

Tutorial for **swfdr** package

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Package overview

This package allows users to estimate the science-wise false discovery rate from Jager and Leek (2013), using an EM approach due to the presence of rounding and censoring. It also allows users to estimate the proportion of true null hypotheses in the presence of covariates, using a regression framework, as per Boca and Leek (2015).

The package is loaded using:

```
library(swfdr)
```

Estimating the proportion of true null hypothesis in the presence of covariates

As in Boca and Leek (2015), we denote by $\pi_0(x)$ the proportion of true null hypotheses as a function of a covariate x . This is estimated based on a list of p-values p_1, \dots, p_m corresponding to a set of null hypotheses, H_{01}, \dots, H_{0m} , and a design matrix X . The design matrix considers relevant meta-data, which could be valuable for improving estimation of the prior probability that a hypothesis is true or false.

Example: Adjust for sample size and allele frequency in BMI GWAS meta-analysis

We consider an example from the meta-analysis of data from a genome-wide association study (GWAS) for body mass index (BMI) from Locke et al. (2015). A subset of this data, corresponding to 50,000 single nucleotide polymorphisms (SNPs), can be loaded using:

```
data(BMI_GIANT_GWAS_sample)
head(BMI_GIANT_GWAS_sample)
```

```
##          SNP A1 A2 Freq_MAF_Hapmap      b      se      p      N
## 1 rs10510371  T  C          0.0250  0.0147  0.0152  0.3335 212965
## 2  rs918232   A  G          0.3417 -0.0034  0.0037  0.3581 236084
## 3  rs4816764  A  C          0.0083  0.0163  0.0131  0.2134 221771
## 4 rs17630047  A  G          0.1667  0.0004  0.0048  0.9336 236177
## 5  rs4609437  C  G          0.2500  0.0011  0.0042  0.7934 236028
## 6 rs11130746  G  A          0.2333 -0.0006  0.0042  0.8864 235634
##  Freq_MAF_Int_Hapmap
## 1      [0.000,0.127)
## 2      [0.302,0.500]
## 3      [0.000,0.127)
## 4      [0.127,0.302)
## 5      [0.127,0.302)
## 6      [0.127,0.302)
```

```
dim(BMI_GIANT_GWAS_sample)
```

```
## [1] 50000      9
```

A description of the variables in `BMI_GIANT_GWAS_sample` can be found on its help page. In particular, `p` gives the p-values for the association between the SNPs and BMI; `N` gives the total sample size considered in the study of a particular SNP; and `Freq_MAF_Hapmap` gives the frequency of the minor (less frequent allele) for a particular SNP in Hapmap. The column `Freq_MAF_Int_Hapmap` provides 3 approximately equal intervals for the Hapmap MAFs:

```
table(BMI_GIANT_GWAS_sample$Freq_MAF_Int_Hapmap)
```

```
##
## [0.000,0.127) [0.127,0.302) [0.302,0.500]
##           16813           16887           16300
```

The `lm_pi0` function

This function estimates $\pi_0(x)$. It inputs the following parameters:

- `pValues` Numerical vector of p-values
- `lambda` Numerical vector of thresholds in $[0, 1)$ at which $\pi_0(x)$ is estimated. Default thresholds are $(0.05, 0.10, \dots, 0.95)$.
- `X` Design matrix (one test per row, one variable per column). Do not include the intercept.
- `smooth.df` Number of degrees of freedom when estimating $\pi_0(x)$ by smoothing. Default is 3.
- `threshold` If TRUE (default), all estimates are thresholded at 0 and 1, if FALSE, none of them are.

To apply it to the BMI GWAS dataset, we first create the design matrix, using natural cubic splines with 5 degrees of freedom to model `N` and 3 discrete categories for the MAFs:

```
X <- model.matrix(~ splines::ns(N,5) + Freq_MAF_Int_Hapmap, data = BMI_GIANT_GWAS_sample)[,-1]
head(X)
```

```
## splines::ns(N, 5)1 splines::ns(N, 5)2 splines::ns(N, 5)3
## 1 7.242962e-01 0.0000000 -0.096623916
## 2 6.214473e-05 0.9873057 0.010529926
## 3 8.482281e-01 0.0000000 -0.054593655
## 4 0.000000e+00 0.9847066 0.012746260
## 5 4.971578e-04 0.9884279 0.009232155
## 6 3.080761e-02 0.9658228 0.002791946
## splines::ns(N, 5)4 splines::ns(N, 5)5 Freq_MAF_Int_Hapmap[0.127,0.302)
## 1 0.193411872 -0.0967879566 0
## 2 0.004207151 -0.0021049077 0
## 3 0.109279996 -0.0546863405 0
## 4 0.005093468 -0.0025463522 1
## 5 0.003688505 -0.0018457495 1
## 6 0.001127918 -0.0005644374 1
## Freq_MAF_Int_Hapmap[0.302,0.500]
## 1 0
## 2 1
## 3 0
## 4 0
## 5 0
## 6 0
```

We then run the `lm_pi0` function:

```
pi0x <- lm_pi0(pValues=BMI_GIANT_GWAS_sample$p,
               X=X, smooth.df=3)
```

```
## [1] "At test #: 10000"
## [1] "At test #: 20000"
## [1] "At test #: 30000"
## [1] "At test #: 40000"
## [1] "At test #: 50000"
```

```
names(pi0x)
```

```
## [1] "pi0"          "pi0.lambda" "lambda"      "pi0.smooth"
```

The following values are returned:

- `pi0` Numerical vector of smoothed estimate of $\pi_0(x)$. The length is the number of rows in X .
- `pi0.lambda` Numerical matrix of estimated $\pi_0(x)$ for each value of `lambda`. The number of columns is the number of tests, the number of rows is the length of `lambda`.
- `lambda` Vector of the values of `lambda` used in calculating `pi0.lambda`.
- `pi0.smooth` Matrix of fitted values from the smoother fit to the $\pi_0(x)$ estimates at each value of `lambda` (same number of rows and columns as `pi0.lambda`).

Results from BMI GWAS meta-analysis example

We first add the estimates of $\pi_0(x)$ for $\lambda = 0.8$, $\lambda = 0.9$, and the final smoothed value to the `BMI_GIANT_GWAS_sample` object:

```
BMI_GIANT_GWAS_sample$fitted0.8 <- pi0x$pi0.lambda[,round(pi0x$lambda,2)==0.8]
BMI_GIANT_GWAS_sample$fitted0.9 <- pi0x$pi0.lambda[,round(pi0x$lambda,2)==0.9]
BMI_GIANT_GWAS_sample$fitted.final.smooth <- pi0x$pi0
```

We next create a long data frame so that we can use the plotting tools in `ggplot2`:

```
ldf <- reshape2::melt(BMI_GIANT_GWAS_sample,
                      id.vars=colnames(BMI_GIANT_GWAS_sample)[-grep("fitted",colnames(BMI_GIANT_GWAS_sample))],
                      value.name = "pi0", variable.name = "lambda")
ldf$lambda <- as.character(ldf$lambda)
ldf$lambda[ldf$lambda=="fitted0.8"] <- "lambda=0.8"
ldf$lambda[ldf$lambda=="fitted0.9"] <- "lambda=0.9"
ldf$lambda[ldf$lambda=="fitted.final.smooth"] <- "final smoothed pi0(x)"

head(ldf)
```

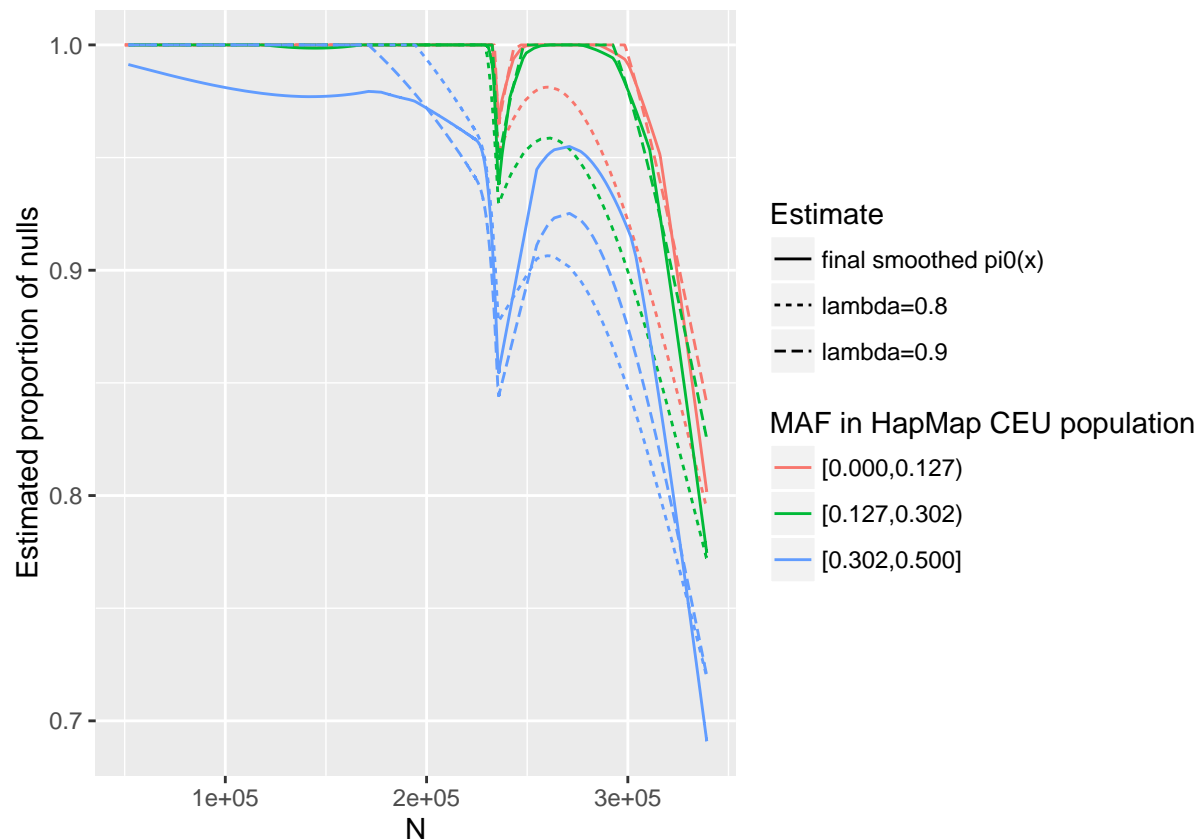
```
##          SNP A1 A2 Freq_MAF_Hapmap      b      se      p      N
## 1 rs10510371  T  C           0.0250  0.0147  0.0152  0.3335 212965
## 2  rs918232   A  G           0.3417 -0.0034  0.0037  0.3581 236084
## 3  rs4816764  A  C           0.0083  0.0163  0.0131  0.2134 221771
## 4  rs17630047 A  G           0.1667  0.0004  0.0048  0.9336 236177
```

```
## 5 rs4609437 C G 0.2500 0.0011 0.0042 0.7934 236028
## 6 rs11130746 G A 0.2333 -0.0006 0.0042 0.8864 235634
## Freq_MAF_Int_Hapmap lambda pi0
## 1 [0.000,0.127) lambda=0.8 1.0000000
## 2 [0.302,0.500] lambda=0.8 0.8776054
## 3 [0.000,0.127) lambda=0.8 1.0000000
## 4 [0.127,0.302) lambda=0.8 0.9301394
## 5 [0.127,0.302) lambda=0.8 0.9298095
## 6 [0.127,0.302) lambda=0.8 0.9313944
```

The plot of the estimates of $\pi_0(x)$ against the sample size N , stratified by the MAF categories can thus be obtained:

```
library(ggplot2)

ggplot(ldf, aes(x=N, y=pi0))+
  geom_line(aes(col=Freq_MAF_Int_Hapmap, linetype=lambda)) +
  ylab("Estimated proportion of nulls") +
  guides(color=guide_legend(title="MAF in HapMap CEU population"),
         linetype=guide_legend(title="Estimate"))
```



References

Boca, Simina M, and Jeffrey T Leek. 2015. “A Regression Framework for the Proportion of True Null Hypotheses.” *BioRxiv*. Cold Spring Harbor Labs Journals, 035675.

Jager, Leah R, and Jeffrey T Leek. 2013. “Empirical Estimates Suggest Most Published Medical Research Is True.” *Biostatistics*.

Locke, Adam E, Bratati Kahali, Sonja I Berndt, Anne E Justice, Tune H Pers, Felix R Day, Corey Powell, et al. 2015. “Genetic Studies of Body Mass Index Yield New Insights for Obesity Biology.” *Nature* 518 (7538). Nature Publishing Group: 197–206.