The DiscreteFDR Package for Multiple Testing with Discrete Data

useR! 2024

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Agenda

1 Introduction

The Multiple Testing Problem

Big data analysis often involves a huge number m of statistical tests, e.g.

- Gene expression analysis ($m \approx 10^5$)
- Next-generation sequencing ($m \approx 10^6$)

m null hypotheses $H_0^1, \ldots, H_0^m \Rightarrow p$-values $p_1, \ldots, p_m$

- For a given significance level $\alpha \in (0, 1)$ it is expected to *falsely* reject $\alpha \cdot m$ hypotheses.
- $P(\text{at least one false discovery}) = 1 - (1 - \alpha)^m \xrightarrow{m \to \infty} 1$

$\Rightarrow$ **The more tests, the higher the risk of making false discoveries!**

$\Rightarrow$ Need for procedures that keep the number of false discoveries low **with good power**.

False Discovery Rate (FDR)

Definition:

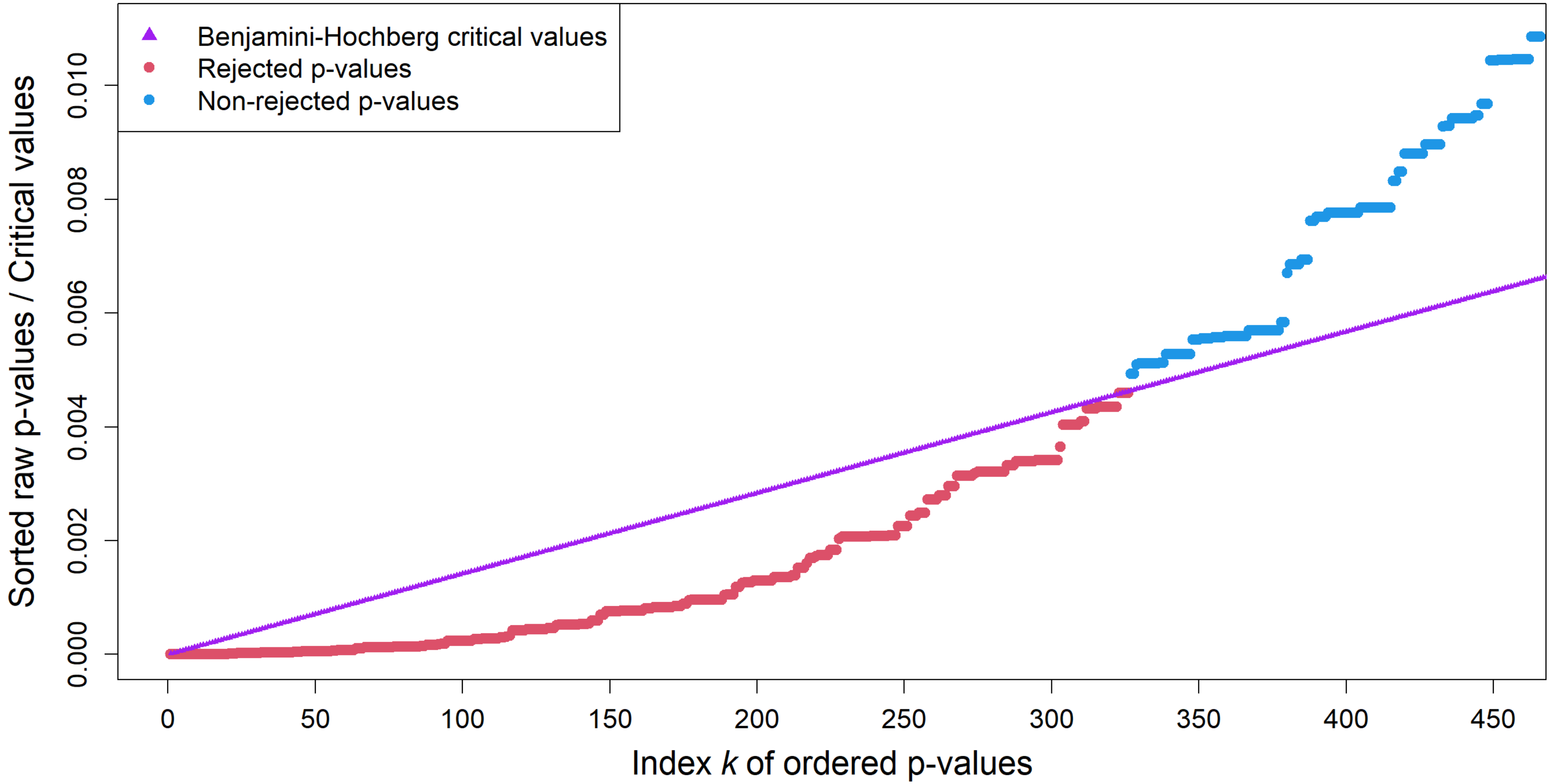
$$FDR := E\left(\frac{\text{number of falsely rejected hypotheses}}{\text{total number of rejected hypotheses}}\right)$$

Benjamini-Hochberg (BH) Procedure

Gold standard:

- Simple
- Powerful
- Guarantees $FDR \leq \alpha$

Idea: Compare ordered p-values $pv_{(k)}$ with critical values $\tau_k^{BH} = \frac{k}{m}\alpha$



Example: 450 smallest p-values out of 3525, BH rejections = 326

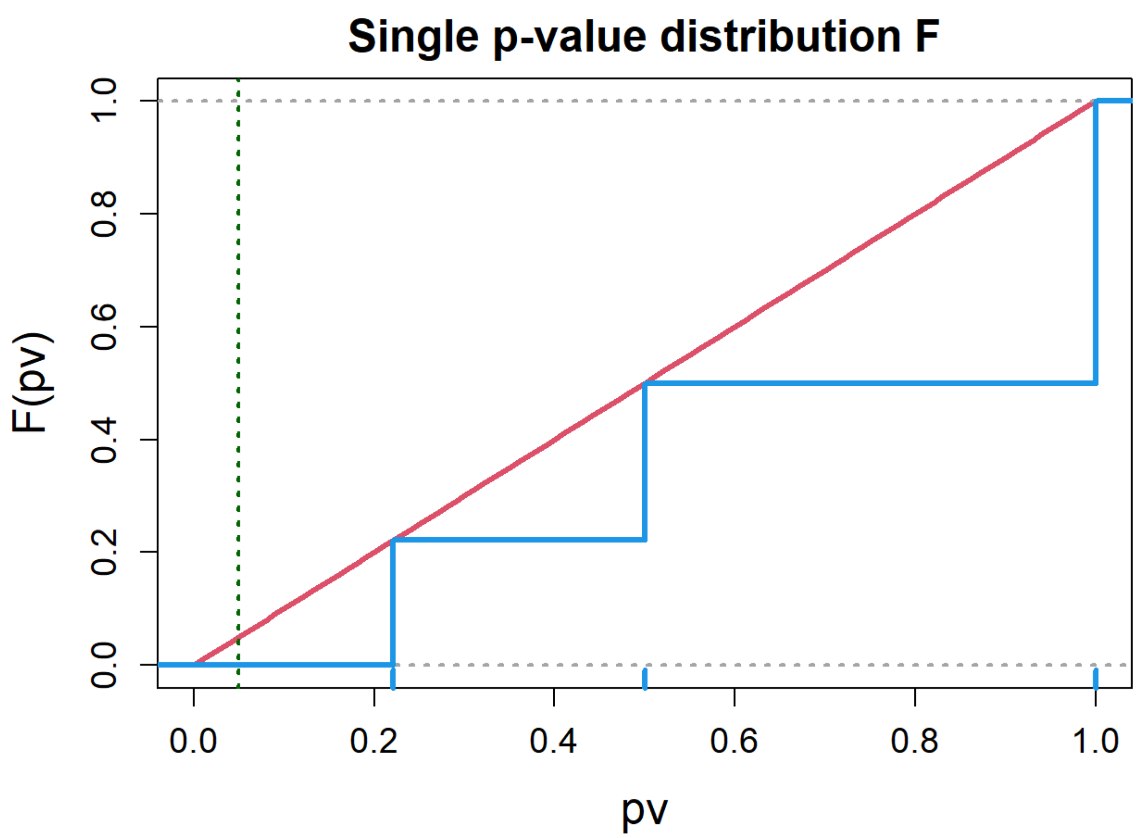
Challenge with Discrete Tests

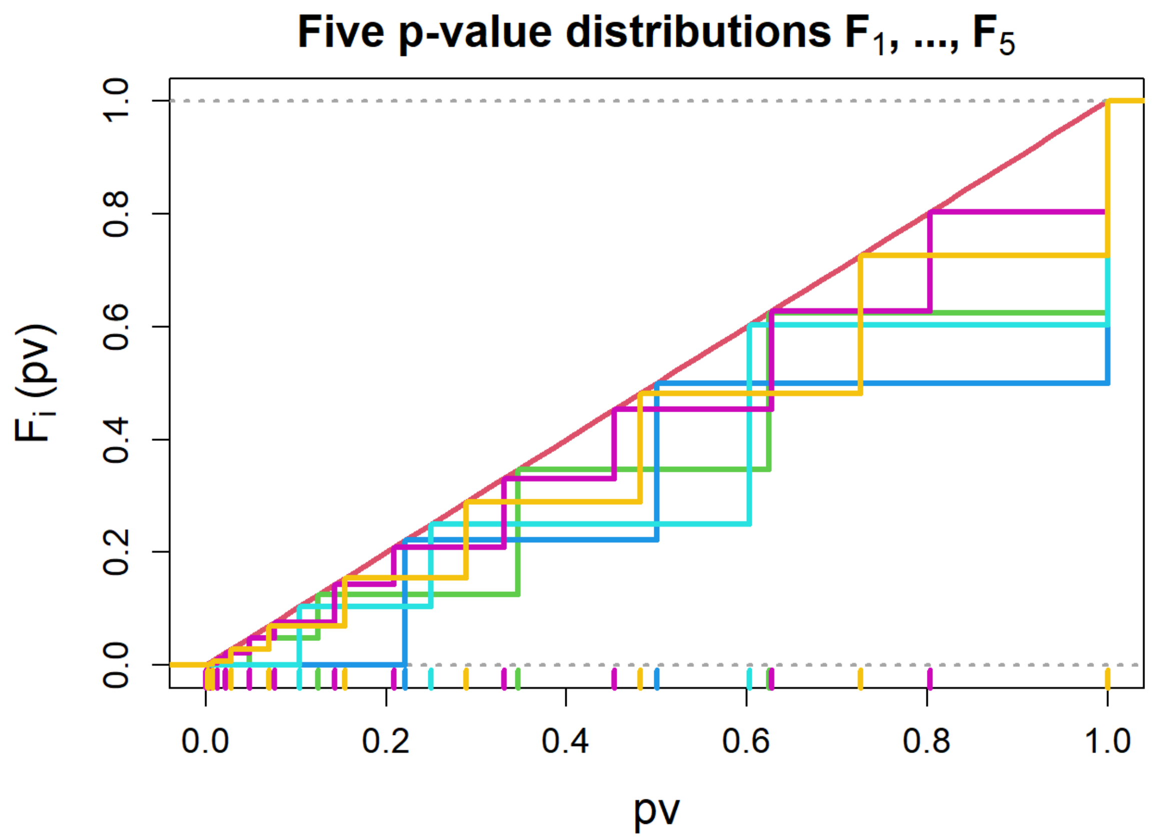
Continuous tests: under H_0, p-values are distributed with $P(PV \leq x) = F(x) = x$

$\Rightarrow$ observable p-value *support*: continuous **interval**

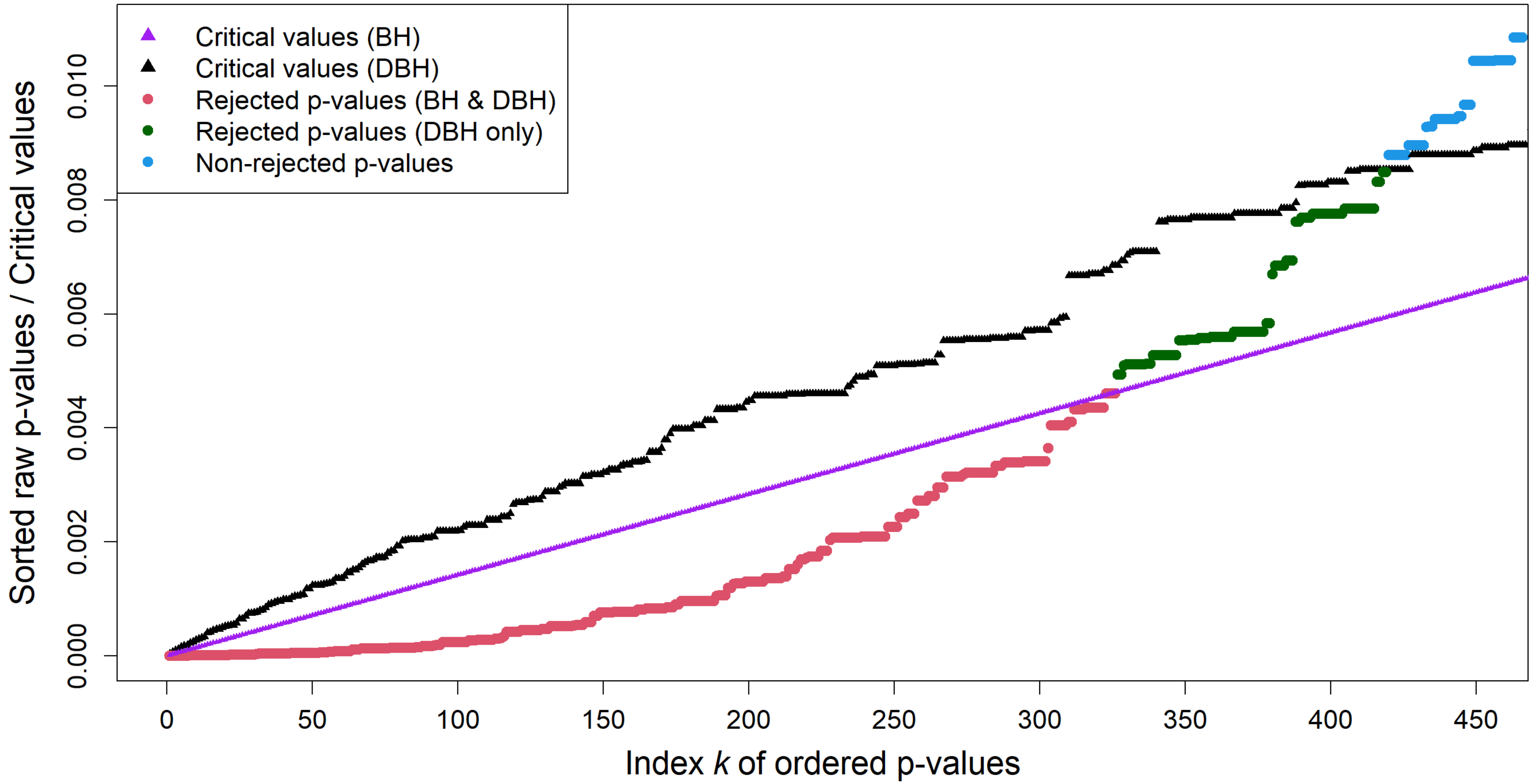
Discrete tests: under H_0, p-values are discretely distributed with $F(x) \leq x$

$\Rightarrow$ observable p-value *support*: discrete **set**





Idea of Discrete Benjamini-Hochberg



Here: BH rejections = 326, DBH rejections = 419

Discrete Benjamini-Hochberg Procedure

From Döhler, Durand & Roquain (2018)

- Central idea: transform p-values for discreteness via $\xi(pv) = \frac{1}{m}\sum_{i=1}^{m}\frac{F_i(pv)}{1-F_i(\tau_m^{DBH})}$
  ($F_1, \ldots, F_m$: p-value distribution functions under their respective nulls)

- Two ways of making decisions:
  a. Use standard BH critical values: $\xi\left(pv_{(k)}\right) \leq \tau_k^{BH}$
  b. Use new discrete critical values: $pv_{(k)} \leq \tau_k^{DBH} = \max\left\{pv \in \mathcal{A} \;\middle|\; \xi(pv) \leq \tau_k^{BH}\right\}$

2 The `DiscreteFDR` R package

Package Family

`DiscreteFDR` is part of a family of packages

- `DiscreteFDR`:
  - originally created and maintained by Guillermo Durand
  - major updates in early July 2024
- `DiscreteTests`:
  - provides vectorised(!) functions for computing exact p-values and their supports of several discrete tests
  - results are output in a `DiscreteTestResults` R6 class object
- `DiscreteDatasets`:
  - provides some benchmark datasets from literature that can be used with `DiscreteTests` and `DiscreteFDR`

Main Function

Generic function `discrete.BH()` with two methods:

```
# "traditional" method
discrete.BH.default()
# new, preferred method
discrete.BH.DiscreteTestResults()
```

most important parameters:

- `test.results`:
  - numeric vector that includes the p-values **or**
  - object of R6 class `DiscreteTestResults` from package `DiscreteTests`
- `pCDFlist`: list of (numeric) support sets; `.default` method only
- `alpha`: FDR level (default: `0.05`)
- `ret.crit.consts`: compute and return critical constants (default: `FALSE`)

Application Example

Preparations

```r
# data
library(DiscreteDatasets)
data("listerdata_four_columns")
print(listerdata_four_columns, max = 12)
```

```
            Col0_Counts.ThisCyto Met13_Counts.ThisCyto
AT1G01070.1                    9                    24
AT1G01070.2                    9                    24
AT1G01150.1                    3                     3
            Col0_Counts.AllOtherCytos Met13_Counts.AllOtherCytos
AT1G01070.1                     34235                      39318
AT1G01070.2                     34235                      39318
AT1G01150.1                     34241                      39339
 [ reached 'max' / getOption("max.print") -- omitted 3522 rows ]
```

```r
# Fisher's exact test (fisher.test.pv returns R6 class object)
library(DiscreteTests)
lister_test <- fisher.test.pv(listerdata_four_columns)
```

Perform Discrete Benjamini-Hochberg

```
library(DiscreteFDR)
# "modern"
DBH_lister <- discrete.BH(lister_test, ret.crit.consts = TRUE)
# "traditional"
DBH_lister <- discrete.BH(lister_test$get_pvalues(), lister_test$get_pvalue_support
                          ret.crit.consts = TRUE)

str(DBH_lister, max.level = 2)
```

```
List of 5
 $ Rejected       : num [1:419] 4.60e-03 4.22e-04 8.79e-06 1.74e-03 5.37e-04 ...
 $ Indices        : int [1:419] 13 17 31 54 61 69 94 101 118 131 ...
 $ Num.rejected   : int 419
 $ Critical.values: num [1:3525] 3.30e-05 6.28e-05 9.29e-05 1.14e-04 1.51e-04 ..
 $ Data           :List of 5
  ..$ Method      : chr "Discrete Benjamini-Hochberg procedure (step-up)"
  ..$ raw.pvalues: num [1:3525] 0.0348 0.0348 1 0.0088 0.2818 ...
  ..$ pCDFlist    :List of 3525
  ..$ FDR.level   : num 0.05
  ..$ Data.name   : chr "lister_test$get_pvalues() and lister_test$get_pvalue_"..
 - attr(*, "class")= chr [1:2] "DiscreteFDR" "list"
```

print and summary methods

```r
# print method
print(DBH_lister)
```

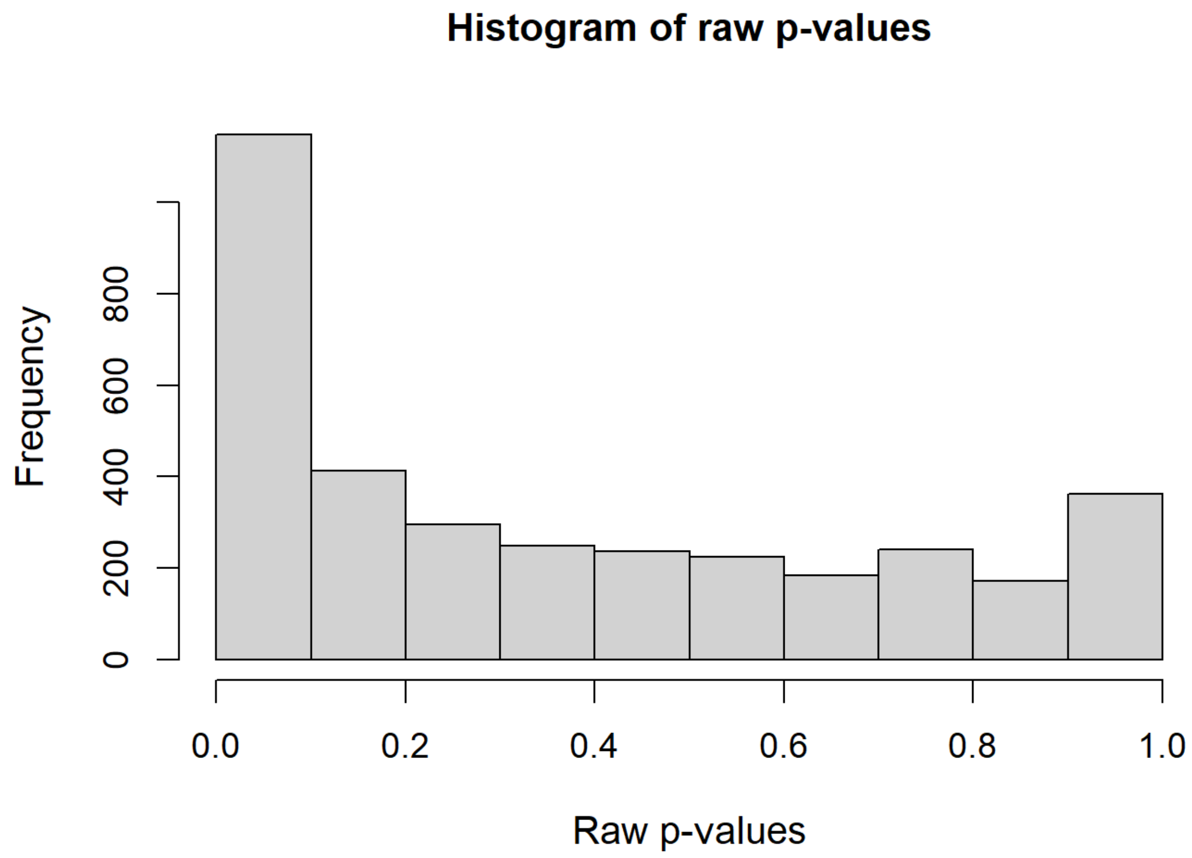
```
	Discrete Benjamini-Hochberg procedure (step-up)

Data:  lister_test$get_pvalues() and lister_test$get_pvalue_supports()
Number of tests = 3525
Number of rejections = 419 at global FDR level 0.05
(Original BH rejections = 326)
Largest rejected p value:  0.008487787
```

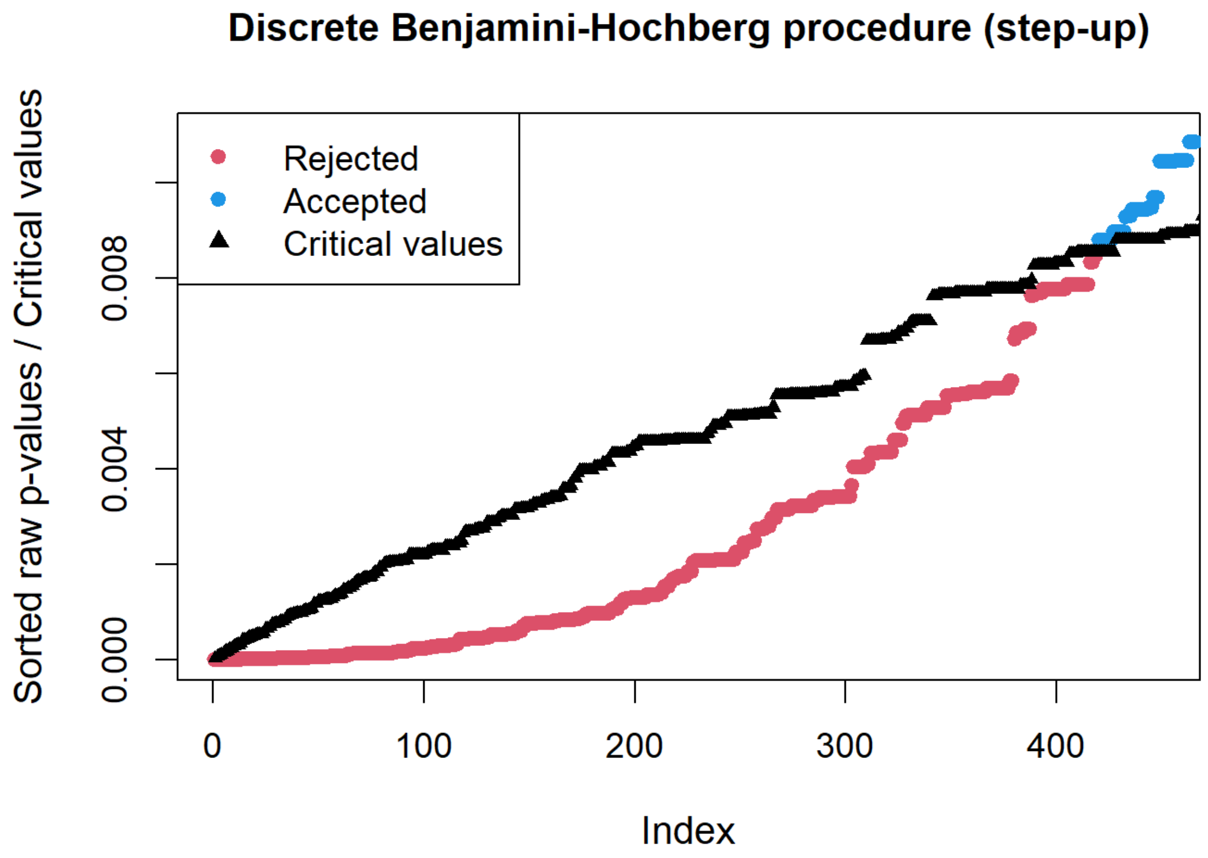
```r
# summary method
summary(DBH_lister)$Table |> head(5)
```

```
  Index      P.value Critical.value Rejected
1   228 1.465774e-07   3.299848e-05     TRUE
2  1705 3.029058e-07   6.277768e-05     TRUE
3  3524 5.742313e-07   9.286340e-05     TRUE
4   942 1.140346e-06   1.141108e-04     TRUE
5  1864 1.179705e-06   1.509283e-04     TRUE
```

hist and plot methods

```
# hist method
hist(DBH_lister)
# plot method
plot(DBH_lister, xlim = c(1, 450), ylim = c(0, 0.011), type.crit = 'p',
     pch = c(20, 20, 17), lwd = c(3, 3, 1), cex = c(1, 1, 0.7), legend = "topleft")
```





Pipes

```r
# pipe
listerdata_four_columns |>
  fisher.test.pv() |>
  discrete.BH() |>
  summary() |>
  with(Table) |>
  head()
```

```
  Index      P.value Rejected
1   228 1.465774e-07     TRUE
2  1705 3.029058e-07     TRUE
3  3524 5.742313e-07     TRUE
4   942 1.140346e-06     TRUE
5  1864 1.179705e-06     TRUE
6  2287 1.179705e-06     TRUE
```

3 Outlook

- `FDX`: apply changes of `DiscreteFDR` package
  - performance improvements
  - enable pipes
- `DiscreteTests`: more discrete tests
- `DiscreteDatasets`: more datasets

Literature

- Döhler, S., Durand, G. and Roquain, E. (2018). New FDR bounds for discrete and heterogeneous tests. *Electronic Journal of Statistics*, *12* (1), pp. 1867-1900. doi: 10.1214/18-EJS1441
- Durand, G., Junge, F., Döhler, S. and Roquain, E. (2019). DiscreteFDR: An R package for controlling the false discovery rate for discrete test statistics. *arXiv*. arXiv: 1904.02054
- Benjamini, Y. and Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society, Series B*. *57* (1), pp. 289–300. doi: 10.1111/j.2517-6161.1995.tb02031.x

Thank you! Any Questions?