2\}$  and  $Q = \{2, 4\}$ . But for  $q = 3$  the minimum is achieved in either  $Q = \{1, 2, 4\}$  or  $Q = \{2, 3, 4\}$ , with

$$\begin{aligned} V_{\mathfrak{R}}^3(S) &= \zeta_1 \wedge |S \cap R_1| + \zeta_2 \wedge |S \cap R_2| + \zeta_4 \wedge |S \cap R_4| + |S \cap \{4\}| \\ &= 1 \wedge 1 + 0 \wedge 2 + 2 \wedge 0 + 0 \\ &= 1. \end{aligned}$$

Finally note that, here, the only element of  $Q$  such that  $|Q| = 3$  and such that the  $R_k$ ,  $k \in Q$ , are pairwise disjoint, is  $Q = \{1, 3, 4\}$  while

$$\zeta_1 \wedge |S \cap R_1| + \zeta_3 \wedge |S \cap R_3| + \zeta_4 \wedge |S \cap R_4| = 2 > V_{\mathfrak{R}}^3(S).$$

We can still recover monotonicity properties in some cases. Let  $q \leq K - 1$ . Assume the following property:

$$\forall Q \subset \mathcal{K}, |Q| = q, \exists j \in \mathcal{K} : R_j \cap \bigcup_{k \in Q} R_k = \emptyset, \quad (\text{B.3.2})$$

that is, for every sequence of  $q$  regions, there exists a  $(q + 1)$ -th region disjoint from them. Then  $V_{\mathfrak{R}}^{q+1}(R) \leq V_{\mathfrak{R}}^q(R)$ . This generalizes a result obtained in Corollary 4.3.1 about families  $\mathfrak{R}$  that satisfy [\(Disjoint\)](#), and is proven the same way (see Section 4.7.3). In example B.3.1, (B.3.2) is trivially true for  $q = 1$ , however, it is not true for  $q = 2$ : there is no region disjoint from  $R_2 \cup R_4$ .

Finally, let us underline that the computation of  $\tilde{V}_{\mathfrak{R}}^q$  and  $\tilde{V}_{\mathfrak{R}}$  is difficult in general, when we are not working with a [\(Forest\)](#) structure. Using  $\mathfrak{R}^{\text{rg}}$  with  $\phi_k = \phi_{HB}$  (see Equation (B.1.2)) provides a counterexample with positive probability to some intuitions about the relation between  $V_{\mathfrak{R}}^q$  and the computation of  $\tilde{V}_{\mathfrak{R}}$ . Namely, the two following conjectures are false:

- for a given  $q$ , if the minimum in  $V_{\mathfrak{R}}^q(S)$  is achieved on some  $Q \in \mathcal{K}$ ,  $|Q| = q$ , such that  $\bigcup_{k \in Q} R_k \cap S = \bigcup_{k \in \mathcal{K}} R_k \cap S$  (that is, the  $R_k \cap S$ ,  $k \in Q$ , recover  $\bigcup_{k \in \mathcal{K}} R_k \cap S$ ), then  $V_{\mathfrak{R}}^q(S) = \tilde{V}_{\mathfrak{R}}(S)$ .
- if  $V_{\mathfrak{R}}^q(S) < V_{\mathfrak{R}}^{q+1}(S)$  then  $V_{\mathfrak{R}}^q(S) < V_{\mathfrak{R}}^{q+l}(S)$  for all  $l \geq 1$ , and  $\tilde{V}_{\mathfrak{R}}(S)$  can be found by searching the smallest  $q$  such that  $V_{\mathfrak{R}}^q(S) < V_{\mathfrak{R}}^{q+1}(S)$ .

*Example B.3.2* (found by Gilles Blanchard). Let  $m = 9$ ,  $K = 4$ ,  $S = R_1 = \{1, \dots, 9\}$ ,  $R_2 = \{1, 2, 3\}$ ,  $R_3 = \{4, 5, 6\}$  and  $R_4 = \{7, 8, 9\}$ . Assume that the  $p$ -values are all true nulls with a uniform distribution over  $[0, 1]$ . Now assume that  $p_1, p_2, p_4, p_5, p_7 \leq \frac{\alpha/4}{9}$ ,  $p_3, p_6, p_9 > \alpha/4$  and finally  $p_8 \in \left(\frac{\alpha/4}{4}, \frac{\alpha/4}{2}\right]$ . Then  $\hat{k}(\alpha/4, R_1) = 5$  and  $\hat{k}(\alpha/4, R_2) = \hat{k}(\alpha/4, R_3) = \hat{k}(\alpha/4, R_4) = 2$ , which implies  $\zeta_1^{\text{rg}}(X) = 4$  and  $\zeta_2^{\text{rg}}(X) = \zeta_3^{\text{rg}}(X) = \zeta_4^{\text{rg}}(X) = 1$ . Hence  $V_{\mathfrak{R}^{\text{rg}}}^1(S) = 4$  and the minimum is realized in  $Q = \{1\}$  with  $R_1 \cap S = \bigcup_{k \in \mathcal{K}} R_k \cap S$ , but  $V_{\mathfrak{R}^{\text{rg}}}^2(S) = 5 > V_{\mathfrak{R}^{\text{rg}}}^1(S)$  and  $V_{\mathfrak{R}^{\text{rg}}}^3(S) = 3 < V_{\mathfrak{R}^{\text{rg}}}^1(S)$ .

## B.4 Application to FWER control

The two calibrations of Sections B.1 and B.2 both can also be viewed as “localized” FWER-controlling multiple testing procedures, that can detect more false nulls than their “non-local” equivalent if the signal is localized in some regions. To do so, we simply take the union of all the rejected hypotheses in all the  $R_k$  subsets. Namely, the rejected

set is

$$\bigcup_{k \in \mathcal{K}} \phi_k \left( \frac{\alpha}{K_n}, R_k \right),$$

with  $n = 1$  (corresponding to  $\mathfrak{R}^{\text{rg}}$ ) or  $n = \hat{\tau}$  (corresponding to  $\mathfrak{R}^{\text{r-rg}}$ ). The resulting FWER is controlled at level  $\alpha$  in both cases, by Equation (B.2.5).

We illustrate the power improvement of this approach under (Disjoint) on both numerical simulations and a theoretical example using the oracle Bonferroni test.

#### B.4.1 Numerical experiments

We want to compare the powers of the HB procedure, and its localized equivalents based on  $\mathfrak{R}^{\text{rg}}$  and  $\mathfrak{R}^{\text{r-rg}}$  (with the HB procedure used as the local procedure), on numerical simulations with nominal level  $\alpha = 0.05$ . The power of a rejection set  $R$  is defined by:

$$\text{Pow}(R) = \mathbb{E} \left[ m_1^{-1} |R \cap \mathcal{H}_1| \right] = \mathbb{E} \left[ m_1^{-1} \sum_{i \in \mathcal{H}_1} \mathbf{1}_{\{i \in R\}} \right],$$

where  $m_1 = |\mathcal{H}_1|$ . Let also  $m_0 = |\mathcal{H}_0|$ .

We choose the following model:  $m = 1000$   $p$ -values are computed from an equi-correlated gaussian vector  $X$  with mean vector  $\mu$  and equi-correlation parameter  $\rho$ , in the Gaussian one-sided setting, which means that  $p_i = \bar{\Phi}(X_i)$  where  $\bar{\Phi}(\cdot) = 1 - \Phi(\cdot)$  and  $\Phi$  is the c.d.f. of a standard normal distribution. Among these hypotheses,  $m_0 = 900$  are true nulls, which means that  $|\{i : \mu_i = 0\}| = 900$ . The signal strength is parametrized by a positive number  $\bar{\mu}$ . For the application of our local procedures, the set of hypotheses is partitioned into 100 regions of size 10 such that  $R_1 = \{1, \dots, 10\}$ ,  $R_2 = \{11, \dots, 20\}$ , and so on.

Four different settings are compared:

- in `const_nobloc`,  $\mathcal{H}_1$  is chosen at random and for all  $i \in \mathcal{H}_1$ ,  $\mu_i = \bar{\mu}$ . This setting serves as a benchmark because the signal is not localized.

In the three remaining settings, the signal is localized in two blocs. Namely,  $\mathcal{H}_1 = \{151, \dots, 183\} \cup \{634, \dots, 700\}$ .

- in `const_bloc`, the signal has a constant value into each bloc: for all  $i \in \mathcal{H}_1$ ,  $\mu_i = \bar{\mu}$ .
- in `gauss_bloc`, the signal is strong in the middle of each bloc, and decreases at bloc extremities, in a gaussian shape. The mean of all the  $\mu_i$ 's in each bloc is  $\bar{\mu}$ .
- in `pois_bloc`, the signal follows a Poisson law of mean  $\bar{\mu}$  (up to a slightly modification to ensure that for all  $i \in \mathcal{H}_1$ ,  $\mu_i > 0$ ).

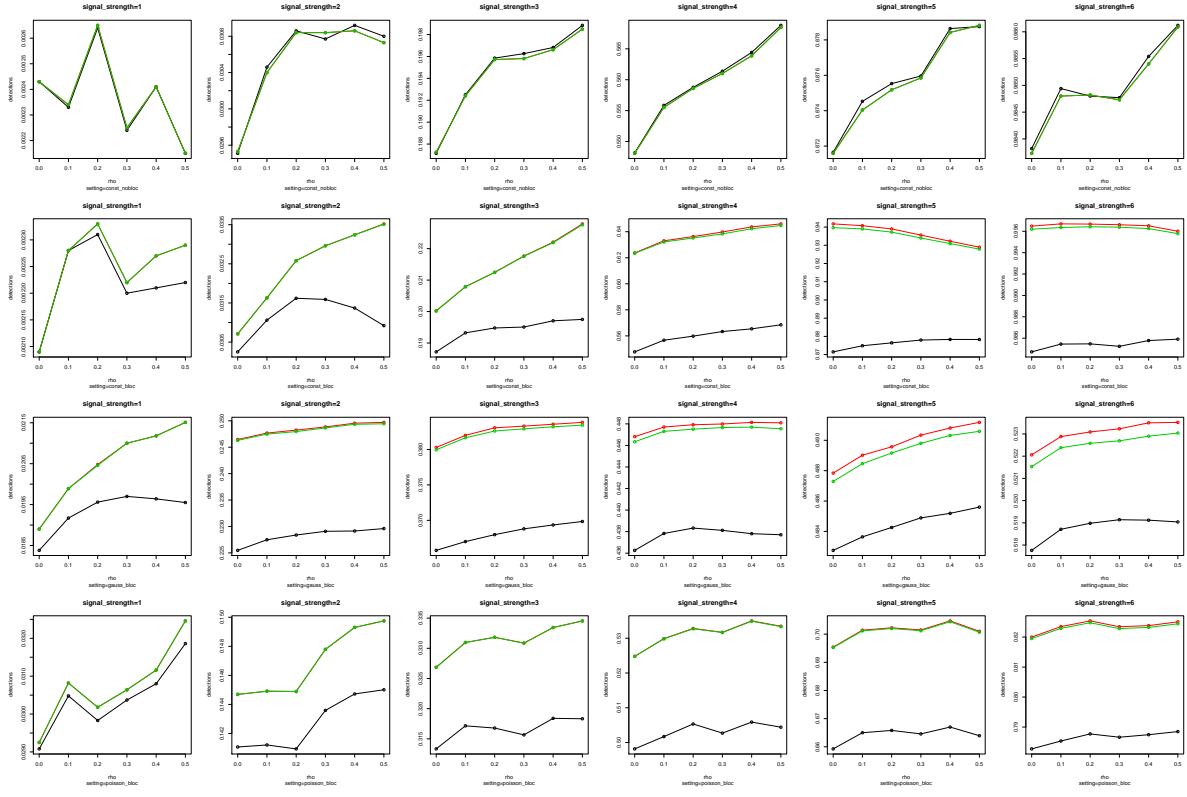


Fig. B.1 Power versus  $\rho$  in different settings and for different values of  $\bar{\mu}$ . First line: `const_nobloc` setting, second line: `const_bloc` setting, third line: `gauss_bloc`, fourth line: `pois_bloc` setting. Columns from left to right:  $\bar{\mu}$  equals 1 to 6. Black line: HB, green line: the localized procedure derived from  $\mathfrak{R}^{\text{rg}}$ , red line: the refinement derived from  $\mathfrak{R}^{\text{r-rg}}$ .

We present the results of 1000 replications of each setting, when  $\bar{\mu}$  varies in  $\{1, \dots, 6\}$  and  $\rho$  varies between 0 and 0.5 with steps of size 0.1. In Figure B.1, we show the plots of the power of our 3 procedures when  $\rho$  increases, for the different values of  $\bar{\mu}$  and the different settings. Similarly, we show the plot of the normalized FWER (that is, the FWER divided by  $\alpha$ ), in Figure B.2.

All observed results were expected:

- The FWER is always controlled and the procedures become more conservative as the correlation (that is,  $\rho$ ) increases.
- The localized procedures show an improvement in power over HB if and only if the signal is localized in blocs.

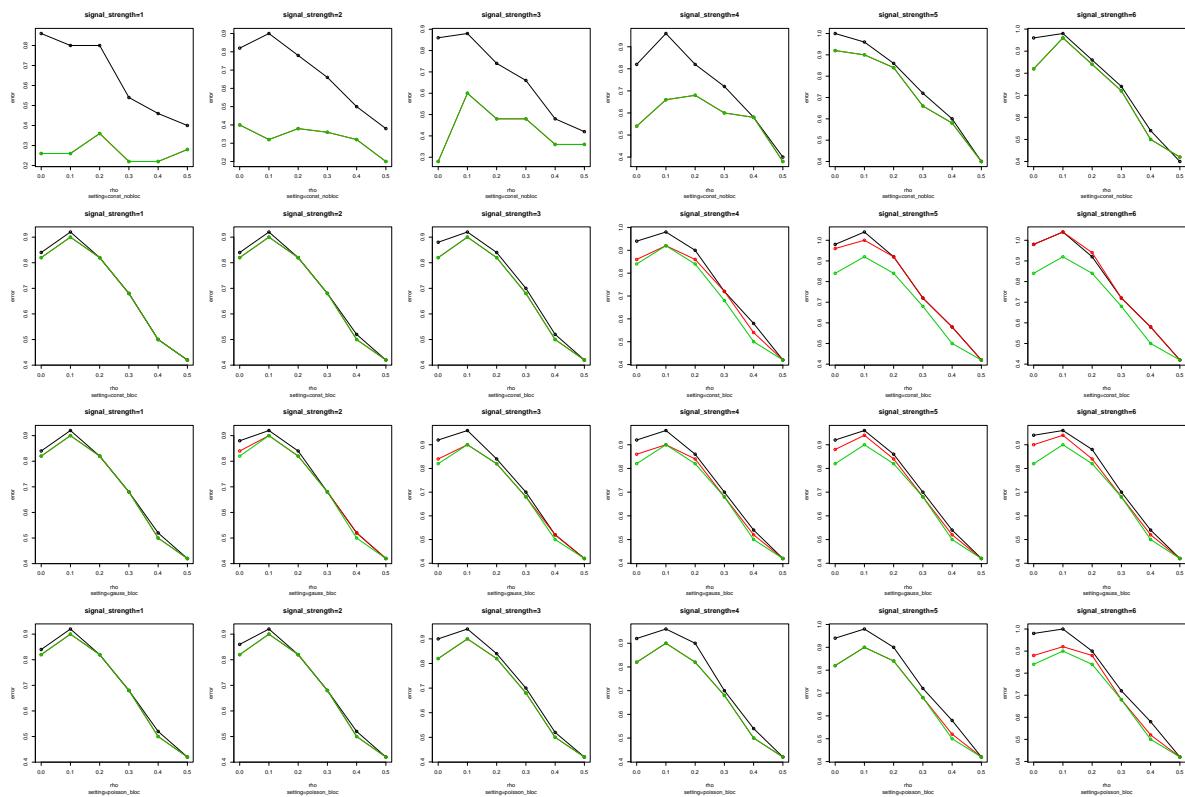


Fig. B.2 Normalized FWER versus  $\rho$  in different settings and for different values of  $\bar{\mu}$ . Same legend as Figure B.1.

- The improvement of the step-down refinement  $\mathfrak{R}^{\text{r-rg}}$  over the procedure derived from  $\mathfrak{R}^{\text{r-rg}}$  is limited and only becomes noticeable in the `gauss_bloc` setting with a high  $\bar{\mu}$ , because for  $\mathfrak{R}^{\text{r-rg}}$  to reject more hypotheses than  $\mathfrak{R}^{\text{rg}}$ , first  $\mathfrak{R}^{\text{rg}}$  has to reject entire regions.

### B.4.2 Oracle analysis

Here we will make use of the oracle Bonferroni as the local procedure, defined by:

$$\phi_{\text{Bonf}^0}(\lambda, R) = \left\{ i \in R : p_i \leq \frac{\lambda}{|R \cap \mathcal{H}_0|} \right\}.$$

We choose a sparse setting as follows: let  $m$  the number of hypotheses tested, clustered in  $K$  pairwise disjoint subsets of a fixed size  $s$ , that is,  $m = sK$  and  $K \xrightarrow[m \rightarrow \infty]{} \infty$ . Among the subsets,  $K_1$  of them contain false nulls in proportion  $r \in (0, 1)$ , that is  $r = \frac{|R_k \cap \mathcal{H}_1|}{s}$ . For the remaining  $K - K_1$  subsets, there is no signal at all, that is  $|R_k \cap \mathcal{H}_1| = 0$ . We let

$$K_1 = \left\lfloor \frac{m^{1-\beta}}{sr} \right\rfloor = \frac{m^{1-\beta}}{sr} + O(1),$$

where  $\beta \in (0, 1)$  is the sparsity parameter. This implies that

$$m_1 = K_1 sr = m^{1-\beta} + O(1).$$

Finally, we choose a Gaussian one-sided setting where the false nulls have mean  $\mu_m$ .

Let  $P_{G,m} = \text{Pow}(\phi_{\text{Bonf}^0}(\alpha, \mathbb{N}_m))$  the power of the global oracle Bonferroni, and  $P_{R,m} = \text{Pow}\left(\bigcup_{k \in \mathcal{K}} \phi_{\text{Bonf}^0}\left(\frac{\alpha}{K}, R_k\right)\right)$  the power of the local procedure associated to  $\mathfrak{R}^{\text{rg}}$ . We now show that  $P_{R,m}$  converges to 0 slower than  $P_{G,m}$  if  $\mu_m$  is below the detection frontier, but converges to 1 faster if  $\mu_m$  is above.

**Proposition B.4.1.** 1. If  $\mu_m = \delta \sqrt{2 \log(m)} + o(\sqrt{\log(m)})$ , where  $\delta \in [0, 1]$ ,

$$\lim_{m \rightarrow \infty} \frac{P_{G,m}}{P_{R,m}} = (1 - r)^{1-\delta} < 1. \quad (\text{B.4.1})$$

2. If  $\mu_m = \delta \sqrt{2 \log(m)} + o(\sqrt{\log(m)})$ , where  $\delta \in (1, \infty)$ ,

$$\lim_{m \rightarrow \infty} \frac{1 - P_{R,m}}{1 - P_{G,m}} = (1 - r)^{\delta-1} < 1. \quad (\text{B.4.2})$$

3. If  $\sqrt{\log(m)} = o(\mu_m)$ ,

$$\lim_{m \rightarrow \infty} \frac{1 - P_{R,m}}{1 - P_{G,m}} = 0. \quad (\text{B.4.3})$$

These results echo the results of Proposition 4.4.2 and Corollary 4.4.1. To prove the proposition, we need a precise asymptotic approximation of  $\bar{\Phi}^{-1}$ , provided by the following Lemma.

**Lemma B.4.1.** *The following asymptotic expansion holds true:*

$$\left( \bar{\Phi}^{-1}(y) \right)^2 \underset{y \rightarrow 0^+}{=} 2 \log \left( \frac{1}{y} \right) - \log_2 \left( \frac{1}{y} \right) - \log(4\pi) + o(1), \quad (\text{B.4.4})$$

where  $\log_2 = \log \log$ .

This result can be retrieved from the proof of Lemma 12.3 (1) of Abramovich et al. (2006) (see the detailed version Abramovich et al. (2005, on arXiv)). A proof is presented after the proof of the Proposition for the sake of completeness.

*Proof of Proposition B.4.1.* We have that

$$P_{G,m} = \mathbb{E} \left[ m_1^{-1} \sum_{i \in \mathcal{H}_1} \mathbb{1}_{\left\{ p_i \leq \frac{\alpha}{m_0} \right\}} \right] = F_m \left( \frac{\alpha}{m_0} \right),$$

where  $F_m$  is the c.d.f. of a  $p$ -value under the alternative, that is  $F_m(\cdot) = \bar{\Phi} \left( \bar{\Phi}^{-1}(\cdot) - \mu_m \right)$ . Likewise,

$$\begin{aligned} P_{R,m} &= \mathbb{E} \left[ m_1^{-1} \sum_{k=1}^K \sum_{i \in R_k \cap \mathcal{H}_1} \mathbb{1}_{\left\{ p_i \leq \frac{\alpha/K}{|R_k \cap \mathcal{H}_0|} \right\}} \right] \\ &= m_1^{-1} K_1 s r F_m \left( \frac{\alpha/K}{s(1-r)} \right) = F_m \left( \frac{\alpha}{m(1-r)} \right). \end{aligned}$$

Using that  $\bar{\Phi}(x) \underset{x \rightarrow \infty}{\sim} \frac{\phi(x)}{x}$  and  $\bar{\Phi}^{-1}(y) \underset{y \rightarrow 0^+}{\sim} \sqrt{2 \log\left(\frac{1}{y}\right)}$ , where  $\phi$  is the density of the standard normal distribution, we have that, in case 1,

$$\begin{aligned} \frac{P_{G,m}}{P_{R,m}} &\underset{m \rightarrow \infty}{\sim} \frac{\bar{\Phi}^{-1}\left(\frac{\alpha}{m(1-r)}\right) - \mu_m}{\bar{\Phi}^{-1}\left(\frac{\alpha}{m_0}\right) - \mu_m} e^{\frac{1}{2}\left(\bar{\Phi}^{-1}\left(\frac{\alpha}{m(1-r)}\right) - \mu_m\right)^2 - \frac{1}{2}\left(\bar{\Phi}^{-1}\left(\frac{\alpha}{m_0}\right) - \mu_m\right)^2} \\ &\underset{m \rightarrow \infty}{\sim} \frac{\sqrt{2 \log\left(\frac{m(1-r)}{\alpha}\right)}}{\sqrt{2 \log\left(\frac{m-m^{1-\beta}}{\alpha}\right)}} e^{A_m - \mu_m B_m} \\ &\underset{m \rightarrow \infty}{\sim} e^{A_m - \mu_m B_m}, \end{aligned} \quad (\text{B.4.5})$$

where

$$A_m = \frac{1}{2} \left( \bar{\Phi}^{-1}\left(\frac{\alpha}{m(1-r)}\right) \right)^2 - \frac{1}{2} \left( \bar{\Phi}^{-1}\left(\frac{\alpha}{m_0}\right) \right)^2,$$

and

$$B_m = \bar{\Phi}^{-1}\left(\frac{\alpha}{m(1-r)}\right) - \bar{\Phi}^{-1}\left(\frac{\alpha}{m_0}\right).$$

Using (B.4.4),  $A_m$  expands to

$$\begin{aligned} A_m &\underset{m \rightarrow \infty}{=} \log(1-r) - \frac{1}{2} \log_2 \left( \frac{m(1-r)}{\alpha} \right) + \frac{1}{2} \log_2 \left( \frac{m(1-\frac{m_1}{m})}{\alpha} \right) + o(1) \\ &\longrightarrow \log(1-r). \end{aligned}$$

Finally,

$$\begin{aligned} B_m &= \frac{2A_m}{\bar{\Phi}^{-1}\left(\frac{\alpha}{m(1-r)}\right) + \bar{\Phi}^{-1}\left(\frac{\alpha}{m_0}\right)} \underset{m \rightarrow \infty}{\equiv} \frac{2 \log(1-r) + o(1)}{2\sqrt{2 \log(m)} + o(\sqrt{\log(m)})} \\ &\underset{m \rightarrow \infty}{\equiv} \frac{\log(1-r)}{\sqrt{2 \log(m)}} + o\left(\log(m)^{-\frac{1}{2}}\right), \end{aligned}$$

hence  $\lim_{m \rightarrow \infty} A_m - \mu B_m = (1 - \delta) \log(1 - r)$  and by plugging that into (B.4.5) we get (B.4.1). In cases 2 and 3, we use that  $1 - \bar{\Phi}(x) \underset{x \rightarrow -\infty}{\sim} \frac{\phi(x)}{-x}$  to get

$$\begin{aligned} \frac{1 - P_{R,m}}{1 - P_{G,m}} &\underset{m \rightarrow \infty}{\sim} \frac{\mu_m - \bar{\Phi}^{-1}\left(\frac{\alpha}{m_0}\right)}{\mu_m - \bar{\Phi}^{-1}\left(\frac{\alpha}{m(1-r)}\right)} e^{\mu_m B_m - A_m} \\ &\underset{m \rightarrow \infty}{\sim} e^{\mu_m B_m - A_m}. \end{aligned}$$

Combining with  $\lim_{m \rightarrow \infty} \mu_m B_m - A_m = (\delta - 1) \log(1 - r)$  (in case 2) or  $\lim_{m \rightarrow \infty} \mu_m B_m - A_m = -\infty$  (case 3), we get (B.4.2) and (B.4.3).  $\square$

*Proof of Lemma B.4.1.* We start with the following inequality (Feller, 1968, Lemma 2, page 175): for all  $x > 0$ ,

$$\left(1 - \frac{1}{x^2}\right) \frac{\phi(x)}{x} \leq \Phi(x) \leq \frac{\phi(x)}{x},$$

from which we deduce that, for all  $y > 0$ ,

$$\mathbb{1}(y)\phi\left(\bar{\Phi}^{-1}(y)\right) \leq y\bar{\Phi}^{-1}(y) \leq \phi\left(\bar{\Phi}^{-1}(y)\right),$$

where  $\mathbb{1}(y) = 1 - \left(\bar{\Phi}^{-1}(y)\right)^{-2} \underset{y \rightarrow 0^+}{\rightarrow} 1$ . Next we write that

$$\begin{aligned} -2 \log(\mathbb{1}(y)) + \bar{\Phi}^{-1}(y)^2 &\geq -2 \log\left(\sqrt{2\pi}y\bar{\Phi}^{-1}(y)\right) \geq \bar{\Phi}^{-1}(y)^2 \\ o(1) + \bar{\Phi}^{-1}(y)^2 &\underset{y \rightarrow 0^+}{\geq} -2 \log(y) - \log(\bar{\Phi}^{-1}(y)^2) - \log(2\pi) \underset{y \rightarrow 0^+}{\geq} \bar{\Phi}^{-1}(y)^2, \end{aligned}$$

from which we deduce that

$$\bar{\Phi}^{-1}(y)^2 \underset{y \rightarrow 0^+}{=} 2 \log\left(\frac{1}{y}\right) - \log(\bar{\Phi}^{-1}(y)^2) - \log(2\pi) + o(1), \quad (\text{B.4.6})$$

where, using that  $\bar{\Phi}^{-1}(y)^2 \underset{y \rightarrow 0^+}{\sim} 2 \log\left(\frac{1}{y}\right)$ ,

$$\begin{aligned} -\log(\bar{\Phi}^{-1}(y)^2) &\underset{y \rightarrow 0^+}{=} -\log\left(2 \log\left(\frac{1}{y}\right) (1 + o(1))\right) \\ &\underset{y \rightarrow 0^+}{=} -\log_2\left(\frac{1}{y}\right) - \log(2) + o(1). \end{aligned}$$

Plugging that into (B.4.6), we get (B.4.4).  $\square$

# Appendix C

## Manual of package DiscreteFDR v1.0

---

### DiscreteFDR-package

*DiscreteFDR: Multiple Testing Procedures with Adaptation for Discrete Tests*

---

### Description

This package implements the [HSU], [HSD], [AHSU], [AHSD] and [HBR-lambda] procedures for discrete tests (see References).

### Details

The functions are reorganised from the reference paper in the following way. [DBH](#) (for Discrete Benjamini-Hochberg) implements [HSU] and [HSD], [ADBH](#) (the "A" stands for Adaptive) implements [AHSU] and [AHSD], and [DBR](#) (for Discrete Blanchard-Roquain) implements [HBR-lambda]. Their main arguments are a vector of raw observed p-values, and a list of the same length, which elements are the discrete supports of the CDFs of the p-values.

The function [fisher.pvalues.support](#) allows to compute such p-values and support in the framework of a Fisher's exact test of association. It has been inspired by an help page of the package [discreteMTP](#).

We also provide the [amnesia](#) data set, used in our examples and in our paper. It is basically the [amnesia](#) data set of package [discreteMTP](#), but slightly reformatted (the difference lies in column 3).

No other function of the package should be used, they are only internal functions called by the main ones.

## References

[Döhler et al. \(2018\)](#)

## Author(s)

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Other contributors:

- Sebastian Döhler [contributor]
- Etienne Roquain [contributor]

## Description

Apply the [AHSU] or [AHSD] procedure, with or without computing the critical constants, to a set of p-values and their discrete support.

## Usage

```
ADBH(pCDFlist, raw.pvalues, alpha = 0.05, direction = "su",
      ret.crit.consts = FALSE, bigMem = FALSE, verbose = TRUE)
```

## Arguments

- |             |   |
|-------------|---|
| pCDFlist    | a list of the supports of the CDFs of the p-values. Each support is represented by a vector that must be in increasing order.           |
| raw.pvalues | vector of the raw observed p-values, as provided by the end user and before matching with their nearest neighbour in the CDFs supports. |

alpha	the target FDR level, a number strictly between 0 and 1.
direction	a character string specifying whether to conduct a step-up ( <code>direction="su"</code> , by default) or step-down procedure ( <code>direction="sd"</code> ).
<code>ret.crit.consts</code>	a boolean. If TRUE, critical constants are computed and returned (this is computationally intensive).
<code>bigMem</code>	a boolean. If TRUE, the code uses matrixes and functions of the <code>apply</code> family as far as possible (faster for small number of hypotheses and support size, but slower otherwise due to memory management overhead). If FALSE, computations are done with <code>for</code> loops and chunks to conserve memory.
<code>verbose</code>	a boolean indicating if <code>msg</code> must be printed. Used when <code>bigMem=TRUE</code> , to print messages informing if in-memory computation was successful or if loops and chunks were used as fallback.

## Details

This version: 2018-02-20.

## Value

A list whose elements are:

Rejected	rejected raw p-values
Indices	indices of rejected hypotheses
Max.k	number of rejections
Alpha	maximum significance level for which a rejection occurred, that is $\text{Alpha} = \text{alpha} * \text{Max.k}/m$
<code>Critical.constants</code>	critical constants (if requested)
Adjusted	adjusted p-values (only for step-down direction).

## Examples

```
data(amnesia)
```

```
#We only keep the first 100 lines to keep the computations fast.
```

```
amnesia<-amnesia[1:100,]

#Construction of the p-values and their support
amnesia.formatted <- fisher.pvalues.support(amnesia)
raw.pvalues <- amnesia.formatted$raw
pCDFlist <- amnesia.formatted$support

ADBH.su.fast <- ADBH(pCDFlist, raw.pvalues)
ADBH.sd.fast <- ADBH(pCDFlist, raw.pvalues, direction="sd")
ADBH.su.crit <- ADBH(pCDFlist, raw.pvalues, ret.crit.consts=TRUE)
ADBH.sd.crit <- ADBH(pCDFlist, raw.pvalues, direction="sd", ret.crit.consts=TRUE)
```

---

amnesia

*Amnesia and other drug reactions in the MHRA pharmacovigilance spontaneous reporting system*

---

## Description

For each of 2446 drugs in the MHRA database (column 1), the number of cases with amnesia as an adverse event (column 2), and the number of cases with other adverse event for this drug (column 3). In total, 682648 adverse drug reactions were reported, among them 2044 cases of amnesia.

## Usage

```
data(amnesia)
```

## Format

A data frame with 2446 rows representing drugs with the following 3 columns:

**DrugName** The name of the drug.

**AmnesiaCases** Number of the amnesia cases reported for the drug.

**OtherAdverseCases** Number of other adverse drug reactions reported for the drug.

## Details

The data was collected from the Drug Analysis Prints published by the Medicines and Healthcare products Regulatory Agency (MHRA), by Heller & Gur. See references for more details.

## References

[Heller and Gur \(2011\)](#)

## Source

[Drug Analysis Prints on MHRA site](#)

---

build.stepfuns      *Building step functions from pCDFlist*

---

## Description

Creates a list of step functions out of p-value CDF supports. That is, creates the list of the CDFs. The end user should not use it.

## Usage

`build.stepfuns(pCDFlist)`

## Arguments

`pCDFlist`      a list of the supports of the CDFs of the p-values. Each support is represented by a vector that must be in increasing order.

## Details

The functions returned are the ones denoted by  $F_i$  in the reference paper, see [DiscreteFDR](#).

This version: 2017-09-09.

## Value

A list of CDFs.

## Examples

```
toyList<-list(c(0.3,0.7,1),c(0.1,0.65,1))
toyStep<-build.stepfuns(toyList)
toyStep[[1]](0.2)
toyStep[[2]](0.2)
toyStep[[1]](0.65)
toyStep[[2]](0.65)
```

DBH

*[HSU] and [HSD] procedures*

## Description

Apply the [HSU] or [HSD] procedure, with or without computing the critical constants, to a set of p-values and their discrete support.

## Usage

```
DBH(pCDFlist, raw.pvalues, alpha = 0.05, direction = "su",
    ret.crit.consts = FALSE, bigMem = FALSE, verbose = FALSE)
```

## Arguments

- pCDFlist** a list of the supports of the CDFs of the p-values. Each support is represented by a vector that must be in increasing order.
- raw.pvalues** vector of the raw observed p-values, as provided by the end user and before matching with their nearest neighbour in the CDFs supports.
- alpha** the target FDR level, a number strictly between 0 and 1.
- direction** a character string specifying whether to conduct a step-up (`direction="su"`, by default) or step-down procedure (`direction="sd"`).
- ret.crit.consts** a boolean. If TRUE, critical constants are computed and returned (this is computationally intensive).

bigMem	a boolean. If TRUE, the code uses matrixes and functions of the apply family as far as possible (faster for small number of hypotheses and support size, but slower otherwise due to memory management overhead). If FALSE, computations are done with for loops and chunks to conserve memory.
verbose	a boolean indicating if msg must be printed. Used when bigMem=TRUE, to print messages informing if in-memory computation was successful or if loops and chunks were used as fallback.

## Details

This version: 2018-02-20.

## Value

A list whose elements are:

Rejected	rejected raw p-values
Indices	indices of rejected hypotheses
Max.k	number of rejections
Alpha	maximum significance level for which a rejection occurred, that is $\text{Alpha} = \alpha * \text{Max.k}/m$
Critical.constants	critical constants (if requested)
Adjusted	adjusted p-values (only for step-down direction).

## Examples

```
data(amnesia)

#We only keep the first 100 lines to keep the computations fast.
amnesia<-amnesia[1:100,]

#Construction of the p-values and their support
amnesia.formatted <- fisher.pvalues.support(amnesia)
raw.pvalues <- amnesia.formatted$raw
pCDFlist <- amnesia.formatted$support
```

```
DBH.su.fast <- DBH(pCDFlist, raw.pvalues)
DBH.sd.fast <- DBH(pCDFlist, raw.pvalues, direction="sd")
DBH.su.crit <- DBH(pCDFlist, raw.pvalues, ret.crit.consts=TRUE)
DBH.sd.crit <- DBH(pCDFlist, raw.pvalues, direction="sd", ret.crit.consts=TRUE)
```

---

DBR*[DBR-lambda] procedure*

---

## Description

Apply the [DBR-lambda] procedure, with or without computing the critical constants, to a set of p-values and their discrete support.

## Usage

```
DBR(pCDFlist, raw.pvalues, alpha = 0.05, lambda = 0.05,
    ret.crit.consts = FALSE, bigMem = FALSE, verbose = FALSE)
```

## Arguments

- |                 |   |
|-----------------|---|
| pCDFlist        | a list of the supports of the CDFs of the p-values. Each support is represented by a vector that must be in increasing order.   |
| raw.pvalues     | vector of the raw observed p-values, as provided by the end user and before matching with their nearest neighbour in the CDFs supports.   |
| alpha           | the target FDR level, a number strictly between 0 and 1.  |
| lambda          | a number strictly between 0 and 1.  |
| ret.crit.consts | a boolean. If TRUE, critical constants are computed and returned (this is computationally intensive).   |
| bigMem          | a boolean. If TRUE, the code uses matrixes and functions of the apply family as far as possible (faster for small number of hypotheses and support size, but slower otherwise due to memory management overhead). If FALSE, computations are done with for loops and chunks to conserve memory. |

verbose a boolean indicating if msg must be printed. Used when bigMem=TRUE, to print messages informing if in-memory computation was successful or if loops and chunks were used as fallback.

## Details

This version: 2018-02-19.

### Value

A list whose elements are:

Rejected	rejected raw p-values
Indices	indices of rejected hypotheses
Max.k	number of rejections
Alpha	maximum significance level for which a rejection occurred, that is $\text{Alpha} = \alpha * \text{Max.k}/m$
<b>Critical.constants</b>	
	critical constants (if requested)
Adjusted	adjusted p-values
Lambda	value of lambda.

## Examples

```
data(amnesia)

#We only keep the first 100 lines to keep the computations fast.
amnesia<-amnesia[1:100,]

#Construction of the p-values and their support
amnesia.formatted <- fisher.pvalues.support(amnesia)
raw.pvalues <- amnesia.formatted$raw
pCDFlist <- amnesia.formatted$support

DBR.su.fast <- DBR(pCDFlist, raw.pvalues)
DBR.su.crit <- DBR(pCDFlist, raw.pvalues, ret.crit.consts=TRUE)
```

---

**fisher.pvalues.support**

*Computing discrete p-values and their support for Fisher's exact tests*

---

**Description**

Computes discrete raw p-values and their support for the test of no association between two categorical variables in 2 x 2 contingency tables using Fisher's exact tests.

**Usage**

```
fisher.pvalues.support(counts, alternative = "greater")
```

**Arguments**

- counts** a data frame of 3 columns and any number of lines, each line being an item for which we want to perform a test. The first column is the name of the item, the second is the count of associations between the item and the condition, the third is the count of no associations.
- alternative** same argument as in [fisher.test](#).

**Details**

The code for this function is inspired from the example in the help page of [p.discrete.adjust](#).

See the Wikipedia article about Fisher's exact test, paragraph Example, for a good depiction of what the code does for each possible value of alternative.

This version: 2018-03-20.

**Value**

A list of two elements:

- raw** raw discrete p-values
- support** a list of the supports of the CDFs of the p-values. Each support is represented by a vector in increasing order.

## References

[Wikipedia \(2018\)](#)

## See Also

[p.discrete.adjust](#), [fisher.test](#)

## Examples

```
data(amnesia)

#We only keep the first 100 lines to keep the computations fast.
amnesia<-amnesia[1:100,]

#Construction of the p-values and their support
amnesia.formatted <- fisher.pvalues.support(amnesia)
raw.pvalues <- amnesia.formatted$raw
pCDFlist <- amnesia.formatted$support
```

---

## Description

Kernel functions that transform observed p-values or their support according to [AHSU] and [AHSD]. The output is used by [ADBH](#). Additionally, `kernel.ADBH.crit` computes and returns the critical constants. The end user should not use them.

## Usage

```
kernel.ADBH.crit(msg = "", stepf, pv.numer, pv.denom, alpha, sorted.pv,
  bigMem = FALSE, verbose = TRUE)

kernel.ADBH.fast(msg = "", stepf, pv.numer, pv.denom, bigMem = FALSE,
  verbose = TRUE)
```

## Arguments

<code>msg</code>	a character string to be displayed if <code>verbose=TRUE</code> .
<code>stepf</code>	a list of the CDFs under the null hypothesis of each p-value.
<code>pv.numer</code>	a numeric vector. Contains all values of the p-values supports if we search for the critical constants. If not, contains only the observed p-values. Must be in increasing order.
<code>pv.denom</code>	a numeric vector. Identical to <code>pv.numer</code> for a step-down procedure. Equals <code>c.m</code> for a step-up procedure.
<code>alpha</code>	the target FDR level, a number strictly between 0 and 1.
<code>sorted.pv</code>	a vector of observed p-values, in increasing order.
<code>bigMem</code>	a boolean. If TRUE, the code uses matrixes and functions of the apply family as far as possible (faster for small number of hypotheses and support size, but slower otherwise due to memory management overhead). If FALSE, computations are done with for loops and chunks to conserve memory.
<code>verbose</code>	a boolean indicating if <code>msg</code> must be printed. Used when <code>bigMem=TRUE</code> , to print messages informing if in-memory computation was successful or if loops and chunks were used as fallback.

## Details

When computing critical constants under step-down, that is, when using `kernel.ADBH.crit` with `pv.numer=pv.denom`, we still need to get transformed p-values to compute the adjusted p-values. Also, note that here the critical constants are computed by the `kernel` function and not by the principal function `ADBH`, contrary to what happens with `DBH`. This is why `sorted.pv` is needed.

This version: 2018-02-20.

## Value

For `kernel.ADBH.crit`, a list which elements are:

`crit.consts` a vector of critical constants

`pval.transf` a vector of transformed p-values (only for step-down direction).

For `kernel.ADBH.fast`, a vector of transformed p-values.

## See Also

[ADBH](#), [DiscreteFDR](#), [kernel.DBH](#), [DBH](#)

## Examples

```
data(amnesia)

#We only keep the first 100 lines to keep the computations fast.
amnesia<-amnesia[1:100,]

#Construction of the p-values and their support
amnesia.formatted <- fisher.pvalues.support(amnesia)
raw.pvalues <- amnesia.formatted$raw
pCDFlist <- amnesia.formatted$support

m <- length(raw.pvalues)
alpha <- 0.05

#Compute the step functions from the supports
stepf <- build.stepfuns(pCDFlist)

#We stay in a step-down context, where pv.numer=pv.denom,
#for the sake of simplicity

#If not searching for critical constants, we use only the observed p-values
sorted.pvals <- sort(raw.pvalues)
y <- kernel.ADBH.fast("", stepf, sorted.pvals, sorted.pvals)

#If searching for critical constants, we use (almost) the complete support
pv.list.all <- unique(sort(as.numeric(unlist(pCDFlist))))
# apply the shortcut drawn from Lemma 4, that is
# c.1 >= the effective critical value associated to alpha/(m + alpha)
pv.list<-short.eff(pv.list.all, alpha/(m + alpha) )
# then re-add the observed p-values (needed to compute the adjusted p-values),
# because we may have removed some of them the shortcut
pv.list <- sort(unique(c(pv.list, sorted.pvals)))
# compute transformed support
y <- kernel.ADBH.crit("", stepf, pv.list, pv.list, alpha, sorted.pvals)
```

---

```

crit.constants <- y$crit.consts
#The following exists only for step-down direction
transformed.pvalues <- y$pval.transf

```

---

**kernel.DBH***Kernel functions for DBH*

## Description

Kernel functions that transform observed p-values or their support according to [HSU] and [HSD]. The output is used by [DBH](#). The end user should not use it.

## Usage

```
kernel.DBH(msg = "", stepf, pv.numer, pv.denom, bigMem = FALSE,
verbose = TRUE)
```

## Arguments

<code>msg</code>	a character string to be displayed if <code>verbose=TRUE</code> .
<code>stepf</code>	a list of the CDFs under the null hypothesis of each p-value.
<code>pv.numer</code>	a numeric vector. Contains all values of the p-values supports if we search for the critical constants. If not, contains only the observed p-values. Must be in increasing order.
<code>pv.denom</code>	a numeric vector. Identical to <code>pv.numer</code> for a step-down procedure. Equals <code>c.m</code> for a step-up procedure.
<code>bigMem</code>	a boolean. If <code>TRUE</code> , the code uses matrixes and functions of the <code>apply</code> family as far as possible (faster for small number of hypotheses and support size, but slower otherwise due to memory management overhead). If <code>FALSE</code> , computations are done with <code>for</code> loops and chunks to conserve memory.
<code>verbose</code>	a boolean indicating if <code>msg</code> must be printed. Used when <code>bigMem=TRUE</code> , to print messages informing if in-memory computation was successful or if loops and chunks were used as fallback.

## Details

This version: 2017-09-14.

### Value

A vector of transformed p-values.

### See Also

[DBH](#), [DiscreteFDR](#)

### Examples

```
data(amnesia)

#We only keep the first 100 lines to keep the computations fast.
amnesia<-amnesia[1:100,]

#Construction of the p-values and their support
amnesia.formatted <- fisher.pvalues.support(amnesia)
raw.pvalues <- amnesia.formatted$raw
pCDFlist <- amnesia.formatted$support

m <- length(raw.pvalues)
alpha <- 0.05

#Compute the step functions from the supports
stepf <- build.stepfuns(pCDFlist)

#We stay in a step-down context, where pv.numer=pv.denom,
#for the sake of simplicity

#If not searching for critical constants, we use only the observed p-values
sorted.pvals <- sort(raw.pvalues)
y <- kernel.DBH("", stepf, sorted.pvals, sorted.pvals)

#If searching for critical constants, we use (almost) the complete support
pv.list.all <- unique(sort(as.numeric(unlist(pCDFlist))))
# apply the shortcut drawn from Lemma 3, that is
```

```
# c.1 >= the effective critical value associated to (alpha/m)/(1 + alpha/m)
pv.list<-short.eff(pv.list.all, (alpha/m)/(1 + alpha/m) )
# then re-add the observed p-values (needed to compute the adjusted p-values),
# because we may have removed some of them the shortcut
pv.list <- sort(unique(c(pv.list, sorted.pvals)))
# compute transformed support
y <- kernel.DBH("", stepf, pv.list, pv.list)
```

---

kernel.DBR*Kernel functions for DBR*

---

## Description

Kernel functions that transform observed p-values or their support according to [DBR-lambda]. The output is used by [DBR](#). Additionally, `kernel.DBR.crit` computes and returns the critical constants. The end user should not use them.

## Usage

```
kernel.DBR.crit(msg = "", stepf, pv.numer, lambda, alpha, sorted.pv,
  bigMem = FALSE, verbose = TRUE)

kernel.DBR.fast(msg = "", stepf, pv.numer, lambda, bigMem = FALSE,
  verbose = TRUE)
```

## Arguments

<code>msg</code>	a character string to be displayed if <code>verbose=TRUE</code> .
<code>stepf</code>	a list of the CDFs under the null hypothesis of each p-value.
<code>pv.numer</code>	a numeric vector. Contains all values of the p-values supports if we search for the critical constants. If not, contains only the observed p-values. Must be in increasing order.
<code>lambda</code>	a number strictly between 0 and 1.
<code>alpha</code>	the target FDR level, a number strictly between 0 and 1.
<code>sorted.pv</code>	a vector of observed p-values, in increasing order.

bigMem	a boolean. If TRUE, the code uses matrixes and functions of the apply family as far as possible (faster for small number of hypotheses and support size, but slower otherwise due to memory management overhead). If FALSE, computations are done with for loops and chunks to conserve memory.
verbose	a boolean indicating if msg must be printed. Used when bigMem=TRUE, to print messages informing if in-memory computation was successful or if loops and chunks were used as fallback.

## Details

When computing critical constants, that is, when using `kernel.DB.R.crit`, we still need to get transformed p-values to compute the adjusted p-values. Also, note that here the critical constants are computed by the kernel function and not by the principal function `DBR`, contrary to what happens with `DBH`. This is why `sorted.pv` is needed.

This version: 2018-02-20.

## Value

For `kernel.DB.R.crit`, a list which elements are:

<code>crit consts</code>	critical constants
<code>pval.transf</code>	transformed p-values
<code>m.lambda</code>	last index of observed p-values such that $\max_i F_i(p) \leq \lambda$ , this needs to be passed to <code>DBR</code> to compute adjusted p-values).

For `kernel.DB.R.fast`, a vector of transformed p-values.

## See Also

[DBR](#), [DiscreteFDR](#), [kernel.DBH](#), [DBH](#)

## Examples

```
data(amnesia)
```

```
#We only keep the first 100 lines to keep the computations fast.  
amnesia<-amnesia[1:100,]
```

```

#Construction of the p-values and their support
amnesia.formatted <- fisher.pvalues.support(amnesia)
raw.pvalues <- amnesia.formatted$raw
pCDFlist <- amnesia.formatted$support

m <- length(raw.pvalues)
alpha <- 0.05
lambda <- 0.05

#Compute the step functions from the supports
stepf <- build.stepfuns(pCDFlist)

#If not searching for critical constants, we use only the observed p-values
sorted.pvals <- sort(raw.pvalues)
y <- kernel.DBR.fast("", stepf, sorted.pvals, lambda)

#If searching for critical constants, we use (almost) the complete support
pv.list.all <- unique(sort(as.numeric(unlist(pCDFlist))))
# apply the shortcut drawn from Corollary 3, that is
# c.1 >= the effective critical value associated to min((1 - lambda) * alpha/m , lambda)
pv.list<-short.eff(pv.list.all, min((1 - lambda) * alpha/m , lambda) )
# then re-add the observed p-values (needed to compute the adjusted p-values),
# because we may have removed some of them the shortcut
pv.list <- sort(unique(c(pv.list, sorted.pvals)))
# compute transformed support
y <- kernel.DBR.crit("", stepf, pv.list, lambda, alpha, sorted.pvals)
crit.constants <- y$crit.consts
transformed.pvalues <- y$pval.transf
last.index <- y$m.lambda

```

## Description

Constructs the observed p-values from the raw observed p-values, by rounding them to their nearest neighbour matching with the supports of their respective CDFs (as in function `p.discrete.adjust` of package `discreteMTP`). The end user should not use it.

## Usage

```
match.pvals(pCDFlist, raw.pvalues)
```

## Arguments

- pCDFlist a list of the supports of the CDFs of the p-values. Each support is represented by a vector that must be in increasing order.
- raw.pvalues vector of the raw observed p-values, as provided by the end user and before matching with their nearest neighbour in the CDFs supports.

## Details

Well computed raw p-values should already belong to their respective CDF support. So this function is called at the beginning of [DBH](#), [ADBH](#), and [DBR](#), just in case raw p-values are biased.

For each raw p-value that needs to be rounded, a warning is issued.

This version: 2017-08-16.

## Value

A vector where each raw p-value has been replaced by its nearest neighbour.

## See Also

[DBH](#), [ADBH](#), [DBR](#)

## Examples

```
toyList<-list(c(0.3,0.7,1),c(0.1,0.65,1))
toyRaw1<-c(0.3,0.65)
match.pvals(toyList,toyRaw1)
toyRaw2<-c(0.31,0.6)
match.pvals(toyList,toyRaw2)
```

---

short.eff

*Shortcuts for critical values computation*

---

## Description

Extracts all values from a sorted vector that are greater than or equal to the effective critical value associated to a threshold.

## Usage

```
short.eff(sorted.num, t)
```

## Arguments

sorted.num a numeric vector in increasing order.

t the threshold, a number between 0 and 1.

## Details

The effective critical value associated to t is the largest value of sorted.num that is less than or equal to t.

This version: 2018-02-12.

## Value

A subvector of sorted.num.

## Examples

```
x<-c(0.1,0.2,0.3,0.4)
short.eff(x,0.2)
short.eff(x,0.35)
```

## Appendix D

# Fixation probability in a two-locus intersexual selection model

This chapter presents a joint work with Sabin Lessard published in *Theoretical population biology* ([Durand and Lessard, 2016](#)). Some minor changes due to formatting exist between the two versions.

**Abstract** We study a two-locus model of intersexual selection in a finite haploid population reproducing according to a discrete-time Moran model with a trait locus expressed in males and a preference locus expressed in females. We show that the probability of ultimate fixation of a single mutant allele for a male ornament introduced at random at the trait locus given any initial frequency state at the preference locus is increased by weak intersexual selection and recombination, weak or strong. Moreover, this probability exceeds the initial frequency of the mutant allele even in the case of a costly male ornament if intersexual selection is not too weak. On the other hand, the probability of ultimate fixation of a single mutant allele for a female preference towards a male ornament introduced at random at the preference locus is increased by weak intersexual selection and weak recombination if the female preference is not costly, and is strong enough in the case of a costly male ornament. The analysis relies on an extension of the ancestral recombination-selection graph for samples of haplotypes to take into account events of intersexual selection, while the symbolic calculation of the fixation probabilities is made possible in a reasonable time by an optimizing algorithm.

## D.1 Introduction

[Darwin \(1871\)](#) considered sexual selection to be an evolutionary process as important as natural selection. The concept arises from the observation that some weapons or ornaments known as secondary sexual traits that have evolved in the animal kingdom, as antlers in deer or tails and colors in birds, appear not to be advantageous for survival or even to be deleterious. A possible explanation is that these traits enhance the reproductive success of their carriers either by deterring rivals of the same sex, usually males (intrasexual selection), or by making them more attractive to individuals of the opposite sex, usually females (intersexual selection). These two forms of sexual selection may be responsible for a large amount of gender differences in structure or appearance in nature.

This paper concerns intersexual selection. As for intrasexual selection, let us just mention that it has been studied, e.g., by applying game theory to evolution in the context of conflicts between males for access to females and reproduction with the key concept of evolutionarily stable strategy ([Maynard Smith, 1982](#)).

[Fisher \(1930, 1958\)](#) described the runaway process by which a preferred conspicuous trait in one sex and a preference for this trait in the other sex could evolve in tandem with the preference being genetically transmitted along with the preferred trait. Taking a plumage character as an example, [Fisher \(1930, p. 137\)](#) writes: *Moreover, as long as there is a net advantage in favour of further plumage development, there will also be a net advantage in favour of giving to it a more decided preference.* This runaway mechanism could reinforce or accelerate phenotypic difference and speciation.

With the above notable exception, however, sexual selection involving mate choice in one sex, most often the female but not always (see, e.g., [Edward and Chapman, 2011](#)), was largely disregarded by most of the leading evolutionary biologists up to the mid 20th century (see, e.g., [Maynard Smith, 2000](#)).

[O'Donald \(1962, 1980\)](#) was one of the first to propose, and study numerically, two-locus models of sexual selection with one locus coding for trait variation in males and one locus influencing mating preferences in females. [Lande \(1981\)](#) analysed models in the case of polygenic inheritance and [Kirkpatrick \(1982\)](#) exact haploid population genetic models. They both showed that, in the absence of direct selection on female preferences, these can evolve as a correlated response to changes in the male trait associated with positive linkage disequilibrium. Moreover, in the framework of an infinite population, they exhibited curves of stable equilibria at which neutral preferences for less viable traits can counterbalance the deleterious effects of the traits. The evolutionary outcome along the line of stable equilibria is left to weaker forces such as genetic drift. The preference

function (see, e.g., Charlesworth and Charlesworth, 1981; Seger, 1985; Carrier, 1995) as well as the recombination rate (see, e.g., Kirkpatrick, 1982; Barton and Turelli, 1991) seem to have little qualitative effects on the conclusions.

Similar conclusions for diploid populations with some discrepancies due to dominance at the trait locus have been reached from simulations (Heisler and Curtsinger, 1990), local stability analyses near fixation either at the trait locus (Gomulkiewicz and Hastings, 1990) or the preference locus (Otto, 1991), as well as quasi-linkage equilibrium analyses away from fixation boundaries (Greenspoon and Otto, 2009).

With selection on female preferences, the line of stable equilibria may collapse to a single, stable point and lead to a balance between selection and drift in finite populations under recurrent mutation. This may be the case for instance with a preference-dependent risk that females remain unmated as supported by simulations of polygenic models (De Jong and Sabelis, 1991). More simulations have shown that adding a cost to female preferences may restrict, but not eliminate, the possibility of ornament diversification and speciation (Mead and Arnold, 2004; Uyeda et al., 2009; Bergen et al., 2012). One of the surprising consequences of sexual selection may be to create a positive correlation between the female preference and the progeny sex ratio (Fawcett et al., 2007).

Note also that there may be a benefit associated with female preferences which is to enhance species recognition and, therefore, fertility (see, e.g., Carrier, 1995). Indeed, sexual preference of females for given traits in males is akin to assortative mating and, combined with drift, can help answer questions related to species divergence (Otto et al., 2008; Servedio, 2011).

Recently, Miller (2000) drew attention to some of Darwin's neglected ideas about human behaviours not clearly connected to survival, such as humour, creativity, and some forms of altruism, that may have been favoured through sexual selection. See Puts (2010) for more references on this subject.

As for a recent review of mathematical models of sexual selection, we refer to Kuijper et al. (2012).

In this paper, we consider a two-locus model of intersexual selection in a finite haploid population with a trait locus expressed in males and a preference locus expressed in females. We use a discrete-time Moran model so that, at each time step, there is one individual produced according to the types of the parents chosen to reproduce and one individual replaced according to the type of the individual chosen to be replaced. We study the probability of fixation of a single mutant introduced at the trait locus given any initial frequency state at the preference locus, and the other way around. We consider the case of a preference for a deleterious trait and the case of a preference for a beneficial trait,

but describe the method at length only in the former. We deduce the leading effects of weak selection and weak recombination using an ancestral recombination-selection graph in the limit of a large population size. This extends a similar approach for a two-locus viability selection model to study the Hill-Robertson effect in favor of recombination (Lessard and Kermany, 2012). The leading effects of weak selection under the assumption of free recombination, actually of any fixed recombination rate as the population size goes to infinity so that recombination and selection events occur at different timescales backwards in time, are also studied. We provide an algorithm which strikingly reduces the time of symbolic calculation.

## D.2 Model

Suppose a large but finite population of  $N$  haploid individuals. The population is assumed to be monoecious (hermaphroditic) so that each individual can act as either the male or the female in sexual reproduction. In particular, an individual can reproduce with itself. Consider two genes at two different loci, each one with two possible alleles. The first gene at a trait locus, denoted by  $T$ , has an effect on viability. It is assumed that a mutant allele  $T_2$  decreases the viability of a male carrying it compared to a resident allele  $T_1$ .

On the other hand, the second gene at the other locus, denoted by  $P$ , codes for sexual preference. It is assumed that a female carrying a mutant allele  $P_2$  shows a preference for males carrying the mutant allele  $T_2$ , while a female carrying a resident allele  $P_1$  does not show any preference. Therefore, the individuals can be of four possible haplotypes, called types for simplicity:  $(T_1P_1)$ ,  $(T_1P_2)$ ,  $(T_2P_1)$  and  $(T_2P_2)$ , or in vector notation  $(1, 1)$ ,  $(1, 2)$ ,  $(2, 1)$  and  $(2, 2)$ , respectively. These are represented by **1**, **2**, **3** and **4**, respectively.

We use a discrete-time Moran model (Moran, 1958). At each time step, two individuals are sampled at random with replacement to mate and to produce an offspring (hence the possibility of reproduction of an individual with itself). The first one is assumed to act as the female and the second one as the male. The sampled individuals reproduce with some probability depending on their types. Actually, a  $P_2$ -female reproduces with a  $T_2$ -male with probability 1 and with a  $T_1$ -male with probability  $1 - As$ . If the female carries allele  $P_1$ , however, reproduction takes place with probability  $1 - \frac{As}{2}$  whatever the type of the male is. Therefore, there is a reproduction cost associated not only with a female being choosy that depends on the type of the male but also with a female not being choosy irrespective of this type.

Here,  $A > 0$  represents a coefficient of intersexual selection with respect to an intensity of selection  $s > 0$ . Weak selection in a large population is modeled by assuming

$$s = \frac{\sigma}{N},$$

where  $\sigma > 0$  represents a population-scaled intensity.

If reproduction takes place, then the type of the offspring produced depends on the parental types and the recombination rate  $r$ . With probability  $1 - r$  the type of the offspring is one of the two parental haplotypes chosen at random (probability  $\frac{1}{2}$  for each), while it is one of the two recombinant haplotypes chosen at random (probability  $\frac{1}{2}$  for each) with the complementary probability  $r$ . Weak recombination in a large population is modeled by assuming

$$r = \frac{R\sigma}{N}, \quad (\text{D.2.1})$$

for some coefficient of recombination  $R > 0$ . Note that weak recombination is scaled at the same order of magnitude as weak selection.

If the two individuals chosen to reproduce does not actually reproduce, the population state does not change. If they produce an offspring, then an individual is sampled at random in the population to be replaced by the offspring. The individual is actually replaced with some probability depending on its haplotype. Replacement occurs with probability

$$1 - cs = 1 - \frac{c\sigma}{N}, \quad (\text{D.2.2})$$

where  $c \geq 0$  is a coefficient of viability selection that depends on the type of the individual to be replaced. In this study we set  $c_1 = c_2 = 1$  and  $c_3 = c_4 = 0$ . This models a selective advantage in favor of allele  $T_1$ . If the individual chosen to be replaced is not actually replaced, then the offspring does not survive so that the population state does not change.

Let  $x_{\mathbf{i}}(\tau)$  be the frequency of type  $\mathbf{i}$  at time step  $\tau \geq 0$  and define the type frequency vector  $\mathbf{x}(\tau) = (x_1(\tau), x_2(\tau), x_3(\tau), x_4(\tau))$ . Initially (time step 0), let allele  $T_2$  be introduced as a mutant at the first locus in a single individual of the population (hence with an initial frequency  $N^{-1}$ ), where alleles  $P_2$  and  $P_1$  are currently segregating at the second locus with frequencies  $x$  and  $1 - x$ , respectively. Therefore, the initial frequencies of the haplotypes  $(T_1P_1)$ ,  $(T_1P_2)$ ,  $(T_2P_1)$  and  $(T_2P_2)$  are given respectively either by

$$x_1(0) = 1 - x, \quad x_2(0) = x - \frac{1}{N}, \quad x_3(0) = 0, \quad x_4(0) = \frac{1}{N}, \quad (\text{D.2.3})$$

or by

$$x_1(0) = 1 - x - \frac{1}{N}, \quad x_2(0) = x, \quad x_3(0) = \frac{1}{N}, \quad x_4(0) = 0. \quad (\text{D.2.4})$$

If the mutant allele  $T_2$  arises in an individual chosen at random, then the former event has probability  $x$  and the latter event probability  $1 - x$ . We focus in the following sections on the probability of ultimate fixation of  $T_2$  under these assumptions.

Note that the probability of ultimate fixation of  $P_2$  introduced as a single mutant at the second locus while  $T_2$  and  $T_1$  are already segregating at the first locus with given frequencies can be studied in a similar way. The assumption that the preferred trait  $T_2$  is beneficial instead of being deleterious can also be analogously dealt with. Only the results are stated in these cases in Section D.6.

Finally, the analysis under the assumption of free recombination which corresponds to the condition  $r = 1/2$ , and actually of any fixed recombination rate  $r$  in the limit of a large population size which corresponds to strong recombination, is slightly different since it involves two timescales, a fast one for recombination and a slow one for selection. Some details and results for this case are given in Appendix D.E and Section D.6.

### D.3 Fixation probability

From time step  $\tau \geq 0$  to time step  $\tau + 1$ , the frequency  $x_i(\tau)$  increases by  $N^{-1}$  if an offspring of type  $\mathbf{i}$  is produced and an individual of type different from  $\mathbf{i}$  is replaced by the offspring. For  $\mathbf{i} = 4$ , for instance, which corresponds to haplotype  $(T_2P_2)$ , we list below the probabilities for a female of type  $\mathbf{j}$  and a male of type  $\mathbf{k}$  to mate and to produce an offspring, and then for this offspring to be of type  $\mathbf{4}$ , respectively.

$x_4(\tau)x_4(\tau)$	1	1
$x_3(\tau)x_4(\tau)$	$1 - \frac{A\sigma}{2N}$	$\frac{1}{2}$
$x_4(\tau)x_3(\tau)$	1	$\frac{1}{2}$
$x_2(\tau)x_4(\tau)$	1	$\frac{1}{2}$
$x_4(\tau)x_2(\tau)$	$1 - \frac{A\sigma}{N}$	$\frac{1}{2}$
$x_2(\tau)x_3(\tau)$	1	$\frac{R\sigma}{2N}$
$x_3(\tau)x_2(\tau)$	$1 - \frac{A\sigma}{2N}$	$\frac{R\sigma}{2N}$
$x_1(\tau)x_4(\tau)$	$1 - \frac{A\sigma}{2N}$	$\frac{1}{2} \left(1 - \frac{R\sigma}{N}\right)$
$x_4(\tau)x_1(\tau)$	$1 - \frac{A\sigma}{N}$	$\frac{1}{2} \left(1 - \frac{R\sigma}{N}\right)$

Moreover, an individual of type  $\mathbf{j}$  is chosen to be replaced with probability  $x_{\mathbf{j}}(\tau)$  and then the replacement occurs with probability  $(1 - c_{\mathbf{j}}\sigma N^{-1})$  for  $\mathbf{j} = \mathbf{1}, \mathbf{2}, \mathbf{3}$ . Therefore, the conditional probability that  $x_4(\tau)$  increases by  $N^{-1}$  is

$$\begin{aligned}
& \mathbb{P} \left( x_4(\tau + 1) = x_4(\tau) + \frac{1}{N} \mid \mathbf{x}(\tau) \right) \\
&= \left( \left(1 - \frac{R\sigma}{N}\right) \left(1 - \frac{3A\sigma}{4N}\right) x_1(\tau)x_4(\tau) + \frac{R\sigma}{N} \left(1 - \frac{A\sigma}{4N}\right) x_2(\tau)x_3(\tau) \right. \\
&\quad \left. + \left(1 - \frac{A\sigma}{2N}\right) x_2(\tau)x_4(\tau) + \left(1 - \frac{A\sigma}{4N}\right) x_3(\tau)x_4(\tau) + x_4(\tau)^2 \right) \\
&\quad \times \left( \left(1 - \frac{c_1\sigma}{N}\right) x_1(\tau) + \left(1 - \frac{c_2\sigma}{N}\right) x_2(\tau) + \left(1 - \frac{c_3\sigma}{N}\right) x_3(\tau) \right). \tag{D.3.1}
\end{aligned}$$

Likewise, the conditional probability that  $x_4(\tau)$  decreases by  $N^{-1}$  is

$$\begin{aligned}
& \mathbb{P}\left(x_4(\tau+1) = x_4(\tau) - \frac{1}{N} \mid \mathbf{x}(\tau)\right) \\
&= \left( \left(1 - \frac{A\sigma}{2N}\right)x_1(\tau)^2 + 2\left(1 - \frac{3A\sigma}{4N}\right)x_1(\tau)x_2(\tau) + 2\left(1 - \frac{A\sigma}{2N}\right)x_1(\tau)x_3(\tau) \right. \\
&\quad + \left(1 + \frac{R\sigma}{N}\right)\left(1 - \frac{3A\sigma}{4N}\right)x_1(\tau)x_4(\tau) + \left(1 - \frac{A\sigma}{N}\right)x_2(\tau)^2 \\
&\quad + \left(2 - \frac{R\sigma}{N}\right)\left(1 - \frac{A\sigma}{4N}\right)x_2(\tau)x_3(\tau) + \left(1 - \frac{A\sigma}{2N}\right)x_2(\tau)x_4(\tau) \\
&\quad + \left(1 - \frac{A\sigma}{2N}\right)x_3(\tau)^2 + \left(1 - \frac{A\sigma}{4N}\right)x_3(\tau)x_4(\tau) \Big) \\
&\quad \times \left(1 - \frac{c_4\sigma}{N}\right)x_4(\tau). \tag{D.3.2}
\end{aligned}$$

For  $\mathbf{i} = \mathbf{3}$  the corresponding conditional probabilities are

$$\begin{aligned}
& \mathbb{P}\left(x_3(\tau+1) = x_3(\tau) + \frac{1}{N} \mid \mathbf{x}(\tau)\right) \\
&= \left( \left(1 - \frac{A\sigma}{2N}\right)x_1(\tau)x_3(\tau) + \frac{R\sigma}{N}\left(1 - \frac{3A\sigma}{4N}\right)x_1(\tau)x_4(\tau) \right. \\
&\quad + \left(1 - \frac{R\sigma}{N}\right)\left(1 - \frac{A\sigma}{4N}\right)x_2(\tau)x_3(\tau) \\
&\quad + \left(1 - \frac{A\sigma}{2N}\right)x_3(\tau)^2 + \left(1 - \frac{A\sigma}{4N}\right)x_3(\tau)x_4(\tau) \Big) \\
&\quad \times \left( \left(1 - \frac{c_1\sigma}{N}\right)x_1(\tau) + \left(1 - \frac{c_2\sigma}{N}\right)x_2(\tau) + \left(1 - \frac{c_4\sigma}{N}\right)x_4(\tau) \right) \tag{D.3.3}
\end{aligned}$$

and

$$\begin{aligned}
& \mathbb{P}\left(x_3(\tau+1) = x_3(\tau) - \frac{1}{N} \mid \mathbf{x}(\tau)\right) \\
&= \left( \left(1 - \frac{A\sigma}{2N}\right)x_1(\tau)^2 + 2\left(1 - \frac{3A\sigma}{4N}\right)x_1(\tau)x_2(\tau) + \left(1 - \frac{A\sigma}{2N}\right)x_1(\tau)x_3(\tau) \right. \\
&\quad + \left(2 - \frac{R\sigma}{N}\right)\left(1 - \frac{3A\sigma}{4N}\right)x_1(\tau)x_4(\tau) + \left(1 - \frac{A\sigma}{N}\right)x_2(\tau)^2 \\
&\quad + \left(1 + \frac{R\sigma}{N}\right)\left(1 - \frac{A\sigma}{4N}\right)x_2(\tau)x_3(\tau) + 2\left(1 - \frac{A\sigma}{2N}\right)x_2(\tau)x_4(\tau) \\
&\quad + \left(1 - \frac{A\sigma}{4N}\right)x_3(\tau)x_4(\tau) + x_4(\tau)^2 \Big) \\
&\quad \times \left(1 - \frac{c_3\sigma}{N}\right)x_3(\tau). \tag{D.3.4}
\end{aligned}$$

The frequency of allele  $T_2$  represented by  $x_{T_2}(\tau) = x_3(\tau) + x_4(\tau)$  has a conditional expected change given by

$$\mathbb{E}(\Delta x_{T_2}(\tau) \mid \mathbf{x}(\tau)) = \mathbb{E}(\Delta x_3(\tau) \mid \mathbf{x}(\tau)) + \mathbb{E}(\Delta x_4(\tau) \mid \mathbf{x}(\tau)), \quad (\text{D.3.5})$$

where

$$\begin{aligned} \mathbb{E}(\Delta x_i(\tau) \mid \mathbf{x}(\tau)) &= \frac{1}{N} \mathbb{P}\left(x_i(\tau+1) = x_i(\tau) + \frac{1}{N} \mid \mathbf{x}(\tau)\right) \\ &\quad - \frac{1}{N} \mathbb{P}\left(x_i(\tau+1) = x_i(\tau) - \frac{1}{N} \mid \mathbf{x}(\tau)\right) \end{aligned} \quad (\text{D.3.6})$$

is the conditional expected value of the change  $\Delta x_i(\tau) = x_i(\tau+1) - x_i(\tau)$  in the frequency of type  $i = 1, 2, 3, 4$ . This leads to

$$\mathbb{E}(\Delta x_{T_2}(\tau) \mid \mathbf{x}(\tau)) = \frac{2}{N^2} \sum_{i,j,k} Q_{i,j,k} x_i(\tau) x_j(\tau) x_k(\tau). \quad (\text{D.3.7})$$

Here, the sum is over all triplets of types  $(i, j, k)$  with  $i \leq j \leq k$ . Moreover, ignoring terms of order  $N^{-1}$ , the coefficients  $Q_{i,j,k}$  are given by

$$\begin{aligned} Q_{1,1,1} &= 0 & Q_{1,1,2} &= 0 \\ Q_{1,1,3} &= \frac{c_3 - c_1}{2} \sigma & Q_{1,1,4} &= -\frac{A + 4c_1 - 4c_4}{8} \sigma \\ Q_{1,2,2} &= 0 & Q_{1,2,3} &= \frac{3A - 4c_1 - 4c_2 + 8c_3}{8} \sigma \\ Q_{1,2,4} &= \frac{A - 4c_1 - 4c_2 + 8c_4}{8} \sigma & Q_{1,3,3} &= \frac{c_3 - c_1}{2} \sigma \\ Q_{1,3,4} &= \frac{3A - 8c_1 + 4c_3 + 4c_4}{8} \sigma & Q_{1,4,4} &= \frac{3A - 4c_1 + 4c_4}{8} \sigma \\ Q_{2,2,2} &= 0 & Q_{2,2,3} &= \frac{3A - 4c_2 + 4c_3}{8} \sigma \\ Q_{2,2,4} &= \frac{A - 2c_2 + 2c_4}{4} \sigma & Q_{2,3,3} &= -\frac{A + 4c_2 - 4c_3}{8} \sigma \\ Q_{2,3,4} &= \frac{A - 8c_2 + 4c_3 + 4c_4}{8} \sigma & Q_{2,4,4} &= \frac{A - 2c_2 + 2c_4}{4} \sigma \\ Q_{3,3,3} &= 0 & Q_{3,3,4} &= 0 \\ Q_{3,4,4} &= 0 & Q_{4,4,4} &= 0 \end{aligned} \quad (\text{D.3.8})$$

Note that these leading terms depend only on the selection parameters.

The Markov chain  $(\mathbf{x}(\tau))_{\tau \geq 0}$  has four absorbing states, namely  $\mathbf{e}_1 = (1, 0, 0, 0)$ ,  $\mathbf{e}_2 = (0, 1, 0, 0)$ ,  $\mathbf{e}_3 = (0, 0, 1, 0)$  and  $\mathbf{e}_4 = (0, 0, 0, 1)$ , corresponding to fixation of types

$(T_1, P_1)$ ,  $(T_1, P_2)$ ,  $(T_2, P_1)$  and  $(T_2, P_2)$ , respectively. All other states which are in the form  $\mathbf{y} = (y_1, y_2, y_3, y_4)$  with  $y_1, y_2, y_3, y_4$  being multiples of  $N^{-1}$  that sum up to 1, are transient. An ergodic theorem (see, e.g., [Karlin and Taylor, 1975](#)) states that  $(\mathbf{x}(\tau))_{\tau \geq 0}$  converges to the four absorbing states. Actually, the probability of transition from state  $\mathbf{x}$  at time step 0 to state  $\mathbf{y}$  at time step  $\tau$  satisfies

$$P_{\mathbf{xy}}(\tau) = \mathbb{P}(\mathbf{x}(\tau) = \mathbf{y} \mid \mathbf{x}(0) = \mathbf{x}) \rightarrow P_{\mathbf{xy}}(\infty), \quad (\text{D.3.9})$$

as  $\tau \rightarrow \infty$ , with  $P_{\mathbf{xy}}(\infty) \neq 0$  only if  $\mathbf{y}$  is absorbing. Here,  $P_{\mathbf{xy}}(\infty)$  represents the conditional probability of ultimate fixation in state  $\mathbf{y}$ , given an initial state  $\mathbf{x}$ . For the frequency of allele  $T_2$ , this leads to

$$\begin{aligned} \mathbb{E}(x_{T_2}(\tau) \mid \mathbf{x}(0) = \mathbf{x}) &= \mathbb{E}(x_3(\tau) + x_4(\tau) \mid \mathbf{x}(0) = \mathbf{x}) \\ &= \sum_{\mathbf{y}=(y_1,y_2,y_3,y_4)} (y_3 + y_4) P_{\mathbf{xy}}(\tau) \\ &\rightarrow P_{\mathbf{xe}_3}(\infty) + P_{\mathbf{xe}_4}(\infty) = u_{T_2}(\mathbf{x}), \end{aligned} \quad (\text{D.3.10})$$

as  $\tau \rightarrow \infty$ . Here, the limit  $u_{T_2}(\mathbf{x})$  represents the conditional probability of ultimate fixation of allele  $T_2$ , given an initial population state  $\mathbf{x}$ .

On the other hand, the frequency of allele  $T_2$  at time step  $\tau$  can be expressed as

$$x_{T_2}(\tau) = x_{T_2}(0) + \sum_{k=0}^{\tau-1} \Delta x_{T_2}(k). \quad (\text{D.3.11})$$

Its conditional expected value given an initial population state  $\mathbf{x}(0) = \mathbf{x}$  with

$$x_{T_2}(0) = x_3(0) + x_4(0) = \frac{1}{N} \quad (\text{D.3.12})$$

takes the form

$$\mathbb{E}(x_{T_2}(\tau) \mid \mathbf{x}(0) = \mathbf{x}) = \frac{1}{N} + \sum_{k=0}^{\tau-1} \mathbb{E}(\Delta x_{T_2}(k) \mid \mathbf{x}(0) = \mathbf{x}). \quad (\text{D.3.13})$$

Note that

$$\mathbb{E}(\Delta x_{T_2}(k) \mid \mathbf{x}(0) = \mathbf{x}) = \mathbb{E}(\mathbb{E}(\Delta x_{T_2}(k) \mid \mathbf{x}(k)) \mid \mathbf{x}(0) = \mathbf{x}). \quad (\text{D.3.14})$$

Letting  $\tau \rightarrow \infty$  yields

$$\begin{aligned}
u_{T_2}(\mathbf{x}) &= \lim_{\tau \rightarrow \infty} \mathbb{E}(x_{T_2}(\tau) \mid \mathbf{x}(0) = \mathbf{x}) \\
&= \frac{1}{N} + \sum_{\tau=0}^{\infty} \mathbb{E}(\Delta x_{T_2}(\tau) \mid \mathbf{x}(0) = \mathbf{x}) \\
&= \frac{1}{N} + \sum_{\tau=0}^{\infty} \mathbb{E}(\mathbb{E}(\Delta x_{T_2}(\tau) \mid \mathbf{x}(\tau)) \mid \mathbf{x}(0) = \mathbf{x}) \\
&= \frac{1}{N} + \sum_{i,j,k} Q_{i,j,k} E_{i,j,k}(\mathbf{x}),
\end{aligned} \tag{D.3.15}$$

where

$$E_{i,j,k}(\mathbf{x}) = \frac{2}{N^2} \sum_{\tau=0}^{\infty} \mathbb{E}(x_i(\tau)x_j(\tau)x_k(\tau) \mid \mathbf{x}(0) = \mathbf{x}). \tag{D.3.16}$$

It remains to compute this quantity in order to obtain the conditional probability of ultimate fixation of allele  $T_2$ . This will be done with the help of the ancestral recombination-selection graph that will provide a development of this quantity up to a given order with respect to the population-scaled intensity of selection and recombination.

## D.4 Ancestral recombination-selection graph

### D.4.1 General description

The ancestral recombination-selection graph is a stochastic process which combines the ancestral recombination graph (Griffiths, 1981; Hudson, 1983) and the ancestral selection graph (Krone and Neuhauser, 1997). It is a process that traces backwards in time the ancestral material of an ordered random sample of individuals at two or more loci under recombination in a population under selection (Donnelly and Kurtz, 1999; Fearnhead, 2003). It was used in Lessard and Kermany (2012) and Kermany and Lessard (2012) to compute the probability of fixation of new mutants in relation with the Hill-Robertson effect in favor of the evolution of recombination. Its topology is represented by events of different types: coalescence, recombination, selection. In this paper, we introduce intersexual selection besides viability selection. When only one event occurs at the same time step, it will be called pure. Simultaneous events can occur but their probability will be negligible in the limit of a large population size.

At each time step, there is no intersexual selection with probability  $1 - As$  in which case, whatever the types of the individuals chosen to reproduce are, they produce an offspring with probability 1. In the case of intersexual selection (which occurs with probability  $As$ ), reproduction is parent-dependent: the probability that an offspring is produced, denoted by  $f_{i,j}$ , depends on the types  $\mathbf{i}$  and  $\mathbf{j}$  of the female and male, respectively, chosen to reproduce. In the situation where  $\mathbf{i} = \mathbf{1}$  or  $\mathbf{3}$ , which means that the female carries allele  $P_1$ , we have  $f_{i,j} = \frac{1}{2}$  whatever the type  $\mathbf{j}$  of the male is. Otherwise, we have

$$\begin{aligned} f_{\mathbf{2},\mathbf{1}} &= f_{\mathbf{2},\mathbf{2}} = f_{\mathbf{4},\mathbf{1}} = f_{\mathbf{4},\mathbf{2}} = 0, \\ f_{\mathbf{2},\mathbf{3}} &= f_{\mathbf{2},\mathbf{4}} = f_{\mathbf{4},\mathbf{3}} = f_{\mathbf{4},\mathbf{4}} = 1. \end{aligned} \tag{D.4.1}$$

This gives

$$q_1 = 1 - As \tag{D.4.2}$$

and

$$q_2 = (1 - As) + As = 1, \tag{D.4.3}$$

for the probabilities of a  $P_2$ -female to produce an offspring with a male carrying alleles  $T_1$  and  $T_2$ , respectively. This has to be compared to

$$q_0 = (1 - As) + \frac{As}{2} = 1 - \frac{As}{2}, \tag{D.4.4}$$

for the probability of a  $P_1$ -female to produce an offspring whatever the type of the male is.

Similarly, an individual chosen to be replaced by an offspring is replaced whatever the type of the individual is with probability  $1 - s$ . On the other hand, there is viability selection in the form of type-dependent replacement with probability  $s$ . Actually in this case, we assume that replacement occurs with probability  $1 - c_i$  if the type of the individual is  $\mathbf{i}$ . We set  $c_1 = c_2 = 1$  et  $c_3 = c_4 = 0$ , so that a  $T_1$ -individual is replaced with probability  $1 - s$  compared to

$$(1 - s) + s = 1, \quad (\text{D.4.5})$$

for a  $T_2$ -individual.

In the following, we consider an ordered sample of  $n$  individuals numbered from 1 to  $n$ , taken at random without replacement in a population of size  $N$  at a given time step. The  $N - n$  other individuals in the population are numbered from  $n + 1$  to  $N$ . The individuals of the population can be assumed to occupy  $N$  distinct sites. The ordered sample is represented by a vector  $\mathbf{z} = (z_1, \dots, z_n)$  where  $z_i$  is the type of individual  $i = 1, \dots, n$ . The corresponding vector for the ancestors (real or virtual, see below) of the sampled individuals one time step back is represented by  $\mathbf{z}'$ . All possible events from the latter to the former backwards in time are considered.

### D.4.2 Pure coalescence events

There is pure coalescence of two individuals  $i$  and  $j$  for  $1 \leq i < j \leq n$  if, one time step back, individual  $j$  is chosen at random (probability  $N^{-1}$ ) to produce a non-recombinant offspring (probability  $1 - R\sigma N^{-1}$ ) irrespective of the types of the parents (probability  $1 - A\sigma N^{-1}$ ) and this offspring replaces the individual at site  $i$  (probability  $N^{-1}$ ) irrespective of its type (probability  $1 - \sigma N^{-1}$ ), or vice versa (factor 2). The probability of the whole event is

$$\frac{2}{N} \left(1 - \frac{A\sigma}{N}\right) \left(1 - \frac{R\sigma}{N}\right) \frac{1}{N} \left(1 - \frac{\sigma}{N}\right) = \frac{2}{N^2} \left(1 + O\left(\frac{1}{N}\right)\right), \quad (\text{D.4.6})$$

in which case the sample size is reduced by 1. Then we have

$$z'_k = \begin{cases} z_k & \text{if } k < j, \\ z_{k+1} & \text{if } k \geq j, \end{cases} \quad (\text{D.4.7})$$

and we write  $\mathbf{z}' = C_{i,j}(\mathbf{z})$ . Note that  $z_i = z_j$ .

### D.4.3 Pure recombination events

There is pure recombination of individual  $i$  for  $1 \leq i \leq n$  if, one time step back, two distinct individuals  $j$  and  $l$  with  $N - n \leq j < l \leq N$  are chosen at random to mate and they produce parent-independently (that is, irrespective of their types) a recombinant offspring which replaces type-independently (that is, irrespective of the type of the individual to be replaced) the individual at site  $i$ . The probability of the whole event is

$$\frac{N-n}{N} \frac{N-n-1}{N} \left(1 - \frac{A\sigma}{N}\right) \frac{R\sigma}{N} \frac{1}{N} \left(1 - \frac{\sigma}{N}\right) = \frac{R\sigma}{N^2} \left(1 + O\left(\frac{1}{N}\right)\right), \quad (\text{D.4.8})$$

in which case the sample size is increased by 1. Without loss of generality, it is assumed that the offspring carries the trait allele of individual  $j$  and the preference allele of individual  $l$ . Letting  $y_j$  and  $y_l$  be the respective types of individuals  $j$  and  $l$ , we have

$$z'_k = \begin{cases} z_k & \text{if } k < i, \\ y_j & \text{if } k = i, \\ y_l & \text{if } k = i+1, \\ z_{k-1} & \text{if } k \geq i+2, \end{cases} \quad (\text{D.4.9})$$

and we write  $\mathbf{z}' = R_i(\mathbf{z})$ . Note that

$$z_i = (z_i(1), z_i(2)) = (z'_i(1), z'_{i+1}(2)), \quad (\text{D.4.10})$$

where  $z_i(1)$  and  $z_i(2)$  refer to the trait and preference alleles, respectively, carried by individual  $i$ .

#### D.4.4 Pure viability selection events

There is pure viability selection of individual  $i$  for  $1 \leq i \leq n$  if, one time step back, individual  $j$  with  $N-n \leq j \leq N$  is chosen at random to produce parent-independently an exact copy of itself and the individual at site  $i$  is chosen to be replaced type-dependently by the offspring. If the type of the individual that was at site  $i$  is  $y_i$ , then the ancestral line of the offspring produced by individual  $j$ , called the incoming line, is real with probability  $1 - c_{y_i}$ , while it is the ancestral line of the individual that was at site  $i$ , called the continuous line, that is real with the complementary probability  $c_{y_i}$ . However, without knowing the type of the individual that was at site  $i$ , we do not know which line is real and which line is not real, called virtual. Therefore, we keep track of both ancestral lines. Moreover, the probability of the whole event is

$$\frac{N-n}{N} \left(1 - \frac{A\sigma}{N}\right) \left(1 - \frac{R\sigma}{N}\right) \frac{1}{N} \frac{\sigma}{N} = \frac{\sigma}{N^2} \left(1 + O\left(\frac{1}{N}\right)\right), \quad (\text{D.4.11})$$

in which case the sample size is increased by 1. Denoting the type of individual  $j$  that produced the offspring by  $y_j$ , we have

$$z'_k = \begin{cases} z_k & \text{if } k < i, \\ y_i & \text{if } k = i, \\ y_j & \text{if } k = i + 1, \\ z_{k-1} & \text{if } k \geq i + 2, \end{cases} \quad (\text{D.4.12})$$

and we write  $\mathbf{z}' = V_i(\mathbf{z})$ . Note that

$$z_i = \begin{cases} z'_i & \text{with probability } c_{z'_i}, \\ z'_{i+1} & \text{with probability } 1 - c_{z'_i}. \end{cases} \quad (\text{D.4.13})$$

#### D.4.5 Pure intersexual selection events

Finally, there is pure intersexual selection of individual at site  $i$  for  $1 \leq i \leq n$  if, one time step back, a female  $j$  and a male  $l$  with  $N - n \leq j, l \leq N$  are chosen to produce type-dependently a non-recombinant offspring and the individual at site  $i$  is chosen to be replaced type-independently by the offspring. The probability of this event is

$$\frac{N-n}{N} \frac{N-n}{N} \frac{A\sigma}{N} \left(1 - \frac{R\sigma}{N}\right) \frac{1}{N} \left(1 - \frac{\sigma}{N}\right) = \frac{A\sigma}{N^2} \left(1 + O\left(\frac{1}{N}\right)\right). \quad (\text{D.4.14})$$

In the limit of a large population size, the possibility that the male and the female are the same individual can be neglected, in which case the sample size is increased by 2.

If  $y_j$  and  $y_l$  represent the respective types of the female  $j$  and the male  $l$ , then we have

$$z'_k = \begin{cases} z_k & \text{if } k \leq i, \\ y_j & \text{if } k = i + 1, \\ y_l & \text{if } k = i + 2, \\ z_{k-2} & \text{if } k \geq i + 3, \end{cases} \quad (\text{D.4.15})$$

and we write  $\mathbf{z}' = S_i(\mathbf{z})$ . Note that

$$z_i = \begin{cases} z'_i & \text{with probability 1 if } z'_{i+1} = \mathbf{2}, \mathbf{4} \text{ and } z'_{i+2} = \mathbf{1}, \mathbf{2}, \\ z'_{i+1} & \text{with probability } \frac{1}{2} \text{ if } z'_{i+1} = \mathbf{2}, \mathbf{4} \text{ and } z'_{i+2} = \mathbf{3}, \mathbf{4}, \\ z'_{i+2} & \text{with probability } \frac{1}{2} \text{ if } z'_{i+1} = \mathbf{2}, \mathbf{4} \text{ and } z'_{i+2} = \mathbf{3}, \mathbf{4}, \\ z'_i & \text{with probability } \frac{1}{2} \text{ if } z'_{i+1} = \mathbf{1}, \mathbf{3}, \\ z'_{i+1} & \text{with probability } \frac{1}{4} \text{ if } z'_{i+1} = \mathbf{1}, \mathbf{3}, \\ z'_{i+2} & \text{with probability } \frac{1}{4} \text{ if } z'_{i+1} = \mathbf{1}, \mathbf{3}. \end{cases} \quad (\text{D.4.16})$$

### D.4.6 Ancestral graph in the limit of a large population

Following the ancestry of a sample of size  $n$  in one time step back, there are  $n(n - 1)/2$  possible pure coalescence events and  $n$  possible pure events of recombination as well as  $n$  of viability selection and  $n$  of intersexual selection. All these events have probabilities of order  $O(N^{-2})$ . On the other hand, simultaneous events have probabilities of order  $O(N^{-3})$ . The probability that at least one event occurs is

$$p_n = \frac{2\lambda_n}{N^2} + O\left(\frac{1}{N^3}\right), \quad (\text{D.4.17})$$

where

$$\lambda_n = \frac{n(n - 1 + \sigma(1 + R + A))}{2}. \quad (\text{D.4.18})$$

Given that at least one event occurs and whatever the time before this event is, we have the conditional probabilities

$$\mathbb{P}(C_n) = \frac{1}{\lambda_n} + O\left(\frac{1}{N}\right), \quad (\text{D.4.19})$$

$$\mathbb{P}(R_n) = \frac{R\sigma}{2\lambda_n} + O\left(\frac{1}{N}\right), \quad (\text{D.4.20})$$

$$\mathbb{P}(V_n) = \frac{\sigma}{2\lambda_n} + O\left(\frac{1}{N}\right), \quad (\text{D.4.21})$$

$$\mathbb{P}(S_n) = \frac{A\sigma}{2\lambda_n} + O\left(\frac{1}{N}\right), \quad (\text{D.4.22})$$

where  $C_n$ ,  $R_n$ ,  $V_n$  et  $S_n$  designate pure events of coalescence, recombination, viability selection and intersexual selection, respectively.

Moreover, the time back in number of time steps before at least one event occurs, represented by  $\tau_n$ , depends only on  $n$  and satisfies

$$\mathbb{P}(\tau_n > \tau) = (1 - p_n)^\tau, \quad (\text{D.4.23})$$

for every integer  $\tau \geq 0$ , which corresponds to a geometric distribution of parameter  $p_n$  with

$$\mathbb{E}(\tau_n) = \sum_{\tau=0}^{\infty} (1 - p_n)^\tau = \frac{1}{p_n}. \quad (\text{D.4.24})$$

The corresponding time in number of  $N^2/2$  time steps in the limit of a large population size, represented by  $T_n$ , has a probability distribution given by

$$\mathbb{P}(T_n > t) = \lim_{N \rightarrow \infty} \mathbb{P}\left(\tau_n > \left\lfloor \frac{tN^2}{2} \right\rfloor\right), \quad (\text{D.4.25})$$

for every real number  $t \geq 0$ , where  $\lfloor \cdot \rfloor$  designates the floor value. Therefore, we have

$$\mathbb{P}(T_n > t) = \lim_{N \rightarrow \infty} (1 - p_n)^{\left\lfloor \frac{tN^2}{2} \right\rfloor} = e^{-\lambda_n t}, \quad (\text{D.4.26})$$

for every real number  $t \geq 0$ , with

$$\mathbb{E}(T_n) = \int_0^{+\infty} e^{-\lambda_n t} dt = \frac{1}{\lambda_n} = \lim_{N \rightarrow \infty} \frac{2}{N^2 p_n} = \lim_{N \rightarrow \infty} \frac{2}{N^2} \mathbb{E}(\tau_n). \quad (\text{D.4.27})$$

In other words, the time for a state change in the ancestry of the sample of size  $n$  in the limit of a large population size  $N$  follows an exponential distribution with parameter  $\lambda_n$  at the end of which a pure event that depends only on the state left occurs. In the same limit, the rates of pure coalescence, recombination, viability selection and intersexual selection are  $n(n - 1)/2$ ,  $n\sigma R/2$ ,  $n\sigma/2$  and  $n\sigma A/2$ , respectively, which sum up to  $\lambda_n$ . These parameters characterize the ancestral graph in the limit of a large population.

## D.5 Application of the ancestral graph

We are now ready to compute the quantity  $E_{i,j,k}(\mathbf{x})$  for three types  $i, j, k$  and an initial population state  $\mathbf{x}(0) = \mathbf{x}$ . Let  $\mathbf{z}(\tau)$  represent the ordered sample of three individuals chosen at random without replacement in the population of size  $N$  at time step  $\tau$ . Define

$$\xi_k^{(i)}(\tau) = \begin{cases} 1 & \text{if individual } i \text{ is of type } k, \\ 0 & \text{otherwise,} \end{cases} \quad (\text{D.5.1})$$

for  $i = 1, 2, 3$ . Given the type frequencies  $x_i(\tau)$ ,  $x_j(\tau)$  and  $x_k(\tau)$ , the random variable  $\xi_i^{(1)}(\tau)\xi_j^{(2)}(\tau)\xi_k^{(3)}(\tau)$  takes the value 1 with probability

$$\frac{N^2}{(N - 1)(N - 2)} x_i(\tau) x_j(\tau) x_k(\tau), \quad (\text{D.5.2})$$

and 0 otherwise. Therefore, we have

$$\begin{aligned}
\mathbb{P}(\mathbf{z}(\tau) = (\mathbf{i}, \mathbf{j}, \mathbf{k}) | \mathbf{x}(0) = \mathbf{x}) &= \mathbb{E}(\xi_{\mathbf{i}}^{(1)}(\tau) \xi_{\mathbf{j}}^{(2)}(\tau) \xi_{\mathbf{k}}^{(3)}(\tau) | \mathbf{x}(0) = \mathbf{x}) \\
&= \mathbb{E}(\mathbb{E}(\xi_{\mathbf{i}}^{(1)}(\tau) \xi_{\mathbf{j}}^{(2)}(\tau) \xi_{\mathbf{k}}^{(3)}(\tau) | x_{\mathbf{i}}(\tau), x_{\mathbf{j}}(\tau), x_{\mathbf{k}}(\tau)) | \mathbf{x}(0) = \mathbf{x}) \\
&= \frac{N^2}{(N-1)(N-2)} \mathbb{E}(x_{\mathbf{i}}(\tau) x_{\mathbf{j}}(\tau) x_{\mathbf{k}}(\tau) | \mathbf{x}(0) = \mathbf{x}). \tag{D.5.3}
\end{aligned}$$

Plugging this into (D.3.16) yields

$$E_{\mathbf{i}, \mathbf{j}, \mathbf{k}}(\mathbf{x}) = \frac{2}{N^2} \left(1 - \frac{1}{N}\right) \left(1 - \frac{2}{N}\right) \sum_{\tau=0}^{\infty} \mathbb{P}(\mathbf{z}(\tau) = (\mathbf{i}, \mathbf{j}, \mathbf{k}) | \mathbf{x}(0) = \mathbf{x}). \tag{D.5.4}$$

Letting  $\mathbf{z} = (\mathbf{i}, \mathbf{j}, \mathbf{k})$  and conditioning on the ancestral graph from time step  $\tau$  to time step 0, we have

$$\mathbb{P}(\mathbf{z}(\tau) = \mathbf{z} | \mathbf{x}(0) = \mathbf{x}) = \sum_{G(\tau)} \mathbb{P}(\mathbf{z}(\tau) = \mathbf{z} | G(\tau), \mathbf{x}(0) = \mathbf{x}) \mathbb{P}(G(\tau)), \tag{D.5.5}$$

where  $G(\tau)$  designates an ancestral graph for three individuals chosen at random without replacement in the population at time step  $\tau$ .

The topology of the graph  $G(\tau)$  is represented by a sequence of events backwards in time  $G = (E_1, E_2, \dots, E_m)$  with  $E_i$  in the form  $R_n, S_n, \dots$ , for  $i = 1, \dots, m$  for some finite number of events  $m$ . The number of ancestors following the last event backwards in time, which is the most ancient event, is denoted by  $n_G$ . Moreover, this last event occurs at time step back  $\tau_G$  and the time spent with these  $n_G$  ancestors is denoted by  $\tau_{n_G}$ . The time  $\tau_G$  is a sum of independent geometric random variables and the time  $\tau_{n_G}$  a geometric random variable independent of  $\tau_G$ . Besides, we must have the inequalities  $\tau_G \leq \tau < \tau_G + \tau_{n_G}$ .

For instance, if  $G = (R_3, V_4, C_5)$ , then we have  $n_G = 4$ ,  $\tau_G = \tau_3 + \tau_4 + \tau_5$  where  $\tau_3, \tau_4$  and  $\tau_5$  are independent geometric random variables of parameters  $p_3, p_4$  and  $p_5$ , respectively, and  $\tau_{n_G}$  is a geometric random variable of parameter  $p_4$  independent of  $\tau_G$ .

The conditional probability that  $\mathbf{z}(\tau) = \mathbf{z}$  given  $G(\tau)$  and  $\mathbf{x}(0) = \mathbf{x}$  depends in fact only on  $G$  and  $\mathbf{x}$ . Therefore, we introduce the notation

$$\mathbb{P}(\mathbf{z}(\tau) = \mathbf{z} | G(\tau), \mathbf{x}(0) = \mathbf{x}) = \mathbb{P}_G(\mathbf{z} | \mathbf{x}). \tag{D.5.6}$$

On the other hand, we have

$$\begin{aligned}
\mathbb{P}(G(\tau)) &= \mathbb{P}(\tau_G \leq \tau < \tau_G + \tau_{n_G}) \mathbb{P}(G) \\
&= \mathbb{P}(\tau_G \leq \tau < \tau_G + \tau_{n_G}) \prod_{i=1}^m \mathbb{P}(E_i) \\
&= (\mathbb{P}(\tau_G + \tau_{n_G} > \tau) - \mathbb{P}(\tau_G > \tau)) \prod_{i=1}^m \mathbb{P}(E_i).
\end{aligned} \tag{D.5.7}$$

Note that

$$\sum_{\tau=0}^{\infty} (\mathbb{P}(\tau_G + \tau_{n_G} > \tau) - \mathbb{P}(\tau_G > \tau)) = \mathbb{E}(\tau_G + \tau_{n_G}) - \mathbb{E}(\tau_G) = \mathbb{E}(\tau_{n_G}). \tag{D.5.8}$$

Then, we have

$$\sum_{\tau=0}^{\infty} \mathbb{P}(\mathbf{z}(\tau) = \mathbf{z} | \mathbf{x}(0) = \mathbf{x}) = \sum_G \mathbb{P}_G(\mathbf{z} | \mathbf{x}) \mathbb{P}(G) \mathbb{E}(\tau_{n_G}). \tag{D.5.9}$$

We conclude that

$$\begin{aligned}
\lim_{N \rightarrow \infty} E_{\mathbf{i}, \mathbf{j}, \mathbf{k}}(\mathbf{x}) &= \lim_{N \rightarrow \infty} \frac{2}{N^2} \sum_{\tau=0}^{\infty} \mathbb{P}(\mathbf{z}(\tau) = \mathbf{z} | \mathbf{x}(0) = \mathbf{x}) \\
&= \sum_G \mathbb{P}_G(\mathbf{z} | \mathbf{x}) \mathbb{P}(G) \mathbb{E}(\tau_{n_G}).
\end{aligned} \tag{D.5.10}$$

Here,  $\mathbb{E}(T_{n_G})$  is the expected time with  $n_G$  ancestors with  $N^2/2$  time steps as unit of time in the limit of a large population size, given by  $\lambda_{n_G}^{-1}$ . The calculation of the probability  $\mathbb{P}_G(\mathbf{z} | \mathbf{x})$  in the limit of a large population size is presented in Appendix D.B. The summation is over all finite topologies  $G$  of the ancestral graph starting with three individuals and involving only pure events, the only ones with positive probabilities in the limit of a large population size. Such graph topologies are called pure. The number of pure graph topologies is actually infinite. However, only a finite number can be considered to get an approximation of any given order of the fixation probability  $u_{T_2}(\mathbf{x})$  with respect to  $\sigma$ , the intensity of selection and recombination.

First, note that in all triplets  $\mathbf{z} = (\mathbf{i}, \mathbf{j}, \mathbf{k})$  such that  $Q_{\mathbf{i}, \mathbf{j}, \mathbf{k}} \neq 0$  in the fixation probability  $u_{T_2}(\mathbf{x})$ , there is at least one type where allele  $T_1$  appears and also at least one type where allele  $T_2$  appears. Therefore,  $\mathbb{P}_G(\mathbf{z} | \mathbf{x}) = 0$  for every graph topology  $G$  such that

the minimum number of ancestors at any point of the graph, denoted by  $|G|$ , is 1. On the other hand,

$$\mathbb{P}_G(\mathbf{z}|\mathbf{x}) \leq \frac{1}{N} \quad (\text{D.5.11})$$

for every graph topology  $G$  such that  $|G| \geq 2$ , since at least one of the ancestors at time step 0 must carry allele  $T_2$ .

For a random sample of  $i$  individuals in a population of size  $N$ , let  $W_i$  be the time back in number of  $N^2/2$  time steps in the limit of a large population size before reaching a unique ancestor. The expected value is given by

$$\mathbb{E}(W_i) = \sum_{G \text{ for } i \text{ individuals : } |G| \geq 2} \mathbb{P}(G) \mathbb{E}(T_{n_G}). \quad (\text{D.5.12})$$

It can be shown (see Appendix D.A) that  $\mathbb{E}(W_i)$  is finite and increasing with  $i$ .

Let  $n_G^+$  be the number of events in a pure graph topology  $G$  corresponding to an increase in the number of ancestors (actually pure events of recombination, viability selection or intersexual selection with increases of one or two ancestors for each). If  $G$  starts with three individuals and  $n_G^+ > k$  for some integer  $k \geq 1$ , then we can write  $G = (G_1, G_2)$  where  $G_1$  and  $G_2$  are pure graph topologies such that  $n_{G_1}^+ = k + 1$  and  $n_{G_2} \leq 2(k + 1) + 3 = 2k + 5$ . Note that this decomposition is not unique but that the number of possible decompositions is finite. Moreover, we have

$$\mathbb{P}(G) = \mathbb{P}(G_1)\mathbb{P}(G_2), \quad (\text{D.5.13})$$

with

$$\mathbb{P}(G_1) = O(\sigma^{k+1}) \quad (\text{D.5.14})$$

and

$$\sum_{G_2: |G_2| \geq 2} \mathbb{P}(G_2) \mathbb{E}(T_{n_{G_2}}) = \mathbb{E}(W_{n_{G_1}}) \leq \mathbb{E}(W_{2k+5}) < \infty. \quad (\text{D.5.15})$$

We conclude that

$$\sum_{G: |G| \geq 2, n_G^+ > k} \mathbb{P}_G(\mathbf{z}|\mathbf{x}) \mathbb{P}(G) \mathbb{E}(T_{n_G}) \leq \frac{1}{N} O(\sigma^{k+1}). \quad (\text{D.5.16})$$

Finally, neglecting all terms of orders  $N^{-1}O(\sigma^{k+1})$  and  $O(N^{-2})$ , we have the approximation

$$E_{\mathbf{i}, \mathbf{j}, \mathbf{k}}(\mathbf{x}) \approx \sum_{G: |G| \geq 2, n_G^+ \leq k} \mathbb{P}_G(\mathbf{z}|\mathbf{x}) \mathbb{P}(G) \mathbb{E}(T_{n_G}). \quad (\text{D.5.17})$$

This approximation can be computed with MATHEMATICA using a development of  $\mathbb{P}_G(\mathbf{z}|\mathbf{x})$  given in Appendix D.B and an algorithm presented in Appendix D.C which significantly shortens the calculation time.

## D.6 Results and discussion

### D.6.1 Fixation at the trait locus

Assume that the sexually preferred but viability-deleterious allele  $T_2$  is introduced at random by a single mutation at the trait locus into a population of size  $N$  when the frequency of allele  $P_2$  at the preference locus is  $x$  so that the population state is  $\mathbf{x} = (1 - x, x, 0, 0)$ . Then the probability of ultimate fixation of  $T_2$  is given by the expression

$$u_{T_2} = xu_{T_2}(\mathbf{x} - N^{-1}\mathbf{e}_2 + N^{-1}\mathbf{e}_4) + (1 - x)u_{T_2}(\mathbf{x} - N^{-1}\mathbf{e}_1 + N^{-1}\mathbf{e}_3). \quad (\text{D.6.1})$$

Under weak selection and weak recombination, we get the approximation

$$\begin{aligned} u_{T_2} \approx & \frac{1}{N} + \sigma \left( -\frac{1}{2N} + \frac{Ax}{4N} \right) \\ & + \sigma^2 \left( \frac{1}{12N} - \frac{Ax}{12N} - \frac{7A^2x}{2160N} + \frac{13A^2x^2}{540N} \right) \\ & + \sigma^3 \left( \frac{283A^2x(1-x)}{86400N} + \frac{41A^2Rx(1-x)}{194400N} \right. \\ & \left. - \frac{7831A^3x}{54432000N} - \frac{5471A^3x^2}{4536000N} + \frac{73483A^3x^3}{54432000N} \right). \end{aligned} \quad (\text{D.6.2})$$

If the viabilities at the trait locus are interchanged so that the single mutant  $T_2$  is viability-beneficial instead of being viability-deleterious, then only three signs in the above expression are changed to give the approximation

$$\begin{aligned} u_{T_2} \approx & \frac{1}{N} + \sigma \left( \frac{1}{2N} + \frac{Ax}{4N} \right) \\ & + \sigma^2 \left( \frac{1}{12N} + \frac{Ax}{12N} - \frac{7A^2x}{2160N} + \frac{13A^2x^2}{540N} \right) \\ & + \sigma^3 \left( -\frac{283A^2x(1-x)}{86400N} + \frac{41A^2Rx(1-x)}{194400N} \right. \\ & \left. - \frac{7831A^3x}{54432000N} - \frac{5471A^3x^2}{4536000N} + \frac{73483A^3x^3}{54432000N} \right). \end{aligned} \quad (\text{D.6.3})$$

These approximations are valid for a population size  $N$  large enough and an intensity of selection and recombination  $\sigma$  small enough so that terms of order  $\sigma^k N^{-l}$  for  $k \geq 4$  or  $l \geq 2$  can be ignored.

As expected, the leading effect of intersexual selection (term in  $\sigma A$ ) is to increase the probability of ultimate fixation of the sexually preferred allele  $T_2$ . Moreover, if  $Ax > 2$ , then this effect is larger than the leading effect of viability selection so that it compensates this effect in the case of a viability-deleterious allele  $T_2$ . Even in this case, the probability of ultimate fixation of  $T_2$  under weak selection may exceed what it would be under neutrality, which is given by its initial frequency  $N^{-1}$  (see Figure D.1).

Surprisingly, the leading effect of recombination, though small (term in  $\sigma^3 R$ ), is also to increase the probability of ultimate fixation of the sexually preferred allele  $T_2$ . This appears to be the case for a viability-deleterious allele as well as a viability-beneficial allele. Random drift in a finite population is known to build up negative linkage disequilibrium (see, e.g. [Barton and Otto, 2005](#), or [Lessard and Kermany, 2012](#), and references therein). Recombination breaks down this disequilibrium and this increases the frequency of association between  $T_2$  and  $P_2$ . The effect of this increase is to promote the spread of  $T_2$  up to fixation.

With free recombination or any fixed recombination rate in the limit of a large population size (see Appendix D.E), the probability of ultimate fixation of a viability-deleterious mutant  $T_2$  that is sexually preferred by  $P_2$ -females of initial frequency  $x$  is approximated under weak selection by

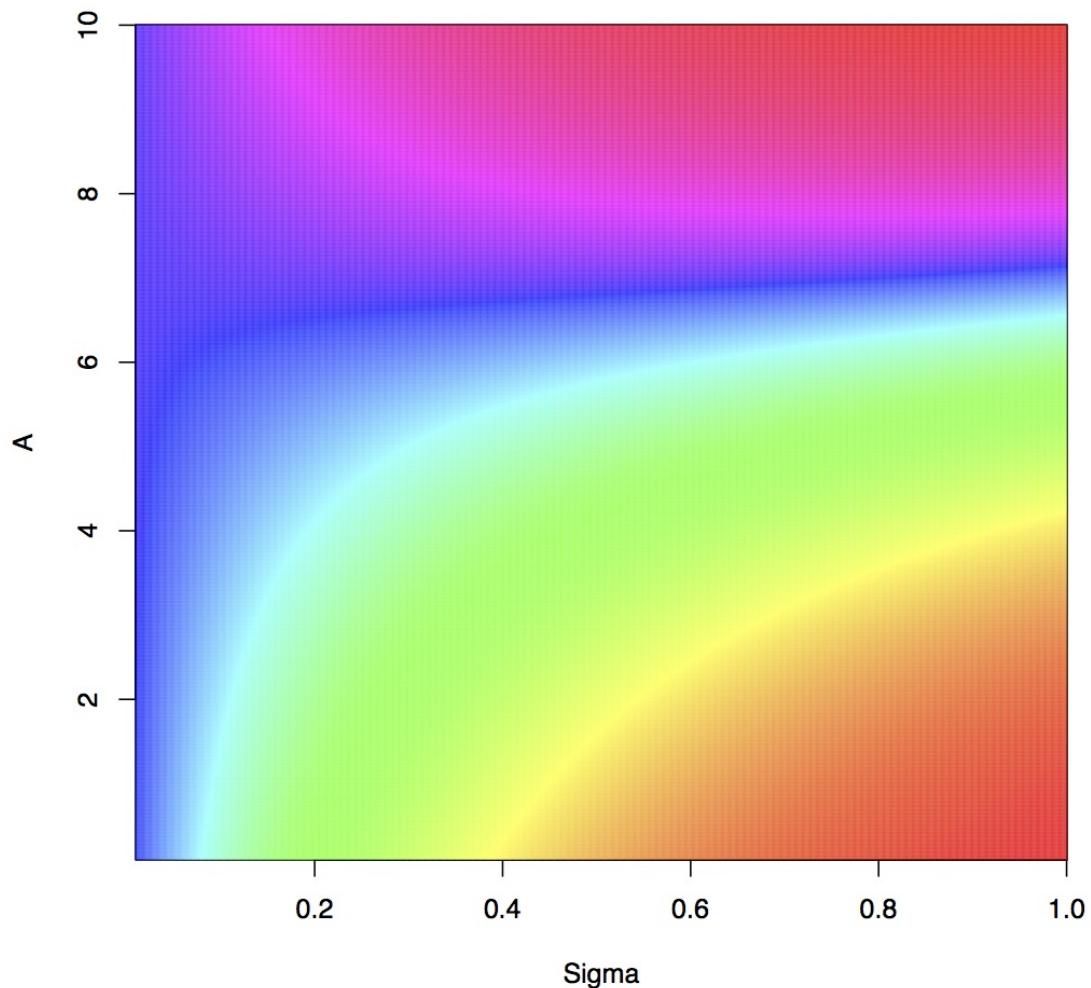


Fig. D.1 Fixation probability  $u_{T_2}$  for a viability-deleterious trait under intersexual selection as a function of the coefficient of selection  $\sigma$  and the coefficient of intersexual selection  $A$  for  $x = 0.3$ ,  $N = 1$  and  $R = 1$ . Note that the approximation is accurate only if  $\sigma \ll 1$ . The value increases from bottom (red) to top (violet).

$$\begin{aligned} u_{T_2} \approx & \frac{1}{N} + \sigma \left( -\frac{1}{2N} + \frac{Ax}{4N} \right) \\ & + \sigma^2 \left( \frac{1}{12N} - \frac{Ax}{12N} - \frac{A^2x}{384N} + \frac{3A^2x^2}{128N} \right) \\ & + \sigma^3 \left( \frac{7A^2x(1-x)}{1536N} - \frac{A^3x}{2048N} - \frac{5A^3x^2}{6144N} + \frac{A^3x^3}{768N} \right). \end{aligned} \quad (\text{D.6.4})$$

The leading term of the difference between this approximation in the case of strong recombination and the previous approximation in the case of weak recombination is given by

$$\sigma^2 \left( -\frac{A^2x}{384N} + \frac{3A^2x^2}{128N} \right) - \sigma^2 \left( -\frac{7A^2x}{2160N} + \frac{13A^2x^2}{540N} \right) \geq 0, \quad (\text{D.6.5})$$

with equality to 0 if and only if  $x = 0$  or  $x = 1$ . This is also the case for a viability-beneficial mutant  $T_2$ . This confirms that recombination favors the fixation of any mutant preferred allele.

The fact that recombination increases the probability of ultimate fixation of a sexually preferred mutant allele  $T_2$  appears to be caused by an increase in linkage disequilibrium between this allele and the allele  $P_2$  coding for the preference. Selection at the preference locus associated with a cost of being choosy or not as assumed in this paper may have a hitchhiking effect on the trait locus so that it may enhance or lessen the effect of recombination on the fixation probability of  $T_2$ . However, this should not change the sign of this effect. Therefore, the same conclusion is expected in the case of a neutral preference locus.

## D.6.2 Fixation at the preference locus

The probability of ultimate fixation of allele  $P_2$  introduced at random by a single mutation at the preference locus into a population of size  $N$  when the frequency of the sexually preferred but viability-deleterious allele  $T_2$  at the trait locus is  $y$  so that the population state is  $\mathbf{y} = (1-y, 0, y, 0)$  can be obtained in a similar way. Its expression is given by

$$u_{P_2} = yu_{P_2}(\mathbf{y} - N^{-1}\mathbf{e}_3 + N^{-1}\mathbf{e}_4) + (1-y)u_{P_2}(\mathbf{y} - N^{-1}\mathbf{e}_1 + N^{-1}\mathbf{e}_2). \quad (\text{D.6.6})$$

Using the coefficients  $Q_{i,j,k}$  in Appendix D for the expected change in the frequency of  $P_2$  and the same algorithm as before in calculating the expected values  $E_{i,j,k}(y)$  under weak selection and weak recombination, we get the approximation

$$\begin{aligned} u_{P_2} \approx & \frac{1}{N} + \sigma \left( -\frac{A}{8N} + \frac{Ay}{4N} \right) \\ & + \sigma^2 \left( -\frac{Ay(1-y)}{36N} + \frac{A^2}{192N} - \frac{37A^2y(1-y)}{2160N} \right) \\ & + \sigma^3 \left( \frac{Ay(1-y)(1-2y)}{1440N} + \frac{493A^2y(1-y)(1-2y)}{259200N} \right. \\ & + \frac{16993A^3y(1-y)(1-2y)}{108864000N} - \frac{101ARy(1-y)}{2592N} \\ & \left. + \frac{7739A^2Ry(1-y)}{777600N} \right). \end{aligned} \quad (\text{D.6.7})$$

If allele  $T_2$  is viability-beneficial, then the approximation is given by

$$\begin{aligned} u_{P_2} \approx & \frac{1}{N} + \sigma \left( -\frac{A}{8N} + \frac{Ay}{4N} \right) \\ & + \sigma^2 \left( \frac{Ay(1-y)}{36N} + \frac{A^2}{192N} - \frac{37A^2y(1-y)}{2160N} \right) \\ & + \sigma^3 \left( \frac{Ay(1-y)(1-2y)}{1440N} - \frac{493A^2y(1-y)(1-2y)}{259200N} \right. \\ & + \frac{16993A^3y(1-y)(1-2y)}{108864000N} + \frac{101ARy(1-y)}{2592N} \\ & \left. + \frac{7739A^2Ry(1-y)}{777600N} \right). \end{aligned} \quad (\text{D.6.8})$$

We see that the leading effect of intersexual selection (term in  $\sigma A$ ) increases the probability of ultimate fixation of  $P_2$  only if the initial frequency of  $T_2$  exceeds the initial frequency of  $T_1$  (actually  $y > 1/2$ ). Under this condition, the expected reproduction cost incurred by a female for not being choosy exceeds the expected reproduction cost incurred by a female for being choosy. This condition is unlikely to occur under the effects of random drift if  $T_2$  is viability-deleterious.

In the critical case where the frequencies of  $T_1$  and  $T_2$  are equal ( $y = 1/2$ ), there is no difference in the expected reproduction cost incurred by choosy females and non-choosy females. In this case, the leading effect of intersexual selection is to increase the probability of ultimate fixation of  $P_2$  if  $T_2$  is viability-beneficial and

$$\sigma^2 \left( \frac{A}{144N} + \frac{A^2}{192N} - \frac{37A^2}{8640N} \right) = \sigma^2 \left( \frac{A}{144N} + \frac{A^2}{1080N} \right) > 0, \quad (\text{D.6.9})$$

which always holds, or if  $T_2$  is viability-deleterious and the coefficient of intersexual selection is large enough so that

$$\sigma^2 \left( -\frac{A}{144N} + \frac{A^2}{192N} - \frac{37A^2}{8640N} \right) = \sigma^2 \left( -\frac{A}{144N} + \frac{A^2}{1080N} \right) > 0, \quad (\text{D.6.10})$$

which holds when  $A > 7.5$ .

Finally, the leading effect of recombination (term in  $\sigma^3 R$ ) is to increase the probability of ultimate fixation of  $P_2$  unless  $T_2$  is viability-deleterious and the coefficient of intersexual selection is not too large so that

$$-\frac{101ARy(1-y)}{2592N} + \frac{7739A^2Ry(1-y)}{777600N} \leq 0, \quad (\text{D.6.11})$$

which occurs for  $0 < y < 1$  when  $A \leq 3.915$ . By diminishing the magnitude of the negative linkage disequilibrium built up by random drift, it seems that recombination strengthens the hitchhiking effect of the trait locus on the preference locus. When the preferred trait is deleterious, the coefficient of intersexual selection must be high enough to compensate this effect.

### D.6.3 Evolution of intersexual selection

In a finite population, conditions that increase the fixation probability of a new mutant may indicate the direction of evolution. We conclude from our findings that the best scenario for the evolution of a sexual preference for a viability-deleterious trait in a finite population is that the preference was neutral at least when introduced as a single mutant and increased in frequency either by random drift or by association with a viability-beneficial preferred trait before a single mutation on this trait rendered it more exaggerated and more preferred but viability-deleterious.

Our findings are in agreement with the phases in the history of a secondary sexual trait that were described by Fisher (1915, p. 187): *In the first it is favoured by natural selection, and being simple and easily apprehended as a "point," its advantage is slowly increased by the development of sexual selection in its favour; in the second phase it owes*

*nothing to natural selection, which may even have turned against it, but it still increases in splendour and perfection, and the importance attached to it by the opposite sex still increases, so long as it retains a balance of advantage. Finally, perhaps, an equilibrium will be attained in which natural selection just balances sexual selection.*

Our results are based on fixation probabilities in the limit of a large finite population under very weak selection. While intersexual selection creates positive linkage disequilibrium, random drift does the opposite. Selection being weaker than drift (of order  $\sigma N^{-1}$  with  $\sigma \ll 1$  compared to  $N^{-1}$ ), linkage disequilibrium tends to be negative. Recombination breaks down this disequilibrium and doing so reinforces intersexual selection so that it can hamper the effect of a viability-deleterious trait and even counterbalance its hitchhiking effect on the preference locus. This effect of recombination distinguishes intersexual selection models in finite populations from their infinite population versions (see, e.g., Kirkpatrick, 1982; Barton and Turelli, 1991).

Our analytical results have been obtained under simplifying assumptions such as a monoecious haploid population. The effects of intersexual selection and recombination may be affected by dioecy and diploidy among other more realistic assumptions. Numerical studies and simulations like those mentioned in the Introduction are more suitable to deal with such assumptions.

## Appendix D.A Bound for $\mathbb{E}(W_i)$

Suppose that  $i \geq 2$  individuals have  $j \geq 2$  ancestors at a given time step. From this time step to the previous one, even allowing for simultaneous events, this number of ancestors can only go from  $j$  to  $j - 1$ ,  $j$ ,  $j + 1$  and  $j + 2$  with positive probabilities. Moreover, these probabilities satisfy

$$\begin{aligned} p_{j,j-1} &\geq \frac{j(j-1)}{N^2} \left(1 - \frac{A\sigma}{N}\right) \left(1 - \frac{R\sigma}{N}\right) \left(1 - \frac{\sigma}{N}\right) \geq \frac{j(j-1)}{2N^2}, \\ p_{j,j+1} &\leq \frac{j}{N} \left(\frac{\sigma}{N} + \frac{R\sigma}{N} + \frac{A\sigma}{N}\right) \leq \frac{j}{12N^2}, \\ p_{j,j+2} &\leq \frac{j}{N} \left(\frac{R\sigma^2}{N^2} + \frac{A\sigma}{N}\right) \leq \frac{j}{12N^2}, \end{aligned} \quad (\text{D.A.1})$$

if  $\sigma$  is small enough, with

$$p_{j,j} = 1 - p_{j,j-1} - p_{j,j+1} - p_{j,j+2}. \quad (\text{D.A.2})$$

Then, the sojourn time back with  $j$  ancestors has expected value

$$\frac{1}{1 - p_{j,j}} \leq \frac{1}{p_{j,j-1}} \leq \frac{2N^2}{j(j-1)} \leq N^2. \quad (\text{D.A.3})$$

In number of  $N^2/2$  time steps, the expected sojourn time back with  $j$  ancestors is bounded by 2. Therefore, the time back in number of  $N^2/2$  time steps in the limit of a large population size before reaching a single ancestor starting with  $i$  individuals, denoted by  $W_i$ , satisfies

$$\mathbb{E}(W_i) \leq 2\mathbb{E}(M_i), \quad (\text{D.A.4})$$

where  $M_i$  represents the number of changes in the number of ancestors before reaching state 1 starting from state  $i$ .

Let  $(U_n)_{n \geq 1}$  be a sequence of independent random variables having a uniform distribution on  $[0, 1]$ . Let  $(X_n)_{n \geq 0}$  be a Markov chain on the positive integers with  $X(0) = i \geq 2$  and 1 as absorbing state, defined by

$$\begin{aligned} X_n - X_{n-1} = & 3\mathbb{1}_{[0, q_{j,j+2}]}(U_n) + \mathbb{1}_{[1-q_{j,j-1}-q_{j,j+1}, 1-q_{j,j-1}]}(U_n) \\ & - \mathbb{1}_{[1-q_{j,j-1}, 1]}(U_n) \end{aligned} \quad (\text{D.A.5})$$

if  $X_{n-1} \neq 1$ , where  $\mathbb{1}_I$  designates the indicator function of the interval  $I$ . The transition probabilities of this Markov chain are given by

$$q_{1,1} = 1, \quad (\text{D.A.6})$$

so that 1 is absorbing,

$$q_{j,j+k} = \frac{p_{j,j+k}}{1 - p_{j,j}} \leq \frac{2jN^2}{12j(j-1)N^2} \leq \frac{1}{6}, \quad (\text{D.A.7})$$

for  $j \geq 2$  and  $k = 1, 2$ , and

$$q_{j,j-1} = 1 - q_{j,j+1} - q_{j,j+2} \geq \frac{2}{3}. \quad (\text{D.A.8})$$

Now, let  $(Y_n)_{n \geq 0}$  be the Markov chain with  $Y_0 = i$  and 1 as absorbing state, defined by

$$Y_n - Y_{n-1} = 2\mathbb{1}_{[0, \frac{1}{6}]}(U_n) + \mathbb{1}_{[\frac{1}{6}, \frac{1}{3}]}(U_n) - \mathbb{1}_{[\frac{1}{3}, 1]}(U_n), \quad (\text{D.A.9})$$

if  $Y_{n-1} \neq 1$ . Then, we have

$$X_n = X_0 + \sum_{l=1}^n (X_l - X_{l-1}) \leq Y_0 + \sum_{l=1}^n (Y_l - Y_{l-1}) = Y_n, \quad (\text{D.A.10})$$

so that

$$\mathbb{P}(X_n > 1 | X_0 = i) \leq \mathbb{P}(Y_n > 1 | Y_0 = i), \quad (\text{D.A.11})$$

for every  $n \geq 0$ . On another hand, we have

$$\mathbb{E}(M_i) = \sum_{n=0}^{\infty} \mathbb{P}(M_i > n) = \sum_{n=0}^{\infty} \mathbb{P}(X_n > 1 | X_0 = i). \quad (\text{D.A.12})$$

Therefore, we have

$$\mathbb{E}(M_i) = \sum_{n=0}^{\infty} \mathbb{P}(X_n > 1 | X_0 = i) \leq \sum_{n=0}^{\infty} \mathbb{P}(Y_n > 1 | Y_0 = i) = \mathbb{E}(N_i), \quad (\text{D.A.13})$$

where  $N_i$  is defined as the number of transitions for the Markov chain  $(Y_n)_{n \geq 0}$  to reach state 1 from state  $i \geq 2$ .

To conclude, we make a parallel between the Markov chain  $(Y_n)_{n \geq 0}$  with initial state  $i \geq 2$  and absorbing state 1 and a Bienaymé-Galton-Watson (BGW) branching process  $(Z_n)_{n \geq 0}$  starting with  $i - 1$  individuals. In this branching process for the size of a population with discrete, non-overlapping generations, every individual independently of all others produces 3, 2 or 0 offspring with respective probabilities  $\frac{1}{6}$ ,  $\frac{1}{6}$  and  $\frac{2}{3}$ . This corresponds to a transition in the process  $(Y_n)_{n \geq 0}$ . Therefore, the number of transitions in this process to reach state 1 from state  $i \geq 2$  corresponds to the total number of individuals in the process  $(Z_n)_{n \geq 0}$  starting with the  $i - 1$  individuals of the initial generation and ending with the extinction of the population with none. This occurs with probability 1, since the expected number of offspring produced by an individual is  $m = \frac{5}{6} < 1$ . Finally, we have

$$\begin{aligned} \mathbb{E}(N_i) &= \mathbb{E}\left(\sum_{n=0}^{\infty} Z_n\right) = \sum_{n=0}^{\infty} \mathbb{E}(Z_n) \\ &= \sum_{n=0}^{\infty} m^n \mathbb{E}(Z_0) = (i-1) \sum_{n=0}^{+\infty} \left(\frac{5}{6}\right)^n = 6(i-1). \end{aligned} \quad (\text{D.A.14})$$

We conclude that

$$\mathbb{E}(W_i) \leq 12(i - 1), \quad (\text{D.A.15})$$

for  $i \geq 2$ . Moreover, it is obvious that this expected value is increasing from  $i \geq 2$  to  $i + 1$ , since the time for reaching a single ancestor from  $i + 1$  individuals is always greater or equal to the time for reaching a single ancestor from any given subset of  $i$  of these individuals.

## Appendix D.B Calculation of $\mathbb{P}_G(\mathbf{z}|\mathbf{x})$

We start with some additional notations. Let  $\mathbf{x}(0) = \mathbf{x} = (x_{\mathbf{i}})_{\mathbf{i}=1,\dots,4}$  be the vector of the initial type frequencies. Moreover, let the type configuration of an ordered sample  $\mathbf{z}$  be given by  $\mathbf{n} = (n_{\mathbf{i}})_{\mathbf{i}=1,\dots,4}$  where  $n_{\mathbf{i}}$  is the number of individuals of type  $\mathbf{i}$  in the sample. Then, the sample size is  $n = |\mathbf{n}| = \sum_{\mathbf{i}=1}^4 n_{\mathbf{i}}$ .

For a graph topology  $G = \emptyset$ , we have

$$\mathbb{P}_G(\mathbf{z}|\mathbf{x}) = P_{\mathbf{x}}(\mathbf{n}) = \frac{1}{N^n} \prod_{\mathbf{i}=1}^4 \frac{N_{\mathbf{i}}!}{(N_{\mathbf{i}} - n_{\mathbf{i}})!} = \prod_{\mathbf{i}=1}^4 x_{\mathbf{i}}^{n_{\mathbf{i}}} + O\left(\frac{1}{N}\right), \quad (\text{D.B.1})$$

where  $(N_{\mathbf{i}})_{\mathbf{i}=1,\dots,4} = N\mathbf{x}$ .

Let us now consider a graph topology of a single pure event represented by  $G = (E_1)$ . Then we have

$$\mathbb{P}_G(\mathbf{z}|\mathbf{x}) = \sum_{\mathbf{z}'} \mathbb{P}_{E_1}(\mathbf{z}|\mathbf{z}') P_{\mathbf{x}}(\mathbf{n}'), \quad (\text{D.B.2})$$

where

$$\mathbb{P}_{E_1}(\mathbf{z}|\mathbf{z}') = \begin{cases} \delta_{z_i, z_j} & \text{if } E_1 = C_n, \mathbf{z}' = C_{i,j}(\mathbf{z}), \\ (1 - c_{z'_i})\delta_{z_i, z'_{i+1}} + c_{z'_i}\delta_{z_i, z'_i} & \text{if } E_1 = V_n, \mathbf{z}' = V_i(\mathbf{z}), \\ \delta_{z_i(1), z'_i(1)}\delta_{z_i(2), z'_{i+1}(2)} & \text{if } E_1 = R_n, \mathbf{z}' = R_i(\mathbf{z}), \\ (1 - f_{z'_{i+1}, z'_{i+2}})\delta_{z_i, z'_i} & \\ + f_{z'_{i+1}, z'_{i+2}}(\frac{1}{2}\delta_{z_i, z'_{i+1}} + \frac{1}{2}\delta_{z_i, z'_{i+2}}) & \text{if } E_1 = S_n, \mathbf{z}' = S_i(\mathbf{z}), \end{cases} \quad (\text{D.B.3})$$

and 0 otherwise, with  $\delta$  denoting Kronecker's delta. Now let

$$\Psi_{E_1}(\mathbf{n}, \mathbf{n}') = \sum_{\mathbf{z}': \mathbf{n}'} \mathbb{P}_{E_1}(\mathbf{z}|\mathbf{z}'), \quad (\text{D.B.4})$$

where the summation is over all ordered samples  $\mathbf{z}'$  having the type configuration  $\mathbf{n}'$ . In the following we always assume  $\mathbf{e}_i \neq \mathbf{e}_j \neq \mathbf{e}_k \neq \mathbf{e}_i$ . Then we have :

$$\Psi_{E_1}(\mathbf{n}, \mathbf{n}') = \begin{cases} \frac{n_i(n_i-1)}{2} & \text{if } E_1 = C_n \\ & \text{and } \mathbf{n}' = \mathbf{n} - \mathbf{e}_i, \\ n(1 - c_i) + \sum_j n_j c_j & \text{if } E_1 = V_n \\ & \text{and } \mathbf{n}' = \mathbf{n} + \mathbf{e}_i, \\ n_i(\delta_{i,(j_1,k_2)} + \delta_{i,(k_1,j_2)}) & \text{if } E_1 = R_n \\ & \text{and } \mathbf{n}' = \mathbf{n} - \mathbf{e}_i + \mathbf{e}_j + \mathbf{e}_k, \\ \sum_{j \neq i} n_j(\delta_{j,(j_1,i_2)} + \delta_{j,(i_1,j_2)}) + n_i & \text{if } E_1 = R_n \\ & \text{and } \mathbf{n}' = \mathbf{n} + \mathbf{e}_i, \\ A_{i,j} & \text{if } E_1 = S_n \\ & \text{and } \mathbf{n}' = \mathbf{n} + \mathbf{e}_i + \mathbf{e}_j, \\ B_i & \text{if } E_1 = S_n \\ & \text{and } \mathbf{n}' = \mathbf{n} + 2\mathbf{e}_i, \end{cases} \quad (\text{D.B.5})$$

and 0 otherwise, where

$$\begin{aligned}
A_{i,j} &= \sum_{l \neq i,j} n_l \left( 2 - f_{i,j} - f_{j,i} + \frac{f_{i,l}}{2} + \frac{f_{l,j}}{2} + \frac{f_{i,l}}{2} + \frac{f_{j,l}}{2} \right) \\
&\quad + n_j \left( f_{j,j} + 2 - \frac{f_{i,j}}{2} - \frac{f_{j,i}}{2} \right) + n_i \left( f_{i,i} + 2 - \frac{f_{i,j}}{2} - \frac{f_{j,i}}{2} \right) \\
&= (n - n_i - n_j) (2 - f_{i,j} - f_{j,i}) + \sum_{l \neq i,j} n_l \left( \frac{f_{i,l}}{2} + \frac{f_{l,j}}{2} + \frac{f_{i,l}}{2} + \frac{f_{j,l}}{2} \right) \\
&\quad + n_j \left( f_{j,j} + 2 - \frac{f_{i,j}}{2} - \frac{f_{j,i}}{2} \right) + n_i \left( f_{i,i} + 2 - \frac{f_{i,j}}{2} - \frac{f_{j,i}}{2} \right)
\end{aligned} \tag{D.B.6}$$

and

$$\begin{aligned}
B_i &= n_i + \sum_{l \neq i} n_l \left( 1 - f_{i,i} + \frac{f_{i,l}}{2} + \frac{f_{l,i}}{2} \right) \\
&= n_i + (n - n_i) (1 - f_{i,i}) + \sum_{l \neq i} n_l \left( \frac{f_{i,l}}{2} + \frac{f_{l,i}}{2} \right).
\end{aligned} \tag{D.B.7}$$

Then we have

$$\mathbb{P}_G(\mathbf{z}|\mathbf{x}) = \sum_{\mathbf{n}'} \Psi_{E_1}(\mathbf{n}, \mathbf{n}') P_{\mathbf{x}}(\mathbf{n}'). \tag{D.B.8}$$

Next we consider  $G = (E_1, E_2)$  where  $E_1, E_2$  are two pure events. We have

$$\mathbb{P}_G(\mathbf{z}|\mathbf{x}) = \sum_{\mathbf{n}''} \Psi_G(\mathbf{n}, \mathbf{n}'') P_{\mathbf{x}}(\mathbf{n}''), \tag{D.B.9}$$

with

$$\begin{aligned}
\Psi_G(\mathbf{n}, \mathbf{n}'') &= \sum_{\mathbf{z}'': \mathbf{n}''} \mathbb{P}_G(\mathbf{z} | \mathbf{z}'') \\
&= \sum_{\mathbf{z}'': \mathbf{n}''} \sum_{\mathbf{z}'} \mathbb{P}_{E_1}(\mathbf{z} | \mathbf{z}') \mathbb{P}_{E_2}(\mathbf{z}' | \mathbf{z}'') \\
&= \sum_{\mathbf{z}'} \mathbb{P}_{E_1}(\mathbf{z} | \mathbf{z}') \Psi_{E_2}(\mathbf{n}', \mathbf{n}'') \\
&= \sum_{\mathbf{n}'} \Psi_{E_1}(\mathbf{n}, \mathbf{n}') \Psi_{E_2}(\mathbf{n}', \mathbf{n}''). \tag{D.B.10}
\end{aligned}$$

Recursively, for a graph topology of  $m$  pure events  $G = (E_1, E_2, \dots, E_m)$ , we obtain

$$\mathbb{P}_G(\mathbf{z} | \mathbf{x}) = \sum_{\mathbf{n}^{(m)}} \Psi_G(\mathbf{n}^{(0)}, \mathbf{n}^{(m)}) P_{\mathbf{x}}(\mathbf{n}^{(m)}), \tag{D.B.11}$$

with

$$\Psi_G(\mathbf{n}^{(0)}, \mathbf{n}^{(m)}) = \sum_{\mathbf{n}^{(1)}} \cdots \sum_{\mathbf{n}^{(m-1)}} \prod_{k=1}^m \Psi_{E_k}(\mathbf{n}^{(k-1)}, \mathbf{n}^{(k)}). \tag{D.B.12}$$

This provides a mean to compute  $\mathbb{P}_G(\mathbf{z} | \mathbf{x})$  with MATHEMATICA.

## Appendix D.C Computation of $E_{i,j,k}(\mathbf{x})$

In order to calculate  $E_{i,j,k}(\mathbf{x})$  in Equation (D.5.17) in the shortest possible time, we use a method inspired by Horner's rule for calculating a polynomial of degree  $n$  evaluated at some specific value  $x_0$ . The rule consists in writing

$$P(x_0) = \sum_{k=0}^n a_k x_0^k \tag{D.C.1}$$

into the form

$$P(x_0) = a_0 + x_0(a_1 + x_0(a_2 + \cdots + x_0(a_{n-1} + x_0 a_n) \cdots)).$$

Here, we write

$$E_{i,j,k}(\mathbf{x}) = \sum_{G \text{ eligible}} \mathbb{P}_G(\mathbf{z} | \mathbf{x}) \mathbb{P}(G) \mathbb{E}(T_{n_G}) \tag{D.C.2}$$

into the form

$$\begin{aligned}
E_{i,j,k}(\mathbf{x}) &= P_{\mathbf{x}}(\mathbf{n}) \mathbb{E}(T_3) + \sum_{E_1: (E_1) \text{ eligible}} \mathbb{P}(E_1) \sum_{\mathbf{n}'} \Psi_{E_1}(\mathbf{n}, \mathbf{n}') \\
&\quad \times \left( P_{\mathbf{x}}(\mathbf{n}') \mathbb{E}(T_{n_{E_1}}) + \sum_{E_2: (E_1, E_2) \text{ eligible}} \mathbb{P}(E_2) \sum_{\mathbf{n}''} \Psi_{E_2}(\mathbf{n}', \mathbf{n}'') \right. \\
&\quad \left. \times \left( P_{\mathbf{x}}(\mathbf{n}'') \mathbb{E}(T_{n_{E_2}}) + \dots \right) \right). \tag{D.C.3}
\end{aligned}$$

Moreover, a graph  $G$  is eligible if  $|G| \geq 2$  and  $n_G^+ \leq k$ . This algorithm reduces the calculation time by a factor 1/2000.

## Appendix D.D Coefficients $Q$ for the probability of fixation of allele $P_2$

$$\begin{aligned}
Q_{1,1,1} &= 0, & Q_{1,1,2} &= \frac{-A-4c_1+4c_2}{8}\sigma, \\
Q_{1,1,3} &= 0, & Q_{1,1,4} &= -\frac{-A-4c_1+4c_4}{8}\sigma, \\
Q_{1,2,2} &= \frac{-A-4c_1+4c_2}{8}\sigma, & Q_{1,2,3} &= \frac{-c_1+2c_2-c_3}{2}\sigma, \\
Q_{1,2,4} &= \frac{A-4c_1+2c_2+2c_4}{4}\sigma, & Q_{1,3,3} &= 0, \\
Q_{1,3,4} &= \frac{-c_1-c_3+2c_4}{2}\sigma, & Q_{1,4,4} &= \frac{3A-4c_1+4c_4}{8}\sigma, \\
Q_{2,2,2} &= 0, & Q_{2,2,3} &= \frac{-3A+4c_2-4c_3}{8}\sigma, \\
Q_{2,2,4} &= 0, & Q_{2,3,3} &= \frac{A+4c_2-4c_3}{8}\sigma, \\
Q_{2,3,4} &= \frac{-A+2c_2-4c_3+2c_4}{4}\sigma, & Q_{2,4,4} &= 0, \\
Q_{3,3,3} &= 0, & Q_{3,3,4} &= \frac{A-4c_3+4c_4}{8}\sigma, \\
Q_{3,4,4} &= \frac{A-4c_3+4c_4}{8}\sigma, & Q_{4,4,4} &= 0. \tag{D.D.1}
\end{aligned}$$

## Appendix D.E Strong recombination

With free recombination or any fixed recombination rate in the limit of a large population size, the ancestral material of a sample of size  $n$  is represented by a vector  $\mathbf{n} = (n_1, n_2, n_3, n_4)$  where  $n_1$  and  $n_2$  are the numbers of lineages that are ancestral at the trait locus with  $T_1$  and  $T_2$ , respectively, at this locus, while  $n_3$  and  $n_4$  are the numbers of lineages that are ancestral at the preference locus with  $P_1$  and  $P_2$ , respectively, at this locus. With  $N^2/2$  time steps as unit of time in a population of size  $N \rightarrow \infty$ , the rate of

viability selection is  $\sigma/2$  and the rate of sexual selection  $A\sigma/2$  for each ancestral lineage, while the rate of coalescence is 1 for each pair of lineages that are ancestral at the same locus. Note that the rate of coalescence of each pair of lineages that are ancestral at different loci is 1, but the lineages are instantaneously separated anew in the limit of a large population size so that no change actually occurs. This leads to a function

$$\Psi_{E_1}(\mathbf{n}, \mathbf{n}') = \begin{cases} \frac{n_i(n_i-1)}{2} & \text{if } E_1 = C_n \\ & \text{and } \mathbf{n}' = \mathbf{n} - \mathbf{e}_i \\ & \text{with } i \in \{1, 2, 3, 4\}, \\ n(1 - c_{ij}) + n_1c_{1j} + n_2c_{2j} & \text{if } E_1 = V_n \\ & + n_3c_{i3} + n_4c_{i4} \quad \text{and } \mathbf{n}' = \mathbf{n} + \mathbf{e}_i + \mathbf{e}_j \\ & \text{with } i \in \{1, 2\}, j \in \{3, 4\}, \\ A_{ij} & \text{if } E_1 = S_n \\ & \text{and } \mathbf{n}' = \mathbf{n} + \mathbf{e}_i + \mathbf{e}_j \\ & \text{with } i \in \{3, 4\}, j \in \{1, 2\}, \\ 0 & \text{otherwise, where} \end{cases} \quad (\text{D.E.1})$$

and 0 otherwise, where

$$\begin{aligned} A_{ij} = & n(1 - f_{ij}) \\ & + \frac{1}{2} (n_1(f_{i,j} + f_{i,1}) + n_2(f_{i,j} + f_{i,2}) + n_3(f_{i,j} + f_{3,j}) + n_4(f_{i,j} + f_{4,j})) \\ & = n \left( 1 - \frac{1}{2} f_{ij} \right) + \frac{1}{2} (n_1 f_{i,1} + n_2 f_{i,2} + n_3 f_{3,j} + n_4 f_{4,j}). \end{aligned} \quad (\text{D.E.2})$$

Note that  $c_{ij}$  represents the probability for an individual of type  $i$  at the trait locus and of type  $j$  at the preference locus to be replaced in the event of viability selection, while  $f_{ij}$  represents the probability for a female of type  $i$  at the preference locus mated to a male of type  $j$  at the trait locus to produce an offspring in the event of sexual selection.

With  $T_2$ -males being viability-deleterious but sexually preferred by  $P_2$ -females, for instance, we have

$$c_{11} = 1, \quad c_{12} = 1, \quad c_{21} = 0, \quad c_{22} = 0,$$

and

$$f_{1,1} = \frac{1}{2}, \quad f_{1,2} = \frac{1}{2}, \quad f_{2,1} = 0, \quad f_{2,2} = 1.$$

