

# Package ‘DiscreteQvalue’

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**Title** Improved q-Values for Discrete Uniform and Homogeneous Tests

**Version** 1.1

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**Description** We consider a multiple testing procedure used in many modern applications which is the q-value method proposed by Storey and Tibshirani (2003), <doi:10.1073/pnas.1530509100>. The q-value method is based on the false discovery rate (FDR), hence versions of the q-value method can be defined depending on which estimator of the proportion of true null hypotheses,  $p_0$ , is plugged in the FDR estimator. We implement the q-value method based on two classical  $\pi_0$  estimators, and furthermore, we propose and implement three versions of the q-value method for homogeneous discrete uniform P-values based on  $\pi_0$  estimators which take into account the discrete distribution of the P-values.

**License** GPL-2

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DiscreteQvalue-package

*Improved q-values for discrete uniform and homogeneous tests*

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## Description

This package implements five different versions of the q-value multiple testing procedure proposed by Storey and Tibshirani (2003). The q-value method is based on the false discovery rate (FDR); different versions of the q-value method can be defined depending on the particular estimator used for the proportion of true null hypotheses,  $\pi_0$ , which is plugged in the FDR formula. The first version of the q-value uses the  $\pi_0$  estimator in Storey (2002), with tuning parameter  $\lambda = 0.5$ ; whereas the second version uses the  $\pi_0$  estimator in Storey and Tibshirani (2003), which is based on an automatic method to select the tuning parameter  $\lambda$ . These two methods are only appropriate when the P-values follow a continuous uniform distribution under the global null hypothesis. This package also provides three other versions of the q-value for homogeneous discrete uniform P-values, which often appear in practice. The first discrete version of the q-value uses the  $\pi_0$  estimator proposed in Liang (2016). The second discrete q-value method uses the estimator of  $\pi_0$  proposed in Chen et al. (2014), when simplified for the special case of homogeneous discrete P-values. The third discrete version of the q-value employs a standard procedure but applied on randomized P-values. Once the estimated q-values are computed, the q-value method rejects the null hypotheses whose q-values are less than or equal to the nominal FDR level. All the versions of the q-value method explained above can be seen in Cousido-Rocha et al. (2019).

## Details

- Package: ‘DiscreteQvalue’
- Version: 1.0
- Maintainer: Marta Cousido Rocha <martacousido@uvigo.es>
- License: GPL-2

## Value

- ‘DQ’

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**References**

- Chen, X., R. W. Doerge, and J. F. Heyse (2014). Methodology Multiple testing with discrete data: proportion of true null hypotheses and two adaptive FDR procedures. arXiv:1410.4274v2.
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- Storey, J. and R. Tibshirani (2003). Statistical significance for genomewide studies. *Proceedings of National Academy of Science* 100, 9440-9445.

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DQ

*Improved q-values for discrete uniform and homogeneous tests*

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**Description**

Performs the five versions of the q-value method considered in Cousido-Rocha et al. (2019). The q-value method is based on the false discovery rate (FDR), and the versions differ in the estimator of the proportion of true null hypotheses,  $\pi_0$ , which is plugged in the FDR estimator. Specifically, we consider as possible estimators for  $\pi_0$ : two usual estimators for continuous and possibly heterogeneous P-values; an estimator for discrete P-values defined in two steps: firstly the P-values are randomized, and then the usual  $\pi_0$  estimator for continuous P-values is applied; and the estimators recently proposed for discrete P-values by Liang (2016) and Chen et al. (2014).

**Usage**

```
DQ(  
  pv,  
  ss = NULL,  
  ss_inf = FALSE,  
  method = c("ST", "SS", "Liang", "Chen", "Rand"),  
  lambda = seq(0.05, 0.95, 0.05)  
)
```

### Arguments

<code>pv</code>	A vector of P-values.
<code>ss</code>	Support of the discrete distribution of the P-values. Only required for “Liang”, “Chen” and “Rand” methods which are specifically proposed for discrete P-values. If the P-values are continuous the methods “ST” and “SS” do not need this argument, hence “ss=NULL” by default.
<code>ss_inf</code>	Logical. Default is FALSE. A variable indicating whether the support of the discrete distribution of the P-values is finite or infinite. See details.
<code>method</code>	The q-value method. By default the “Chen” method is computed.
<code>lambda</code>	The value of the tuning parameter to estimate $\pi_0$ when the method is “ST”. See details.

### Details

The function implements the five different versions of the q-value method in Cousido-Rocha et al. (2019). Three versions are novel adaptations for the case of homogeneous discrete uniform P-values, whereas the other two are classical versions of the q-value method for P-values which follow a continuous uniform distribution under the global null hypothesis. The classical versions are the q-value method based on the  $\pi_0$  estimator proposed in Storey (2002) with tuning parameter  $\lambda = 0.5$ , and the q-value procedure which uses the  $\pi_0$  estimator in Storey and Tibshirani (2003) who proposed an automatic method to estimate  $\pi_0$ . We refer to these methods as “SS” and “ST”, respectively. On the other hand the three adaptations of the q-value method for homogeneous discrete uniform P-values are: “Liang” which considers the  $\pi_0$  estimator proposed in Liang (2016); “Chen” which uses a simplification for homogeneous discrete P-values of the algorithm for the estimation of  $\pi_0$  proposed in Chen et al. (2014); and “Rand” which employs the standard q-value procedure but applied to randomized P-values. For details of the different q-value versions, in particular for the novel adaptations for homogeneous discrete uniform P-values, see Cousido-Rocha et al. (2019).

As we mentioned above the novel adaptations of the q-value method are developed for homogeneous discrete uniform P-values. Specifically, suppose that we test a large number of null hypothesis,  $p$ , and that the P-values  $\{pv_1, \dots, pv_p\}$  are observations of the random variables  $PV_i, i = 1, \dots, p$ . Homogeneous means that all the P-values share an identical support  $S$  with  $0 < t_1 < \dots < t_s < t_{s+1} \equiv 1$ . On the other hand, making an abuse of language, we say that the P-values follow a discrete uniform distribution if it holds  $Pr(PV_i \leq t) = t$  for  $t \in S, i = 1, \dots, p$ . The classical discrete uniform distribution is a particular case.

The argument “lambda” must be a sequence of values in  $[0, 1)$ , for details of this parameter see Storey (2002) or Storey and Tibshirani (2003). The latter paper recommends the default value “lambda=seq(0.05,0.95,0.05)”.

The support of the discrete distribution of the P-values can be finite or infinite. Hence the parameter “ss inf” must be “FALSE” if the support is finite and “TRUE” if the support is infinite. See examples where a poisson setting is considered.

Finally, it is relevant to mention that Cousido-Rocha et al. (2019) verified (via simulations) that the results of the different q-values methods for dependent P-values are very similar to the ones corresponding to the independent setting.

**Value**

A list containing the following components:

$\pi_0$	An estimate of the proportion of null P-values.
q.values	A vector of the estimated q-values (the main quantities of interest).

**Author(s)**

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**References**

- Chen, X., R. W. Doerge, and J. F. Heyse (2014). Methodology Multiple testing with discrete data: proportion of true null hypotheses and two adaptive FDR procedures. arXiv:1410.4274v2.
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- Storey, J. and R. Tibshirani (2003). Statistical significance for genomewide studies. Proceedings of National Academy of Science 100, 9440-9445.

**Examples**

```
# We consider a simple simulated data set to illustrate the use of the DQ function.
# We have simulated the following situation.
# We have two groups, for example, 5 patients with tumor 1 and 5 patients
# with tumor 2. For each patient 100 variables are measured, for example,
# gene expression levels. Besides, the distributions of 30 of the variables
# are different in the two groups, and the differences are in location.

# We consider a collection of densities {f1=N(0,1), f2=N(0,1/4), f3=N(2,1), f4=N(2,1/4)}. In
# the first group (tumor 1) the sample of each variable (gene) comes from one of
# the four densities with the same probability 1/4. On the other hand, in the second
# group the sample of each variable comes from the same density as in the first
# group except for 30 randomly selected variables for which the density changes
# producing location differences. Specifically, if the variable follows
# f1 in the first group, its density, in the second group, is f3 producing a
# change on its location parameter. The situation for the other cases is as follows:
# the density f2 (f3 or f4) in group 1 leads to density f4 (f1 or f2, respectively)
# in the second one.
```

```

set.seed(123)
p <- 100
n = m = 5
inds <- sample(1:4, p, replace = TRUE)
X <- matrix(rep(0, n * p), ncol = n)

for (j in 1:p){
  if (inds[j] == 1){
    X[j, ] <- rnorm(n)}
  if (inds[j] == 2){
    X[j, ] <- rnorm(n, sd = sqrt(1/4))
  }
  if (inds[j] == 3){
    X[j, ]<-rnorm(n, mean = 2)
  }
  if (inds[j] == 4){
    X[j, ]<-rnorm(n, mean = 2, sd = sqrt(1/4))
  }
}

rho <- 0.3

ind <- sample(1:p, rho * p)
li <- length(ind)
indsy <- inds

for (l in 1:li){
  if (indsy[ind[l]] == 1){indsy[ind[l]] = 3} else{
    if (indsy[ind[l]] == 2){indsy[ind[l]] = 4} else {
      if (indsy[ind[l]] == 3){indsy[ind[l]] = 1}
      else{indsy[ind[l]] = 2}}}}

Y <- matrix(rep(0, m * p), ncol = m)

for (j in 1:p){
  if (indsy[j] == 1){
    Y[j, ] <- rnorm(m)}
  if (indsy[j] == 2){
    Y[j, ] <- rnorm(m, sd = sqrt(1/4))
  }
  if (indsy[j] == 3){
    Y[j, ] <- rnorm(m, mean = 2)
  }
  if (indsy[j] == 4){
    Y[j, ]<- rnorm(m, mean = 2, sd = sqrt(1/4))
  }
}

# We can see which are the variables with different distributions in the two data sets.

dif <- which(inds != indsy)

```

```
# Cross table for (X,Y) density indexes:

table(inds,indsy)

# Our interest is to identify which variables have a different distribution in the two groups.
# Hence, since the differences between the distributions are in location, we applied
# Wilcoxon-Mann-Whitney test to verify for each variable the equality of distribution
# in the two groups.

library(exactRankTests)
library(coin)

# We compute the P-values

p <- nrow(X)
pv <- 1:p
for (i in 1:p){
  pv[i] <- wilcox.exact(X[i, ], Y[i, ])$p.value
}

# When the sample size is small, in this case n=m=5, the distribution of
# the Wilcoxon's statistic is calibrated using an exact permutation test. Hence,
# the P-values are homogeneous discrete uniform distributed with support points
# of such distribution:

ss <- c(1, 2, 4, 7, 12, 19, 28, 39, 53,69, 87, 106, 126) / 126

# When the number of P-values is large enough "ss" is equal to:
sort(unique(pv))

# For details about the Wilcoxon-Mann-Whitney test and its exact distribution
# see Section 9.2 of Gibbons and Chakraborti (1992).

# We apply Chen method:

R <- DQ(pv, ss = ss, method = "Chen")

# The estimate of the proportion of null P-values:

R$pi0

# Summary of the vector of the estimated q-values:

summary(R$q.values)

# How many null hypotheses are rejected?
alpha <- 0.05
sum(R$q.values < alpha)

# Which variables correspond to such null hypotheses?
```

```

which(R$q.values < alpha)

# Classification table (Decision at nominal level alpha vs. reality):

table(R$q.values < alpha, inds != indsy)

# The conclusion from the previous table is that Chen method reports
# 21 true positives and 9 false negatives.

# We can also apply Liang and SS methods as follows.
RLiang <- DQ(pv, ss = ss, method = "Liang")
RSS <- DQ(pv, ss = ss, method = "SS")

# The next graphic help us to see that Liang method (for discrete P-values)
# is more powerful than SS method (only suitable for continuous P-values).

plot(RSS$q.values, RLiang$q.values)
abline(a = 0, b = 1, col = 2, lty = 2)

# We consider a poisson setting to show a case where the support of the discrete
# distribution of the P-values is infinite.
# We generate 100 values of a poisson distribution with event rate 10.
# Then we compute the probability that each of the values come from a
# a poisson distribution with event rate 10. This set of probabilities
# are considered as our set of P-values.

p <- 100
N <- rpois(p, lambda = 10)
pv <- 1:p
for(i in 1:p){
  pv[i] <- ppois(N[i], lambda = 10)
}

# It is well know that the support of a poisson distribution is infinite
# and equal to the natural numbers. Hence to know the support of the P-values
# defined above, we compute for 1,..., 50 their corresponding P-value.
# We only considered 50 values because for large values than 50 the P-value is 1 again.

nn_0 <- 50
ss <- 1:(nn_0 + 1)
for (i in 1:(nn_0 + 1)){
  ss[i] <- ppois(i - 1, lambda = 10)
}

# We eliminate repeated values.
ss <- unique(ss)
# For Chen method the relevant support points are only the values below tau[100] = 0.5.
# We define the support ss as such values. Then, we can apply Chen method. Of
# course s_inf = TRUE.

indicator <- which(ss <= 0.5)

```



```
ssi <- ss[indicator]
R <- DQ(pv, ss = ssi, ss_inf = "TRUE", method = "Chen")
# For Liang method the relevant support values are also the values below 0.5, hence
# ss defined above is suitable.
R <- DQ(pv, ss = ssi, ss_inf = "TRUE", method = "Liang")

# For Rand method the relevant support values are those ones with match with
# the P-values, and also the largest support points smaller than each one of such P-values.
# Hence, ss only includes the relevant points, as we can see below.
pv_unique <- unique(pv)
p_u <- length(pv_unique)
ind <- 1:p_u
for(i in 1:p_u){
  ind[i] <- which(ss == pv_unique[i])
}
p_u == length(ind)
ind_minus <- ind - 1
ind_final <- unique(sort(c(ind, ind_minus)))
ss <- ss[ind_final]
# Now, we can apply Rand method.
R <- DQ(pv, ss = ss, ss_inf = "TRUE", method = "Rand")
```

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