

# TESTING FOR STOCHASTIC ORDERING ASSUMING MARGINAL COMPATIBILITY

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## 1. PRELIMINARIES

First we need to set up the C file so that it can access the R internals.

```
"..\src\ReprodCalcs.c" 1a≡  
  
#include <stdlib.h>  
#include <R.h>  
#include <Rdefines.h>  
#include <Rmath.h>  
#include <R_ext/Applic.h>  
◇
```

File defined by [1ab](#), [2](#), [10b](#), [11b](#), [13bc](#), [14ab](#), [15](#), [16ab](#), [17](#), [18](#), [19ab](#), [20b](#), [23](#), [24](#).

We will be using object of `CBDData` class, which is defined in `CBDData.w`.

## 2. MARGINAL COMPATIBILITY

**2.1. Estimation.** The following C code implements the EM-algorithm for estimating the probabilities of response assuming marginal compatibility.

$$\pi_{rM}^{(t+1)} = \frac{1}{N} \sum_{i=1}^N h(r_i, r, n_i) \frac{\pi_{r,M}^{(t)}}{\pi_{r_i, n_i}^{(t)}}, \quad (1)$$

First we write a help-function that calculates all the probabilities  $\pi_{r,n}$  given the set of  $\theta_r = \pi_{r,M}$ . While there are a variety of ways doing this, we use a recursive formula:

$$\pi_{r,n} = \frac{n+1-r}{n+1} \pi_{r,n+1} + \frac{r+1}{n+1} \pi_{r+1,n+1} \quad (2)$$

```
"..\src\ReprodCalcs.c" 1b≡
```

```
double static **Marginals(double* theta, int maxsize)  
{  
    double **res;  
    int r, n;  
  
    res = malloc((maxsize+1)*sizeof(double *));  
    for (n=0; n<=maxsize; n++){  
        res[n] = calloc(n+1, sizeof(double));  
    }  
  
    for (r=0; r<=maxsize; r++){  
        res[maxsize][r] = theta[r];  
    }  
  
    for (n=maxsize-1; n>=1; n--){  
        for (r=0; r<=n; r++){  
            res[n][r] = (n+1.0-r)/(n+1.0)*res[n+1][r] + (r+1.0)/(n+1.0)*res[n+1][r+1];  
        }  
    }  
}
```

```

    }
}

return res;
}
◇

```

File defined by [1ab](#), [2](#), [10b](#), [11b](#), [13bc](#), [14ab](#), [15](#), [16ab](#), [17](#), [18](#), [19ab](#), [20b](#), [23](#), [24](#).

The actual EM iterations are performed in `ReprodEstimates`.

"..\src\ReprodCalcs.c" 2≡

```

SEXP ReprodEstimates(SEXP nvec, SEXP rvec, SEXP freqvec)
{
    double *theta, *thetaneu, abseerror, **marg;
    int i, maxsize, nr, ntot, r, ri, ni, n, fri, start;
    SEXP res;
    const double eps=1e-16;

    nr = LENGTH(nvec);
    maxsize = 0;
    ntot = 0;
    for (i=0; i<nr; i++){
        if (INTEGER(nvec)[i]>maxsize){
            maxsize = INTEGER(nvec)[i];
        }
        ntot += INTEGER(freqvec)[i];
    }

    theta = malloc((maxsize+1) * sizeof(double));
    thetaneu = malloc((maxsize+1) * sizeof(double));
    //starting values
    for (r=0; r<=maxsize; r++){
        theta[r] = 1.0/(maxsize+1);
    }
    abseerror = 1;
    //EM update
    while (abseerror>eps){
        abseerror = 0;
        marg = Marginals(theta, maxsize);
        for (r=0; r<=maxsize; r++) thetaneu[r] = 0;
        for (i=0; i<nr; i++){
            ri = INTEGER(rvec)[i];
            ni = INTEGER(nvec)[i];
            fri = INTEGER(freqvec)[i];
            for (r=ri; r<=maxsize-ni+ri; r++){
                thetaneu[r] += choose(ni,ri)*choose(maxsize-ni,r-ri)*theta[r]*fri*1.0/
                    marg[ni][ri] ;
            }
        }
        for (r=0; r<=maxsize; r++){
            thetaneu[r] = thetaneu[r]/(ntot*choose(maxsize,r)*1.0);
            abseerror += fabs(thetaneu[r]-theta[r]);
            theta[r] = thetaneu[r];
        }
        for(n = 0; n <= maxsize; n++) free(marg[n]);
        free(marg);
    }
}

```

```

PROTECT(res = allocMatrix(REALSXP, maxsize+1, maxsize));
marg = Marginals(theta, maxsize);
for (n=1, start=0; n<=maxsize; n++, start+=(maxsize+1)){
  for (r=0; r<=n; r++){
    REAL(res)[start+r] = marg[n][r];
  }
  for (r=n+1; r<=maxsize; r++){
    REAL(res)[start+r] = NA_REAL;
  }
}

for(n = 0; n <= maxsize; n++) free(marg[n]);
free(marg);
free(theta);
free(thetaneu);

UNPROTECT(1);
return res;

}
◇

```

File defined by [1ab](#), [2](#), [10b](#), [11b](#), [13bc](#), [14ab](#), [15](#), [16ab](#), [17](#), [18](#), [19ab](#), [20b](#), [23](#), [24](#).  
 Defines: `ReprodEstimates` [4b](#).

We will call the C function from R to calculate estimates separately by treatment group. For the package the compiled library needs to be loaded.

```
"../R/aaa-generics1.R" 4a≡
```

```
#'Distribution of the number of responses assuming marginal compatibility.
#
#'#The \code{mc.est} function estimates the distribution of the number of
#'#responses in a cluster under the assumption of marginal compatibility:
#'#information from all cluster sizes is pooled. The estimation is performed
#'#independently for each treatment group.
#
#'#The EM algorithm given by Stefanescu and Turnbull (2003) is used for the binary data.
#
#'#@useDynLib CorrBin, .registration=TRUE
#'#@export
#'#@param object a \code{\link{CBData}} or \code{\link{CMDData}} object
#'#@param \dots other potential arguments; not currently used
#'#@return For \code{CBData}: A data frame giving the estimated pdf for each treatment and
#'#clustersize. The probabilities add up to 1
#'#for each \code{Trt}/\code{ClusterSize} combination. It has the following columns:
#'#@return \item{Prob}{numeric, the probability of \code{NResp} responses in a
#'#cluster of size \code{ClusterSize} in group \code{Trt}}
#'#@return \item{Trt}{factor, the treatment group}
#'#@return \item{ClusterSize}{numeric, the cluster size}
#'#@return \item{NResp}{numeric, the number of responses}
#'#@author Aniko Szabo
#'#@references Stefanescu, C. & Turnbull, B. W. (2003) Likelihood inference for
#'#exchangeable binary data with varying cluster sizes. \emph{Biometrics}, 59,
#'#18-24
#'#@keywords nonparametric models
#'#@examples
#
#'#data(shelltox)
#'#sh.mc <- mc.est(shelltox)
#
#'#if (require(lattice)){
#'#xyplot(Prob~NResp|factor(ClusterSize), groups=Trt, data=sh.mc, subset=ClusterSize>0,
#'# type="l", as.table=TRUE, auto.key=list(columns=4, lines=TRUE, points=FALSE),
#'# xlab="Number of responses", ylab="Probability P(R=r|N=n)")
#'#}
#'#@name mc.est

mc.est <- function(object,...) UseMethod("mc.est")
```

◇  
File defined by [4a](#), [5](#).  
Uses: `mc.est` [4b](#).

```
"../R/Reprod.R" 4b≡
```

```
#'#@rdname mc.est
#'#@method mc.est CBData
#'#@export

mc.est.CBData <- function(object, ...){
  cbdata <- object[object$Freq>0, ]
  #by trt
  do.est.fun <- function(x){
    est <- .Call("ReprodEstimates", as.integer(x$ClusterSize), as.integer(x$NResp),
                  as.integer(x$Freq), PACKAGE="CorrBin")
```

```

est <- cbind(c(1,rep(NA,nrow(est)-1)), est)
idx <- upper.tri(est,diag=TRUE)
est.d <- data.frame(Prob=est[idx], ClusterSize=as.integer(col(est)[idx]-1),
                    NResp=as.integer(row(est)[idx]-1),
                    Trt=x$Trt[1])

est.d}

est.list <- by(cbind(est, list(Trt=cbdata$Trt)), do.est.fun)
do.call(rbind, est.list)}

```

File defined by [4b](#), [6](#), [7](#), [8](#), [9](#), [10a](#), [11c](#), [12a](#), [26ab](#), [27](#), [28](#), [29ab](#), [30](#), [31](#).

Defines: `mc.est` [4a](#), [5](#), [7](#), [8](#), [9](#), [26b](#).

Uses: `ReprodEstimates` [2](#).

**2.2. Testing marginal compatibility.** The `mc.test.chisq` function implements Pang and Kuk's version of the test for marginal compatibility. Note that it only tests that the marginal probability of response  $p_i$  does not depend on the cluster size. The original test was only defined for one group and the test statistic was compared to  $\chi_1^2$  (or more precisely, it was a z-test), however the test is easily generalized by adding the test statistics for the  $G$  separate groups and using a  $\chi_G^2$  distribution.

$$Z_g = \left[ \sum_{i=1}^{N_g} (c_{n_{g,i}} - \bar{c}_g) r_{g,i} \right] / \left[ \hat{p}_g (1 - \hat{p}_g) \sum_{i=1}^{N_g} n_{g,i} (c_{n_{g,i}} - \bar{c}_g)^2 \{1 + (n_{g,i} - 1) \hat{p}_g\} \right]^{1/2}, \quad (3)$$

where  $c_n$  are the scores for the Cochran-Armitage test usually chosen as  $c_n = n - (M + 1)/2$ ,  $\bar{c}_g = (\sum_{i=1}^{N_g} n_{g,i} c_{n_{g,i}}) / (\sum_{i=1}^{N_g} n_{g,i})$  is a weighted average of the scores;  $\hat{p}_g = (\sum_{i=1}^{N_g} r_{g,i}) / (\sum_{i=1}^{N_g} n_{g,i})$  is the raw response probability, and  $\hat{\rho}_g = 1 - [\sum_{i=1}^{N_g} (n_{g,i} - r_{g,i}) r_{g,i} / n_{g,i}] / [\hat{p}_g (1 - \hat{p}_g) \sum_{i=1}^{N_g} (n_{g,i} - 1)]$  is the Fleiss-Cuzack estimate of the intra-cluster correlation for the  $g$ th treatment group.

$$X^2 = \sum_{g=1}^G Z_g^2 \sim \chi_G^2 \text{ under } H_0. \quad (4)$$

"../R/aaa-generics1.R" 5≡

```

#'Test the assumption of marginal compatibility
#'
#'\code{mc.test.chisq} tests whether the assumption of marginal compatibility is
#'\violated in the data.
#'
#'\The assumption of marginal compatibility (AKA reproducibility or interpretability) implies that
#'\the marginal probability of response does not depend on clustersize.
#'\Stefanescu and Turnbull (2003), and Pang and Kuk (2007) developed a
#'\Cochran-Armitage type test for trend in the marginal probability of success
#'\as a function of the clustersize. \code{mc.test.chisq} implements a
#'\generalization of that test extending it to multiple treatment groups.
#'
#'\@export
#'\@param object a \code{\link{CBData}} or \code{\link{CMDData}} object
#'\@param \dots other potential arguments; not currently used
#'\@return A list with the following components:
#'\@return \item{overall.chi}{the test statistic; sum of the statistics for each
#'\group}
#'\@return \item{overall.p}{p-value of the test}
#'\@return \item{individual}{a list of the results of the test applied to each
#'\group separately: \itemize{ \item chi.sq the test statistic for the group
#'\item p p-value for the group}}
#'\@author Aniko Szabo

```

```
#'@seealso \code{\link{mc.est}} for estimating the distribution under marginal
#'compatibility.
#'@references Stefanescu, C. & Turnbull, B. W. (2003) Likelihood inference for
#'exchangeable binary data with varying cluster sizes. \emph{Biometrics}, 59,
#'18-24
#'
#'Pang, Z. & Kuk, A. (2007) Test of marginal compatibility and smoothing
#'methods for exchangeable binary data with unequal cluster sizes.
#'\emph{Biometrics}, 63, 218-227
#'@keywords htest
#'@examples
#'
#'data(shelltox)
#'mc.test.chisq(shelltox)
#'
```

```
mc.test.chisq <- function(object,...) UseMethod("mc.test.chisq")
```

◇

File defined by [4a](#), [5](#).

Uses: [mc.est](#) [4b](#), [mc.test.chisq](#) [6](#).

"../R/Reprod.R" 6≡

```
#'@rdname mc.test.chisq
#'@method mc.test.chisq CBData
#'@export
#'@importFrom stats pchisq

mc.test.chisq.CBData <- function(object,...){
  cbdata <- object[object$Freq>0, ]

  get.T <- function(x){
    max.size <- max(x$ClusterSize)
    scores <- (1:max.size) - (max.size+1)/2
    p.hat <- with(x, sum(Freq*NResp) / sum(Freq*ClusterSize))
    rho.hat <- with(x, 1-sum(Freq*(ClusterSize-NResp)*NResp/ClusterSize) /
      (sum(Freq*(ClusterSize-1))*p.hat*(1-p.hat))) #Fleiss-Cuzick estimate
    c.bar <- with(x, sum(Freq*scores[ClusterSize]*ClusterSize) / sum(Freq*ClusterSize))
    T.center <- with(x, sum(Freq*(scores[ClusterSize]-c.bar)*NResp))
    Var.T.stat <- with(x,
      p.hat*(1-p.hat)*sum(Freq*(scores[ClusterSize]-c.bar)^2*ClusterSize*(1+(ClusterSize-1)*rho.hat)))
    X.stat <- (T.center)^2/Var.T.stat
    X.stat}

  chis <- by(cbdata, cbdata$Trt, get.T)
  chis <- chis[1:length(chis)]
  chi.list <- list(chi.sq=chis, p=pchisq(chis, df=1, lower.tail=FALSE))
  overall.chi <- sum(chis)
  overall.df <- length(chis)
  list(overall.chi=overall.chi, overall.p=pchisq(overall.chi, df=overall.df, lower.tail=FALSE),
    individual=chi.list)
}
◇
```

File defined by [4b](#), [6](#), [7](#), [8](#), [9](#), [10a](#), [11c](#), [12a](#), [26ab](#), [27](#), [28](#), [29ab](#), [30](#), [31](#).

Defines: [mc.test.chisq](#) [5](#).

## 3. ESTIMATION UNDER STOCHASTIC ORDERING

We implement the estimation of the stochastically ordered MLE based on the mixture representation following Hoff. The parameter `turn` controls the extension to unimodal down-then-up orderings. The default value of `turn=1` corresponds to the stochastically ordered  $H_a$ .

The actual calculations will be done in C; the following function sets up the call from R. The input dataset should have variables `NResp`, `ClusterSize`, `Trt` and `Freq` – it is most easily achieved by creating a “CBData” object.

The computational details are controlled by setting the `control` argument. It should be a list with parameter settings; the simplest way to generate a correct list is a call to the `soControl()` function. `S` gives the basis of the mixing distribution – its rows are all the possible non-decreasing vectors (see below for how it is obtained). `Q` is the mixing distribution, it is a  $G$ -dimensional matrix ( $G$  is the number of treatment groups). For the ISDM method it is initialized so that the constant vectors of  $S$  are given equal probability ( $H_0$  puts weight only on the constant vectors), that is  $Q[0, 0, \dots, 0] = Q[1, 1, \dots, 1] = \dots = Q[N, N, \dots, N] = 1/(N + 1)$ . For the EM method we have to put some weight on all possible  $\mathbf{v}$  vectors, because it changes  $Q$  only multiplicatively.

"../R/Reprod.R" 7≡

```
#'Order-restricted MLE assuming marginal compatibility
#
#'\code{SO.mc.est} computes the nonparametric maximum likelihood estimate of
#the distribution of the number of responses in a cluster \eqn{P(R=r|n)} under
#a stochastic ordering constraint. Umbrella ordering can be specified using
#the \code{turn} parameter.
#
#Two different algorithms: EM and ISDM are implemented. In general, ISDM (the
#default) should be faster, though its performance depends on the tuning
#parameter \code{max.directions}: values that are too low or too high slow the
#algorithm down.
#
#'\code{SO.mc.est} allows extension to an umbrella ordering: \eqn{D_1 \geq^{st}
#\cdots \geq^{st} D_k \leq^{st} \cdots \leq^{st} D_n} \{D_1 \geq \ldots \geq D_k \leq
\ldots \leq D_n\} by specifying the value of \eqn{k} as the \code{turn}
#parameter. This is an experimental feature, and at this point none of the
#other functions can handle umbrella orderings.
#
#'\code{useDynLib CorrBin, .registration=TRUE}
#'\code{export}
#'\code{importFrom stats xtabs}
#'\code{param cbdata} an object of class \code{\link{CBData}}.
#'\code{param turn} integer specifying the peak of the umbrella ordering (see
#Details). The default corresponds to a non-decreasing order.
#'\code{param control} an optional list of control settings, usually a call to
#\code{\link{soControl}}. See there for the names of the settable control
#values and their effect.
#'\code{return} A list with components:
#
#Components \code{Q} and \code{D} are unlikely to be needed by the user.
#'\code{return} \code{MLEst} {data frame with the maximum likelihood estimates of
#\eqn{P(R_i=r|n)}}
#'\code{return} \code{Q} {numeric matrix; estimated weights for the mixing distribution}
#'\code{return} \code{D} {numeric matrix; directional derivative of the log-likelihood}
#'\code{return} \code{loglik} {the achieved value of the log-likelihood}
#'\code{return} \code{converge} {a 2-element vector with the achieved relative error and
#the performed number of iterations}
#'\code{author} Aniko Szabo, aszabo@mcw.edu
#'\code{seealso} \code{\link{soControl}}
#'\code{references} Szabo A, George EO. (2010) On the Use of Stochastic Ordering to
```





```

names(res0$converge) <- c("rel.error", "n.iter")
res <- res0$Mlest

dimnames(res) <- list(NResp=0:size, ClusterSize=1:size, Trt=1:ntrt)
res <- as.data.frame.table(res)
names(res) <- c("NResp", "ClusterSize", "Trt", "Prob")
res$NResp <- as.numeric(as.character(res$NResp))
res$ClusterSize <- as.numeric(as.character(res$ClusterSize))
res <- res[res$NResp <= res$ClusterSize,]
levels(res$Trt) <- levels(cbddata$Trt)

attr(res, "loglik") <- res0$loglik
attr(res, "converge") <- res0$converge
res
}
◇

```

File defined by [4b](#), [6](#), [7](#), [8](#), [9](#), [10a](#), [11c](#), [12a](#), [26ab](#), [27](#), [28](#), [29ab](#), [30](#), [31](#).

Defines: [S0.mc.est](#) [7](#), [26b](#).

Uses: [DownUpMatrix](#) [12a](#), [mc.est](#) [4b](#), [ReprodISDM](#) [20b](#), [soControl](#) [10a](#).

The values supplied in the call to `soControl` replace the defaults and a list with all possible arguments is returned. The returned list is used as the control argument to the `S0.mc.est` function.

The `method` argument allows to select either the EM, or the ISDM method.

"../R/Reprod.R" 9≡

```

#'Control values for order-constrained fit
#'
#'The values supplied in the function call replace the defaults and a list with
#'all possible arguments is returned. The returned list is used as the control
#'argument to the \code{\link{mc.est}}, \code{\link{S0.LRT}}, and
#' \code{\link{S0.trend.test}} functions.
#'
#'@export
#'@param method a string specifying the maximization method
#'@param eps a numeric value giving the maximum absolute error in the
#'log-likelihood
#'@param max.iter an integer specifying the maximal number of iterations
#'@param max.directions an integer giving the maximal number of directions
#'considered at one step of the ISDM method. If zero or negative, it is set to
#'the number of non-empty cells. A value of 1 corresponds to the VDM algorithm.
#'@param start a string specifying the starting setup of the mixing
#'distribution; "H0" puts weight only on constant vectors (corresponding to the
#'null hypothesis of no change), "uniform" puts equal weight on all elements.
#'Only a "uniform" start can be used for the "EM" algorithm.
#'@param verbose a logical value; if TRUE details of the optimization are
#'shown.
#'@return a list with components for each of the possible arguments.
#'@author Aniko Szabo aszabo@mcw.edu
#'@seealso \code{\link{mc.est}}, \code{\link{S0.LRT}},
#' \code{\link{S0.trend.test}}
#'@keywords models
#'@examples
#'
## decrease the maximum number iterations and
## request the "EM" algorithm
#' soControl(method="EM", max.iter=100)
#

```

◇

File defined by 4b, 6, 7, 8, 9, 10a, 11c, 12a, 26ab, 27, 28, 29ab, 30, 31.

Uses: `mc.est` 4b, `S0.trend.test` 28, `soControl` 10a.

"../R/Reprod.R" 10a≡

```
soControl <- function(method=c("ISDM","EM"), eps=0.005, max.iter=5000,
  max.directions=0, start=ifelse(method=="ISDM", "H0", "uniform"), verbose=FALSE){
  method <- match.arg(method)
  start <- match.arg(start, c("uniform","H0"))
  list(method = match.arg(method), eps = eps, max.iter = max.iter,
    max.directions = max.directions, start=start, verbose = verbose)
}
```

◇

File defined by 4b, 6, 7, 8, 9, 10a, 11c, 12a, 26ab, 27, 28, 29ab, 30, 31.

Defines: `soControl` 7, 8, 9, 26ab, 27, 28, 29ab, 30, 31.

The `makeSmatrix` function creates a matrix the rows of which are all the possible non-decreasing vectors. The idea is the following: there is a one-to-one correspondence between a non-decreasing sequence of length  $k$  using the values  $0, 1, \dots, n$  and combinations of  $k$  elements out of  $n + k$ . Imagine  $n$  balls and  $k$  sticks; each of the possible arrangements of these  $n + k$  objects into a row is a combination. We can transform it to a nondecreasing sequence by counting the number of balls to the left of the first stick, second stick, etc. For example, with  $n = 5$  and  $k = 4$ , a possible arrangement is  $\circ | \circ || \circ \circ \circ |$ ; this corresponds to the sequence (1,2,2,5). The `Comb` function generates all possible combinations of  $k$  elements out of  $N = n + k$  elements by recursion on  $N$ , and when a combination is ready, it transforms it to a non-decreasing sequence and puts it into the output matrix. The code for generating the combinations was written by Joe Sawada, 1997 and obtained from the Combinatorial Object Server (<http://theory.cs.uvic.ca/inf/comb/CombinationsInfo.html>), but was rewritten without nested functions.

"..\src\ReprodCalcs.c" 10b≡

```
void Comb(int j, int m, int nn, int kk, int nS, int* a, int* pos, SEXP res) {
  int i, val, step;
  if (j > nn) {
    < Convert 'a' to non-decreasing sequence and insert into 'res' 11a >
  }
  else {
    if (kk-m < nn-j+1) {
      a[j] = 0; Comb(j+1, m, nn, kk, nS, a, pos, res);
    }
    if (m < kk) {
      a[j] = 1; Comb(j+1, m+1, nn, kk, nS, a, pos, res);
    }
  }
}
```

◇

File defined by 1ab, 2, 10b, 11b, 13bc, 14ab, 15, 16ab, 17, 18, 19ab, 20b, 23, 24.

Defines: `Comb` 11b.

$\langle \text{Convert 'a' to non-decreasing sequence and insert into 'res' 11a} \rangle \equiv$

```

        val = 0;
        step = 0;
        for (i=1; i<=nn; i++) {
            if (a[i]==1){
                INTEGER(res)[*pos+step]=val;
                step += nS;
            }
            else { //a[i]=0;
                val++;
            }
        }
        *pos = *pos+1;

```

◇  
Fragment referenced in [10b](#).

"..\src\ReprodCalcs.c" 11b≡

```

SEXP makeSmatrix(SEXP size, SEXP ntrt){
int *a, i, pos, nn, kk, nS;
SEXP res;
    nn = asInteger(size) + asInteger(ntrt);
    kk = asInteger(ntrt);
    a = calloc(nn+1, sizeof(int));
    for (i=1; i<=kk; i++) a[i]=1;

    nS = choose(nn,kk);
    PROTECT(res = allocMatrix(INTSXP, nS, kk));
    pos = 0;

    Comb(1, 0, nn, kk, nS, a, &pos, res);

    UNPROTECT(1);
    free(a);

    return res;
}

```

◇  
File defined by [1ab](#), [2](#), [10b](#), [11b](#), [13bc](#), [14ab](#), [15](#), [16ab](#), [17](#), [18](#), [19ab](#), [20b](#), [23](#), [24](#).  
Defines: `makeSmatrix` [12bc](#), [13a](#).  
Uses: `Comb` [10b](#).

`DownUpMatrix` extends the capabilities of `makeSmatrix` to generate vectors that have  $q$  non-increasing elements followed  $k - q$  non-decreasing elements.

The general outline of the algorithm is as follows ( $n$  is `size`,  $k$  is `ntrt`, and  $q$  is `turn`):

"../R/Reprod.R" 11c≡

```

#'Internal CorrBin objects
#'
#'Internal CorrBin objects.
#'
#'These are not to be called by the user.
#'
#'@rdname CorrBin-internal
#'@aliases .required DownUpMatrix
#'@keywords internal

```

◇  
 File defined by 4b, 6, 7, 8, 9, 10a, 11c, 12a, 26ab, 27, 28, 29ab, 30, 31.  
 Uses: DownUpMatrix 12a.

"../R/Reprod.R" 12a≡

```
DownUpMatrix <- function(size, ntrt, turn){
  if ((turn<1)|(turn>ntrt)) stop("turn should be between 1 and ntrt")
  < Take care of turn=1 and turn=ntrt 13a >
  < Generate non-increasing sequences of length turn with values ≤ size 12b >
  res2list <- list()
  for (sq in 0:size){
    < Generate non-decreasing sequences of length ntrt-turn with values between sq and size 12c >
  }
  < Combine the two parts of the sequences 12d >
}
```

◇  
 File defined by 4b, 6, 7, 8, 9, 10a, 11c, 12a, 26ab, 27, 28, 29ab, 30, 31.  
 Defines: DownUpMatrix 8, 11c.

Non-increasing sequences are generated by subtracting non-decreasing sequences from  $n$ :

*< Generate non-increasing sequences of length turn with values ≤ size 12b >* ≡

```
res1 <- .Call("makeSmatrix", as.integer(size), as.integer(turn),PACKAGE="CorrBin")
res1 <- size - res1;
```

◇  
 Fragment referenced in 12a.  
 Uses: makeSmatrix 11b.

**res2list** will be a list of matrices defining non-decreasing sequences for all possible starting points  $s_q$ . We get them by generating all non-decreasing sequences with values  $\leq n - s_q$  and then adding  $s_q$ .

*< Generate non-decreasing sequences of length ntrt-turn with values between sq and size 12c >* ≡

```
S <- .Call("makeSmatrix", as.integer(size-sq), as.integer(ntrt-turn),PACKAGE="CorrBin")
res2list <- c(res2list, list(sq+S))
```

◇  
 Fragment referenced in 12a.  
 Uses: makeSmatrix 11b.

To match all possible starts with all possible ends, we split **res1** into a list based on the last value ( $s_q$ ) and do a Cartesian product (everything-to- everything merge) with the corresponding elements of **res2list**:

*< Combine the two parts of the sequences 12d >* ≡

```
res1list <- by(res1, res1[,turn], function(x)x)
res <- mapply(merge, res1list, res2list, MoreArgs=list(by=NULL), SIMPLIFY=FALSE)
res <- data.matrix(do.call(rbind, res))
rownames(res) <- NULL
colnames(res) <- NULL
res
```

◇  
 Fragment referenced in 12a.

When  $q = 1$  or  $q = k$ , no merging is needed and we can speed up the algorithm by treating them as special cases:

$\langle \text{Take care of turn}=1 \text{ and turn=ntrt } 13a \rangle \equiv$

```

    if (turn==1){
      res <- .Call("makeSmatrix", as.integer(size), as.integer(ntrt),PACKAGE="CorrBin")
      return(res)
    }
    if (turn==ntrt){
      res <- .Call("makeSmatrix", as.integer(size), as.integer(ntrt),PACKAGE="CorrBin")
      return(size - res)
    }
  }

```

Fragment referenced in 12a.

Uses: `makeSmatrix` 11b.

**3.1. ISDM estimation.** In the ISDM algorithm, at each step we move toward a new mixing distribution by maximizing

$$l(\alpha_0 Q^{(t)} + \sum_i \alpha_i \delta_{\mathbf{v}_t^i}), \quad (5)$$

where  $\mathbf{v}_t^1, \dots, \mathbf{v}_t^m$  corresponding to the at most  $m_0$  largest positive values of the directional derivative  $D_{Q^{(t)}}(\mathbf{v})$ , where

$$D_Q(\mathbf{v}) = \sum_{g,i} \frac{h(r_{g,i}, v_g, n_{g,i})}{\sum_{\mathbf{q}} h(r_{g,i}, q_g, n_{g,i}) Q(\mathbf{q})} - N. \quad (6)$$

First we define a variety of help-functions.

`GetTabElem` allows easy access using three indices to the 3-dimensional data matrix `tab` that gets converted to a long vector when it is passed from R. Another option would have been to set up a C-style array of pointers to pointers to rows.

"..\src\ReprodCalcs.c" 13b≡

```

double GetTabElem(SEXP tab, int size, int n, int r, int j){
  return REAL(tab)[(n-1)+size*(r+(size+1)*j)];
}

```

File defined by 1ab, 2, 10b, 11b, 13bc, 14ab, 15, 16ab, 17, 18, 19ab, 20b, 23, 24.

`HyperTable` makes a 3-dimensional C-style array with the hyper-geometric probabilities  $h(i, j, k) = \binom{j}{i} \binom{N-j}{k-i} / \binom{N}{k}$ . R's `dhyper` function does the actual calculations.

"..\src\ReprodCalcs.c" 13c≡

```

double ***HyperTable(int size){
  // dhyper(i, j, size-j, k), i=0:size; j=0:size; k=0:size
  double ***res;
  int i, j, k;

  res = malloc((size+1)*sizeof(double*));
  for (i=0; i<=size; i++){
    res[i] = malloc((size+1)*sizeof(double*));
    for (j=0; j<=size; j++) res[i][j] = calloc(size+1, sizeof(double));
  }

  for (i=0; i<=size; i++){
    for (j=i; j<=size; j++){
      for (k=i; k<=size-j+i; k++)
        res[i][j][k] = dhyper(i, j, size-j, k, 0);
    }
  }
}

```

```

    return res;
}
◇

```

File defined by [1ab](#), [2](#), [10b](#), [11b](#), [13bc](#), [14ab](#), [15](#), [16ab](#), [17](#), [18](#), [19ab](#), [20b](#), [23](#), [24](#).  
 Defines: [HyperTable](#) [14b](#), [20b](#), [24](#).

The matrix  $S$  created by `makeSmatrix` contains the numeric values of the non-decreasing vectors. `IndexVector` and `IndexVectorC` create a vector of indices corresponding to the location of each row of  $S$  in a vectorized  $G$ -dimensional  $N \times N \times \dots \times N$  array ( $Q$ ). That is if a row of  $S$  is  $(0, 1, 4)$ , then the corresponding element of the index vector will point to the  $[0,1,4]$ th element of a  $N \times N \times N$  matrix that is represented by a long (length=  $N^3$ ) vector. This setup is needed as the number of dimensions of  $Q$  depends on the number of treatments, so it is not known at compile time.

The difference between the two functions is that `IndexVector` works for an R-style matrix (that has been converted to a vector during the transfer), while `IndexVectorC` works for a C-style matrix (an array of pointers to arrays).

"..\src\ReprodCalcs.c" 14a≡

```

int static *IndexVectorC(int **S, int N, int G, int nrowS){
  int *idx, i, j;

  idx = calloc(nrowS, sizeof(int));

  for (j=G-1; j>=0; j--){
    for (i=0; i<nrowS; i++){
      idx[i] = N*idx[i] + S[i][j];
    }
  }

  return idx;
}
int static *IndexVector(SEXP S, int N, int G, int nrowS){
  int *idx, i, j, start;

  idx = calloc(nrowS, sizeof(int));

  for (j=G-1, start=(G-1)* nrowS; j>=0; j--, start -= nrowS){
    for (i=0; i<nrowS; i++){
      idx[i] = N*idx[i] + INTEGER(S)[start+i];
    }
  }

  return idx;
}
◇

```

File defined by [1ab](#), [2](#), [10b](#), [11b](#), [13bc](#), [14ab](#), [15](#), [16ab](#), [17](#), [18](#), [19ab](#), [20b](#), [23](#), [24](#).  
 Defines: `IndexVector`, Never used, `IndexVectorC` [20b](#).

`CalcMarginals` calculates the marginal probabilities in the denominator of (13)

$$Q_{gn}(r) = P(r \text{ responses} | \text{treatment } g, \text{cluster size } n) = \sum_{\mathbf{q}} h(r, q_g, n) Q^{(t)}(\mathbf{q}) \quad (7)$$

for  $j = 1, \dots, G$ ,  $n = 1, \dots, N$ ,  $r = 0, \dots, n$ . It returns a 3-dimensional C-style matrix.

"..\src\ReprodCalcs.c" 14b≡

```

double ***CalcMarginals(SEXP S, SEXP Q, double ***ht, int *idx, int ntrt, int size, int nS){
    int j, i, n, x, start, sj;
    double ***marg;
    //ht is from HyperTable, it is passed to avoid recalculation

    marg = malloc(ntrt*sizeof(double*));
    for (j=0; j<ntrt; j++){
        marg[j] = malloc((size+1)*sizeof(double*));
        for (n=1; n<=size; n++) marg[j][n] = calloc(n+1, sizeof(double));
    }

    for (i=0; i<nS; i++){
        for (j=0, start=0; j<ntrt; j++, start+=nS){
            sj = INTEGER(S)[start+i];
            for (n=1; n<=size; n++){
                for (x=imax2(0,sj-size+n); x<=imin2(sj,n); x++){
                    marg[j][n][x] += REAL(Q)[idx[i]]*ht[x][n][sj];
                }
            }
        }
    }
    return marg;
}

```

◇

File defined by [1ab](#), [2](#), [10b](#), [11b](#), [13bc](#), [14ab](#), [15](#), [16ab](#), [17](#), [18](#), [19ab](#), [20b](#), [23](#), [24](#).

Defines: [CalcMarginals](#) [20b](#), [23](#), [24](#).

Uses: [HyperTable](#) [13c](#).

`CalcD` calculates the directional derivative of the log-likelihood into the direction of each possible  $\mathbf{v}$  (that is for each row of  $S$ ) as defined in (6). Note that the denominator contains the marginal probabilities defined above. The function does not have a return value, the first parameter  $D$  is modified (or rather, the value it points to is modified).

"..\src\ReprodCalcs.c" 15≡

```

void CalcD(SEXP D, SEXP S, SEXP tab, int *idx, double ***ht, double ***marg, int ntrt,
    int nS, int size, int ntot){
    int j, i, n, x, sj, start, t;
    //ntot = sum(tab) -- passing it avoids having to recalculate it
    for (i=0; i<nS; i++){
        REAL(D)[idx[i]] = -ntot;
        for (j=0, start=0; j<ntrt; j++, start+=nS){
            sj = INTEGER(S)[start+i];
            for (n=1; n<=size; n++){
                for (x=imax2(0,sj-size+n); x<=imin2(sj,n); x++){
                    t = GetTabElem(tab,size,n,x,j);
                    if (t>0) REAL(D)[idx[i]] += t*ht[x][n][sj]/marg[j][n][x];
                }
            }
        }
    }
}

```

◇

File defined by [1ab](#), [2](#), [10b](#), [11b](#), [13bc](#), [14ab](#), [15](#), [16ab](#), [17](#), [18](#), [19ab](#), [20b](#), [23](#), [24](#).

Defines: `calcD` Never used.

maxD finds the largest value of the directional derivative  $D$  – it will be used for error rate estimation, since

$$l(\hat{Q}|\mathbf{X}) - l(Q|\mathbf{X}) \leq \max_{\mathbf{v}} D_Q(\mathbf{v}). \quad (8)$$

"..\src\ReprodCalcs.c" 16a≡

```
double maxD(SEXP D, int *idx, int nS){
    int i;
    double currmax, val;

    currmax = 0;
    for (i=0; i<nS; i++){
        val = REAL(D)[idx[i]];
        if (val > currmax) currmax = val;
    }
    return currmax;
}
```

File defined by [1ab](#), [2](#), [10b](#), [11b](#), [13bc](#), [14ab](#), [15](#), [16ab](#), [17](#), [18](#), [19ab](#), [20b](#), [23](#), [24](#).  
 Defines: MaxD Never used.

CalcTopD gets the vectors from  $S$  corresponding to the at most ‘limit’ positive  $D$  values (that is it calculates  $\mathbf{v}_t^1, \dots, \mathbf{v}_t^m$ ). The return value is a C-style matrix with each row a non-decreasing vector. The number  $m$  of the selected vectors is returned through the pointer nselect.

"..\src\ReprodCalcs.c" 16b≡

```
int **CalcTopD(SEXP D, SEXP S, int *idx, int limit, int *nselect, int ntrt, int nS){
    int **res, nmx, i, j, pos, start;
    double *posDvec, dcut;

    // count the number of non-negative elements in D
    nmx = 0;
    for (i=0; i<nS; i++){
        if (REAL(D)[idx[i]] >= 0){
            nmx++;
        }
    }
    if (nmx == 0){
        res = 0;
        *nselect = 0;
        return res;
    }

    if (nmx > limit){ //find the limit-th largest D
        posDvec = malloc(nmx*sizeof(double));
        pos = 0;
        for (i=0; i<nS; i++){
            if (REAL(D)[idx[i]] >= 0){
                posDvec[pos] = -REAL(D)[idx[i]]; //negation is needed, because rPsort uses
                pos++;
            }
        }
        rPsort(posDvec, nmx, limit);
        dcut = -posDvec[limit]; //the cutoff for determining the limit-th largest values
        free(posDvec);
    }
    else dcut = 0;

    nmx = imin2(limit, nmx);
```



```

    res = (int**) Calloc(nmx, int*);
    pos = 0;
    for (i=0; i<nS; i++){
        if (pos >= nmx) break;
        if (REAL(D)[idx[i]] < dcut) continue;
        res[pos] =(int*) Calloc(ntrt, int); //copy the ith row of S
        for (j=0, start=0; j<ntrt; j++, start+=nS) res[pos][j] = INTEGER(S)[start+i];
        pos++;
    }

    *nselect = nmx;
    return res;
}

```

File defined by [1ab](#), [2](#), [10b](#), [11b](#), [13bc](#), [14ab](#), [15](#), [16ab](#), [17](#), [18](#), [19ab](#), [20b](#), [23](#), [24](#).  
 Defines: [CalcTopD](#) [20b](#).

`NegLogLik` calculates the negative log-likelihood at a potential new mixing distribution as a function of  $(\alpha_0, \alpha_1, \dots, \alpha_m)$ , where  $\sum_{i=0}^m \alpha_i = 1$  and  $\alpha_i \geq 0$ . To remove the sum-to-one constraint, we reparameterize to  $\text{par}_i = \gamma_i = \alpha_i / \alpha_0 \geq 0$ ,  $i = 1, \dots, m$ . With this reparametrization,  $\alpha_0 = 1 / (1 + \sum \gamma_i)$  and  $\alpha_i = \alpha_0 \gamma_i$ ,  $i = 1, \dots, m$ , and the constraints are  $\gamma_i \geq 0$ . The potential new mixing distribution is

$$Q^\gamma = (Q + \sum_i \gamma_i \delta_{\mathbf{v}^i}) / (1 + \sum_i \gamma_i)$$

The corresponding log-likelihood is

$$l(Q^\gamma) = \sum_{g,n,r} A_{gnr} \log Q_{gn}^\gamma(r) = \sum_{g,n,r} A_{gnr} \log (Q_{gn}(r) + \sum_i \gamma_i h(r, \mathbf{v}_g^i, n)) - N \log(1 + \sum_i \gamma_i), \quad (9)$$

where  $A_{gnr}$  is the observed number of clusters of size  $n$  with  $r$  responses in treatment group  $g$ .

`lmS` stores the  $\mathbf{v}_t^1, \dots, \mathbf{v}_t^m$  vectors calculated by `CalcTopD`. The required variables (`ntrt`, `size`, `ntot`, `marg`, `ht`, `lmS`) will be declared as global and will be available for the procedure, while `tab` will be passed through the `*ex` pointer.

"..\src\ReprodCalcs.c" 17≡

```

< Declare global variables 20a >
double NegLogLik(int npar, double *par, void *ex){
    //par[j] = (alpha_(j+1)/alpha_0), j=0,...,nmax-1
    int j, n, r, i, sj, x;
    double res, sum;
    SEXP tab;

    tab = (SEXP)ex;
    res = 0;

    for (j=0; j<ntrt; j++){
        for (n=1; n<=size; n++){
            for (r=0; r<=n; r++){
                x = GetTabElem(tab,size,n,r,j);
                if (x>0){
                    sum = marg[j][n][r];
                    for (i=0; i<npar; i++){
                        sj = lmS[i][j];
                        sum += par[i]*ht[r][n][sj];
                    }
                    res += x*log(sum);
                }
            }
        }
    }
}

```



```

                                if (x>0){
                                    sj = lmS[i][j];
                                    sum += x*ht[r][n][sj]/denom[j][n][r];
                                }
                            }
                        }
                    }
                gr[i] = -sum;
            }

            for (j=0; j<ntrt; j++){
                for (n=1; n<=size; n++) free(denom[j][n]);
                free(denom[j]);
            }
            free(denom);
        }
    }

```

File defined by [1ab](#), [2](#), [10b](#), [11b](#), [13bc](#), [14ab](#), [15](#), [16ab](#), [17](#), [18](#), [19ab](#), [20b](#), [23](#), [24](#).

**UpdateQ** performs the updating step of the ISDM algorithm once the optimal  $\alpha_i$  values have been found (the input parameter **g** has the reparameterized **par** values at the optimum): the mixing distribution is moved toward the values with the largest directional derivative.

$$Q^{(t+1)} = (Q + \sum_i \gamma_i \delta_{\mathbf{v}^i}) / (1 + \sum_i \gamma_i) \quad (11)$$

**lmS\_idx** is the index vector corresponding to the location in  $Q$  of the selected directions.

"..\src\ReprodCalcs.c" 19a≡

```

void UpdateQ(SEXP Q, double *g, int nS, int nmax, int *idx, int *lmS_idx){
    double alpha0;
    int i;

    alpha0 = 1;
    for (i=0; i<nmax; i++) alpha0 += g[i];
    alpha0 = 1/alpha0;

    for (i=0; i<nS; i++) REAL(Q)[idx[i]] *= alpha0;
    for (i=0; i<nmax; i++) REAL(Q)[lmS_idx[i]] += alpha0 * g[i];
}

```

File defined by [1ab](#), [2](#), [10b](#), [11b](#), [13bc](#), [14ab](#), [15](#), [16ab](#), [17](#), [18](#), [19ab](#), [20b](#), [23](#), [24](#).

Defines: **UpdateQ** [20b](#).

**UpdateMarginals** updates the marginal distribution calculated by **CalcMarginals** after each iterative step – this is faster than recalculating them again. **lmS** contains the selected directions.

$$Q_{gn}^\gamma(r) = (Q_{gn}(r) + \sum_i \gamma_i f(r, v_g^i, n)) \frac{1}{1 + \sum_i \gamma_i} \quad (12)$$

"..\src\ReprodCalcs.c" 19b≡

```

void UpdateMarginals(double ***marg, double *g, double ***ht, int **lmS,
                    int ntrt, int size, int nmax){
    double alpha0;
    int i, j, n, r, sj;

    alpha0 = 1;
    for (i=0; i<nmax; i++){
        alpha0 += g[i];
    }
}

```

```

    }
    alpha0 = 1/alpha0;

    for (j=0; j<ntrt; j++){
        for (n=1; n<=size; n++){
            for (r=0; r<=n; r++){
                for (i=0; i<nmax; i++){
                    sj = lmS[i][j];
                    marg[j][n][r] += g[i] * ht[r][n][sj];
                }
                marg[j][n][r] *= alpha0;
            }
        }
    }
}

```

◇

File defined by [1ab](#), [2](#), [10b](#), [11b](#), [13bc](#), [14ab](#), [15](#), [16ab](#), [17](#), [18](#), [19ab](#), [20b](#), [23](#), [24](#).

Defines: [UpdateMarginals](#) [20b](#).

Finally, **ReprodISDM** sets up all the required matrices, and runs the ISDM iterations while monitoring the error. The maximization of the log-likelihood is done by the built-in R function **lbfgsb** which implements the quasi-Newton method of Byrd95 that allows boundary constraints for optimization. It is actually a minimization routine, so the negative likelihood defined above is used. The **MaxDirection** parameter controls the number of directions which are considered at each step of the ISDM algorithm. Values of 0 (or less) mean setting it to the number of non-empty cells in the data. The variables required by the log-likelihood function and its derivative are declared global.

*< Declare global variables 20a > ≡*

```

int ntrt, size, **lmS;
double ntot, ***ht, ***marg;

```

◇

Fragment referenced in [17](#).

"..\src\ReprodCalcs.c" 20b≡

```

SEXP ReprodISDM(SEXP Q, SEXP S, SEXP tab, SEXP MaxIter, SEXP MaxDirections,
                SEXP eps, SEXP verbose){
    SEXP dims, D, res, margSXP, tmp;
    int i, j, n, r, *idx, nS, niter, nmax, fncount, grcount, fail,
        *boundtype, limit, *lmS_idx, nenforced;
    double rel_error, *gamma, *lower, *upper, NLLmin;
    char msg[60];

    PROTECT(dims = GET_DIM(tab));
    size = INTEGER(dims)[0];
    ntrt = INTEGER(dims)[2];
    UNPROTECT(1);

    PROTECT(dims = GET_DIM(S));
    nS = INTEGER(dims)[0];
    UNPROTECT(1);

    PROTECT(D = duplicate(Q));
    for (i=0; i<length(Q); i++) REAL(D)[i] = 0;

```

```

idx = IndexVector(S, size+1, ntrt, nS);
ht = HyperTable(size);

ntot=0;
for (i=0; i<length(tab); i++) ntot += REAL(tab)[i];

limit = INTEGER(coerceVector(MaxDirections, INTSXP))[0];
if (limit <= 0){ //set it to the number of non-empty cells
  limit=0;
  for (i=0; i<length(tab); i++){
    if (REAL(tab)[i]>0) limit++;
  }
}

marg = CalcMarginals(S, Q, ht, idx, ntrt, size, nS);
CalcD(D, S, tab, idx, ht, marg, ntrt, nS, size, ntot);

rel_error = maxD(D, idx, nS);
niter = 0;
nenforced = 0;

while (niter < asInteger(MaxIter) && rel_error > asReal(eps)){
  R_CheckUserInterrupt();
  niter++;

  lmS = CalcTopD(D, S, idx, limit, &nmax, ntrt, nS);
  lmS_idx = IndexVectorC(lmS, size+1, ntrt, nmax);

  if (nmax == limit) nenforced++;

  gamma = (double*) Calloc(nmax, double);
  lower = (double*) Calloc(nmax, double);
  upper = (double*) Calloc(nmax, double);
  boundtype = (int*) Calloc(nmax, int);

  for (i=0; i<nmax; i++){
    gamma[i] = 0;
    lower[i] = 0;
    upper[i] = imin2(1e6/nmax, 100); // => alpha0>1e-6
    boundtype[i] = 1; //lower bound only
  }

  lbfgsb(nmax, 5, gamma, lower, upper, boundtype, &NLLmin, NegLogLik, NegLogLikDeriv,
    &fail, tab, 1e5, 0, &fnccount, &grccount, 1000, msg, asInteger(verbose), 10);

  UpdateMarginals(marg, gamma, ht, lmS, ntrt, size, nmax);
  CalcD(D, S, tab, idx, ht, marg, ntrt, nS, size, ntot);
  UpdateQ(Q, gamma, nS, nmax, idx, lmS_idx); //only needed to be able to return Q
  rel_error = maxD(D, idx, nS);
  if (asInteger(verbose)==1)
    Rprintf("Step %d, rel.error=%f, NLL=%f\n", niter, rel_error, NLLmin);

  Free(gamma);
  Free(lower);
  Free(upper);
  Free(boundtype);
}

```

```

        for (i=0; i<nmax; i++){
            Free(lmS[i]);
        }
        Free(lmS);
        free(lmS_idx);
    }

    free(idx);
    for(j=0; j<=size; j++){
        for (n=0; n<=size; n++) free(ht[j][n]);
        free(ht[j]);
    }
    free(ht);

    PROTECT(margSXP = allocVector(REALSXP, ntrt*size*(size+1)));
    PROTECT(dims = allocVector(INTSXP,3));
    INTEGER(dims)[0] = size+1;    INTEGER(dims)[1] = size;    INTEGER(dims)[2] = ntrt;
    i = 0;
    for(j=0; j<ntrt; j++){
        for (n=1; n<=size; n++){
            for (r=0; r<=n; r++){
                REAL(margSXP)[i] = marg[j][n][r];
                i++;
            }
            for (r=n+1; r<=size; r++){
                REAL(margSXP)[i] = NA_REAL;
                i++;
            }
        }
    }
    dimgets(margSXP, dims);
    UNPROTECT(1);    //dims
    for(j=0; j<ntrt; j++){
        for (n=1; n<=size; n++) free(marg[j][n]);
        free(marg[j]);
    }
    free(marg);

    PROTECT(res = allocVector(VECSXP,5));
    if (asInteger(verbose)==1)
        Rprintf("Limit=%d; %d Iterations; Limit enforced %d times (%4.2f percent)\n",
            limit, niter, nenforced, nenforced*100.0/niter);

    SET_VECTOR_ELT(res, 0, margSXP);
    SET_VECTOR_ELT(res, 1, Q);
    SET_VECTOR_ELT(res, 2, D);
    SET_VECTOR_ELT(res, 3, ScalarReal(-NLLmin));
    PROTECT(tmp = allocVector(REALSXP,2));
    REAL(tmp)[0] = rel_error;
    REAL(tmp)[1] = niter;
    SET_VECTOR_ELT(res, 4, tmp);
    UNPROTECT(4);    //tmp, res, margSXP, D

    return res;
}

```

◇

Defines: `ReprodISDM` 8.

Uses: `CalcMarginals` 14b, `CalcTopD` 16b, `HyperTable` 13c, `IndexVectorC` 14a, `NegLogLik` 17, `UpdateMarginals` 19b, `UpdateQ` 19a.

**3.2. EM estimation.** The `MixReprodQ` function implements the EM-based fitting:

$$Q^{(t+1)}(\mathbf{v}) = \frac{1}{N} \sum_{g,i} \frac{h(r_{g,i}, v_g, n_{g,i}) Q^{(t)}(\mathbf{v})}{\sum_{\mathbf{q}} h(r_{g,i}, q_g, n_{g,i}) Q^{(t)}(\mathbf{q})}. \quad (13)$$

Note that from (6)

$$Q^{(t+1)}(\mathbf{v}) = Q^{(t)}(\mathbf{v}) + \frac{1}{N} D_Q(\mathbf{v}) Q^{(t)}(\mathbf{v}), \quad (14)$$

so we will be able to use the `CalcMarginals` and `CalcD` functions defined earlier.

`UpdateReprodQ` performs the updating step defined in (13).

"..\src\ReprodCalcs.c" 23≡

```
SEXP UpdateReprodQ(SEXP Q, SEXP S, SEXP tab, int size, int ntrt, int nS,
                  double*** ht, int* idx){
    int ntot, i, j, n;
    double ***marg;
    SEXP resobj, D;

    PROTECT(resobj = duplicate(Q));
    for (i=0; i<length(Q); i++) REAL(resobj)[i] = 0;

    ntot=0;
    for (i=0; i<length(tab); i++) ntot += REAL(tab)[i];

    marg = CalcMarginals(S, Q, ht, idx, ntrt, size, nS);

    PROTECT(D = duplicate(Q));
    for (i=0; i<length(Q); i++) REAL(D)[i] = 0;
    CalcD(D, S, tab, idx, ht, marg, ntrt, nS, size, ntot);

    // update Q values
    for (i=0; i<length(Q); i++){
        REAL(resobj)[i] = REAL(Q)[i] * (1+REAL(D)[i]/ntot);
    }

    //cleanup
    for(j=0; j<ntrt; j++){
        for (n=1; n<=size; n++) free(marg[j][n]);
        free(marg[j]);
    }
    free(marg);

    UNPROTECT(2);
    return resobj;
}
```

File defined by 1ab, 2, 10b, 11b, 13bc, 14ab, 15, 16ab, 17, 18, 19ab, 20b, 23, 24.

Defines: `UpdateReprodQ` 24.

Uses: `CalcMarginals` 14b.

And, finally, `MixReprodQ` performs the actual EM iterations. `eps` controls the precision of the estimate of the log-likelihood. Since

$$l(\hat{Q}|\mathbf{X}) - l(Q^{(t)}|\mathbf{X}) \leq N \frac{Q^{(t+1)}(\mathbf{v}) - Q^{(t)}(\mathbf{v})}{Q^{(t)}(\mathbf{v})}, \quad (15)$$

we control the largest relative change in  $Q$  during updating. If the `verbose` option is selected, the current value of the relative change is displayed at every 10th iteration.

"..\src\ReprodCalcs.c" 24≡

```
SEXP MixReprodQ(SEXP Q, SEXP S, SEXP tab, SEXP MaxIter, SEXP eps, SEXP verbose){
  double rel_error, ***ht, ntot, re, ***marg, loglik;
  int niter, size, ntrt, nS, i, j, n, r, *idx, Qlength;
  SEXP D, Qnew, resQ, dims, resobj, tmp, margSXP, Qdims;

  PROTECT(Qdims = GET_DIM(Q));
  Qlength = 1;
  for (i=0; i<length(Qdims); i++) Qlength *= INTEGER(Qdims)[i];

  PROTECT(resQ = duplicate(Q));

  PROTECT(dims = GET_DIM(tab));
  size = INTEGER(dims)[0];
  ntrt = INTEGER(dims)[2];
  UNPROTECT(1); //dims

  PROTECT(dims = GET_DIM(S));
  nS = INTEGER(dims)[0];
  UNPROTECT(1); //dims

  ntot=0;
  for (i=0; i<length(tab); i++) ntot += REAL(tab)[i];

  idx = IndexVector(S, size+1, ntrt, nS);
  ht = HyperTable(size);

  PROTECT(tmp = allocVector(REALSXP, 2));
  rel_error = 1;
  niter = 0;
  while ((niter<asInteger(MaxIter))&&(rel_error>asReal(eps))){
    R_CheckUserInterrupt();
    niter++;
    PROTECT(Qnew = UpdateReprodQ(resQ, S, tab, size, ntrt, nS, ht, idx));
    rel_error = 0;
    for (i=0; i<length(Qnew); i++){
      if (REAL(resQ)[i]>0){
        re = ntot*(REAL(Qnew)[i]-REAL(resQ)[i])/REAL(resQ)[i];
        if (rel_error < re) rel_error = re;
      }
      REAL(resQ)[i] = REAL(Qnew)[i];
    }
    UNPROTECT(1); //Qnew
    if ((asInteger(verbose) == 1)&&(niter%10 == 1)){
      REAL(tmp)[1] = rel_error;
      REAL(tmp)[0] = niter;
      PrintValue(tmp);
    }
  }
  UNPROTECT(1); //tmp
}
```



```

//calculate ML estimates for the output
marg = CalcMarginals(S, resQ, ht, idx, ntrt, size, nS);
PROTECT(margSXP = allocVector(REALSXP, ntrt*size*(size+1)));
PROTECT(dims = allocVector(INTSXP,3));
    INTEGER(dims)[0] = size+1;    INTEGER(dims)[1] = size;    INTEGER(dims)[2] = ntrt;
    i = 0;
    for(j=0; j<ntrt; j++){
        for (n=1; n<=size; n++){
            for (r=0; r<=n; r++){
                REAL(margSXP)[i] = marg[j][n][r];
                i++;
            }
            for (r=n+1; r<=size; r++){
                REAL(margSXP)[i] = NA_REAL;
                i++;
            }
        }
    }
dimgets(margSXP, dims);
UNPROTECT(1); //dims

PROTECT(D = allocVector(REALSXP, Qlength));
dimgets(D, Qdims);
for (i=0; i<Qlength; i++) REAL(D)[i] = 0;
CalcD(D, S, tab, idx, ht, marg, ntrt, nS, size, ntot);

//calculate log-likelihood for the output
loglik = 0;
for(j=0; j<ntrt; j++){
    for (n=1; n<=size; n++){
        for (r=0; r<=n; r++){
            loglik += GetTabElem(tab, size, n, r, j)*log(marg[j][n][r]);
        }
    }
}

for(j=0; j<ntrt; j++){
    for (n=1; n<=size; n++) free(marg[j][n]);
    free(marg[j]);
}
free(marg);

for(j=0; j<=size; j++){
    for (n=0; n<=size; n++) free(ht[j][n]);
    free(ht[j]);
}
free(ht);
free(idx);

PROTECT(resobj = allocVector(VECSXP, 5));
SET_VECTOR_ELT(resobj, 0, margSXP);
SET_VECTOR_ELT(resobj, 1, resQ);
SET_VECTOR_ELT(resobj, 2, D);
SET_VECTOR_ELT(resobj, 3, ScalarReal(loglik));
PROTECT(tmp = allocVector(REALSXP,2));
REAL(tmp)[0] = rel_error;
REAL(tmp)[1] = niter;

```



```

SO.LRT <- function(cbddata, control=soControl()){
  # LL under null hypothesis of equality (+ reproducibility)
  a <- with(cbddata, aggregate(Freq, list(ClusterSize=ClusterSize,NResp=NResp), sum))
  names(a)[names(a)=="x"] <- "Freq"
  a$ClusterSize <- as.integer(as.character(a$ClusterSize))
  a$NResp <- as.integer(as.character(a$NResp))
  a$Trt <- 1
  class(a) <- c("CBData", "data.frame")

  b <- mc.est(a)
  b <- merge(cbddata, b, all.x=TRUE, by=c("ClusterSize","NResp"))
  l10 <- with(b, sum(Freq*log(Prob)))

  # LL under alternative hypothesis of stoch ordering (+ reproducibility)
  res <- SO.mc.est(cbddata, control=control)
  l11 <- attr(res, "loglik")
  lrt <- 2*(l11 - l10)
  attr(lrt, "l10") <- l10
  attr(lrt, "l11") <- l11
  lrt
}

```

◇

File defined by [4b](#), [6](#), [7](#), [8](#), [9](#), [10a](#), [11c](#), [12a](#), [26ab](#), [27](#), [28](#), [29ab](#), [30](#), [31](#).

Uses: `mc.est` [4b](#), `SO.mc.est` [8](#), `soControl` [10a](#).

To get the p-value for the LRT, we use a permutation testing approach. The `SO.trend.test` function relies on the `boot` library for this, thus both the permutation test is straightforward to implement. `R` specifies the number of resamples, method could be either “ISDM” or “EM”, and `eps` is the precision of the LRT estimate.

"../R/Reprod.R" 27≡

```

#'Likelihood ratio test of stochastic ordering
#'
#'Performs a likelihood ratio test of stochastic ordering versus equality using
#'permutations to estimate the null-distribution and the p-value. If only the
#'value of the test statistic is needed, use \link{SO.LRT} instead.
#'
#'The test is valid only under the assumption that the cluster-size
#'distribution does not depend on group. During the estimation of the
#'null-distribution the group assignments of the clusters are permuted keeping
#'the group sizes constant; the within-group distribution of the cluster-sizes
#'will vary randomly during the permutation test.
#'
#'The default value of \code{R} is probably too low for the final data
#'analysis, and should be increased.
#'
#'@import boot
#'@export
#'@param cbddata a \link{CBData} object.
#'@param R an integer -- the number of random permutations for estimating the
#'null distribution.
#'@param control an optional list of control settings, usually a call to
#'\code{\link{soControl}}. See there for the names of the settable control
#'values and their effect.
#'@return A list with the following components

```

```

#'@return \item{LRT}{the value of the likelihood ratio test statistic. It has two
#'attributes: \code{ll0} and \code{ll1} - the values of the log-likelihood
#'under  $H_0$  and  $H_a$  respectively.}
#'@return \item{p.val}{the estimated one-sided p-value.}
#'@return \item{boot.res}{an object of class "boot" with the detailed results of
#'the permutations. See \code{\link[boot]{boot}} for details.}
#'@author Aniko Szabo, aszabo@mcw.edu
#'@seealso \code{\link{SO.LRT}} for calculating only the test statistic,
#\code{\link{soControl}}
#'@references Szabo A, George EO. (2010) On the Use of Stochastic Ordering to
#'Test for Trend with Clustered Binary Data. Biometrika 97(1), 95-108.
#'@keywords htest nonparametric
#'@examples
#'\donttest{
#'data(shelltox)
#'set.seed(45742)
#'sh.test <- SO.trend.test(shelltox, R=10, control=soControl(eps=0.1, max.directions=25))
#'sh.test
#'\a plot of the resampled LRT values
#'\would look better with a reasonable value of R
#'\ null.vals <- sh.test$boot.res$t[,1]
#'\ hist(null.vals, breaks=10, freq=FALSE, xlab="Test statistic", ylab="Density",
#'\       main="Simulated null-distribution", xlim=range(c(0,20,null.vals)))
#'\ points(sh.test$LRT, 0, pch="*", col="red", cex=3)
#'}
#'\
◇

```

File defined by [4b](#), [6](#), [7](#), [8](#), [9](#), [10a](#), [11c](#), [12a](#), [26ab](#), [27](#), [28](#), [29ab](#), [30](#), [31](#).

Uses: `SO.trend.test` [28](#), `soControl` [10a](#).

"../R/Reprod.R" 28≡

```

SO.trend.test <- function(cbdata, R=100, control=soControl()){
  dat2 <- cbdata[rep(1:nrow(cbdata), cbdata$Freq),] #each row is one sample
  dat2$Freq <- NULL

  boot.LRT.fun <- function(dat, idx){
    dat.new <- cbind(dat[idx, c("ClusterSize", "NResp")], Trt=dat$Trt) #rearrange clusters
    dat.f <- aggregate(dat.new$Trt,
      list(Trt=dat.new$Trt, ClusterSize=dat.new$ClusterSize, NResp=dat.new$NResp),
      names(dat.f)[names(dat.f)=="x"] <- "Freq"
    dat.f$ClusterSize <- as.numeric(as.character(dat.f$ClusterSize))
    dat.f$NResp <- as.numeric(as.character(dat.f$NResp))
    class(dat.f) <- c("CBData", class(dat.f))

    stat <- SO.LRT(dat.f, control=control)
    stat}

  res <- boot(dat2, boot.LRT.fun, R=R, sim="permutation")

  p <- mean(res$t[,1] >= res$t0)
  LRT <- res$t0
  list(LRT=LRT, p.val=p, boot.res=res)}
◇

```

File defined by [4b](#), [6](#), [7](#), [8](#), [9](#), [10a](#), [11c](#), [12a](#), [26ab](#), [27](#), [28](#), [29ab](#), [30](#), [31](#).

Defines: `SO.trend.test` [9](#), [26a](#), [27](#), [29a](#).

Uses: `soControl` [10a](#).

**4.2. Universal trend test function.** `trend.test` provides a common interface for the Rao-Scott, GEE, and stochastic order based trend tests.

"../R/Reprod.R" 29a≡

```
#'Test for increasing trend with correlated binary data
#
#The \code{trend.test} function provides a common interface to the trend tests
#implemented in this package: \code{\link{SO.trend.test}},
#\code{\link{RS.trend.test}}, and \code{\link{GEE.trend.test}}. The details of
#each test can be found on their help page.
#
# @export
# @param cbdata a \code{\link{CBDData}} object
# @param test character string defining the desired test statistic. "RS"
# performs the Rao-Scott test (\code{\link{RS.trend.test}}), "SO" performs the
# stochastic ordering test (\code{\link{SO.trend.test}}), "GEE", "GEEtrend",
# "GEEall" perform the GEE-based test (\code{\link{GEE.trend.test}}) with
# constant, linearly modeled, and freely varying scale parameters,
# respectively.
# @param exact logical, should an exact permutation test be performed. Only an
# exact test can be performed for "SO". The default is to use the asymptotic
# p-values except for "SO".
# @param R integer, number of permutations for the exact test
# @param control an optional list of control settings for the stochastic order
# ("SO") test, usually a call to \code{\link{soControl}}. See there for the
# names of the settable control values and their effect.
# @return A list with two components and an optional "boot" attribute that
# contains the detailed results of the permutation test as an object of class
# \code{\link[boot]{boot}} if an exact test was performed.
# @return \item{statistic}{numeric, the value of the test statistic}
# @return \item{p.val}{numeric, asymptotic one-sided p-value of the test}
# @author Aniko Szabo, aszabo@mcw.edu
# @seealso \code{\link{SO.trend.test}}, \code{\link{RS.trend.test}}, and
# \code{\link{GEE.trend.test}} for details about the available tests.
# @keywords htest nonparametric
# @examples
#
# data(shelltox)
# trend.test(shelltox, test="RS")
# set.seed(5724)
# #R=50 is too low to get a good estimate of the p-value
# trend.test(shelltox, test="RS", R=50, exact=TRUE)
#
◇
```

File defined by [4b](#), [6](#), [7](#), [8](#), [9](#), [10a](#), [11c](#), [12a](#), [26ab](#), [27](#), [28](#), [29ab](#), [30](#), [31](#).

Uses: `SO.trend.test` [28](#), `soControl` [10a](#).

"../R/Reprod.R" 29b≡

```
trend.test <- function(cbdata, test=c("RS","GEE","GEEtrend","GEEall","SO"), exact=test=="SO",
  R=100, control=soControl()){
  test <- match.arg(test)
  if (!exact && !(test=="SO")){
    res <- switch(test, RS=RS.trend.test(cbdata),
```

```

      GEE=GEE.trend.test(cbindata,scale.method="fixed"),
      GEEtrend=GEE.trend.test(cbindata,scale.method="trend"),
      GEEall=GEE.trend.test(cbindata,scale.method="all"))
    }
  else {
    dat2 <- cbindata[rep(1:nrow(cbindata), cbindata$Freq),] #each row is one sample
    dat2$Freq <- NULL

    boot.LRT.fun <- function(dat, idx){
      dat.new <- cbind(dat[idx, c("ClusterSize","NResp")], Trt=dat$Trt) #rearrange clusters
      dat.f <- aggregate(dat.new$Trt,
        list(Trt=dat.new$Trt, ClusterSize=dat.new$ClusterSize, NResp=dat.new$NResp), length)
      names(dat.f)[names(dat.f)=="x"] <- "Freq"
      dat.f$ClusterSize <- as.numeric(as.character(dat.f$ClusterSize))
      dat.f$NResp <- as.numeric(as.character(dat.f$NResp))
      class(dat.f) <- c("CBData", class(dat.f))

      stat <- switch(test, SO=SO.LRT(dat.f, control=control),
        RS=RS.trend.test(dat.f)$statistic,
        GEE=GEE.trend.test(dat.f, scale.method="fixed")$statistic,
        GEEtrend=GEE.trend.test(cbindata,scale.method="trend")$statistic,
        GEEall=GEE.trend.test(cbindata,scale.method="all")$statistic)

      stat}

    bootres <- boot(dat2, boot.LRT.fun, R=R, sim="permutation")
    res <- list(statistic=bootres$t0, p.val= mean(bootres$t[,1] >= bootres$t0))
    attr(res, "boot") <- bootres
  }
  res}

```

File defined by 4b, 6, 7, 8, 9, 10a, 11c, 12a, 26ab, 27, 28, 29ab, 30, 31.  
 Uses: soControl 10a.

**4.3. Finding the NOAEL.** The NOSTASOT dose is the No-Statistical-Significance-Of-Trend dose – the largest dose at which no trend in the rate of adverse events has been observed.

"../R/Reprod.R" 30≡

```

#'Finding the NOSTASOT dose
#'
#'The NOSTASOT dose is the No-Statistical-Significance-Of-Trend dose -- the
#'largest dose at which no trend in the rate of response has been observed. It
#'is often used to determine a safe dosage level for a potentially toxic
#'compound.
#'
#'A series of hypotheses about the presence of an increasing trend overall,
#'with all but the last group, all but the last two groups, etc. are tested.
#'Since this set of hypotheses forms a closed family, one can test these
#'hypotheses in a step-down manner with the same \code{sig.level} type I error
#'rate at each step and still control the family-wise error rate.
#'
#'The NOSTASOT dose is the largest dose at which the trend is not statistically
#'significant. If the trend test is not significant with all the groups
#'included, the largest dose is the NOSTASOT dose. If the testing sequence goes
#'down all the way to two groups, and a significant trend is still detected,
#'the lowest dose is the NOSTASOT dose. This assumes that the lowest dose is a
#'control group, and this convention might not be meaningful otherwise.
#'

```

```

#'@export
#'@param cbdata a \code{\link{CBData}} object
#'@param test character string defining the desired test statistic. See
#' \code{\link{trend.test}} for details.
#'@param exact logical, should an exact permutation test be performed. See
#' \code{\link{trend.test}} for details.
#'@param R integer, number of permutations for the exact test
#'@param sig.level numeric between 0 and 1, significance level of the test
#'@param control an optional list of control settings for the stochastic order
#'("SO") test, usually a call to \code{\link{soControl}}. See there for the
#'names of the settable control values and their effect.
#'@return a list with two components
#'@return \item{NOSTASOT}{character string identifying the NOSTASOT dose.}
#'@return \item{p}{numeric vector of the p-values of the tests actually performed.}
#'The last element corresponds to all doses included, and will not be missing.
#'p-values for tests that were not actually performed due to the procedure
#'stopping are set to NA.
#'@author Aniko Szabo, aszabo@mcw.edu
#'@seealso \code{\link{trend.test}} for details about the available trend
#'tests.
#'@references Tukey, J. W.; Ciminera, J. L. & Heyse, J. F. (1985) Testing the
#'statistical certainty of a response to increasing doses of a drug.
#'\emph{Biometrics} 41, 295-301.
#'@keywords htest nonparametric
#'@examples
#'
#'data(shelltox)
#'\code{NOSTASOT(shelltox, test="RS")}
#'
◇

```

File defined by [4b](#), [6](#), [7](#), [8](#), [9](#), [10a](#), [11c](#), [12a](#), [26ab](#), [27](#), [28](#), [29ab](#), [30](#), [31](#).

Uses: NOSTASOT [31](#), soControl [10a](#).

"../R/Reprod.R" 31≡

```

NOSTASOT <- function(cbdata, test=c("RS","GEE","GEEtrend","GEEall","SO"), exact=test=="SO",
                     R=100, sig.level=0.05, control=soControl()){
  ntrt <- nlevels(cbdata$Trt)
  control.gr <- levels(cbdata$Trt)[1]
  p.vec <- array(NA, ntrt-1)
  names(p.vec) <- levels(cbdata$Trt)[-1]
  NOSTASOT.found <- FALSE
  curr.gr.idx <- ntrt
  curr.gr <- levels(cbdata$Trt)[ntrt]

  while (!NOSTASOT.found & (curr.gr.idx>1)){
    d1 <- cbdata[unclass(cbdata$Trt)<=curr.gr.idx, ]
    d1$Trt <- factor(d1$Trt) #eliminate unused levels
    tr.test <- trend.test(d1, test=test, exact=exact, R=R, control=control)
    p.vec[curr.gr] <- tr.test$p.val
    if (tr.test$p.val < sig.level){ #NOSTASOT not found yet
      curr.gr.idx <- curr.gr.idx - 1
      curr.gr <- levels(cbdata$Trt)[curr.gr.idx]
    }
    else { #NOSTASOT
      NOSTASOT.found <- TRUE
    }
  }
}

```

```

    list(NOSTASOT = curr.gr, p=p.vec)
  }
  ◇

```

File defined by [4b](#), [6](#), [7](#), [8](#), [9](#), [10a](#), [11c](#), [12a](#), [26ab](#), [27](#), [28](#), [29ab](#), [30](#), [31](#).

Defines: `NOSTASOT` [30](#).

Uses: `soControl` [10a](#).

## 5. FILES

"../R/aaa-generics1.R" Defined by [4a](#), [5](#).

"../R/Reprod.R" Defined by [4b](#), [6](#), [7](#), [8](#), [9](#), [10a](#), [11c](#), [12a](#), [26ab](#), [27](#), [28](#), [29ab](#), [30](#), [31](#).

"../src\ReprodCalcs.c" Defined by [1ab](#), [2](#), [10b](#), [11b](#), [13bc](#), [14ab](#), [15](#), [16ab](#), [17](#), [18](#), [19ab](#), [20b](#), [23](#), [24](#).

## 6. MACROS

⟨ Combine the two parts of the sequences [12d](#) ⟩ Referenced in [12a](#).

⟨ Convert 'a' to non-decreasing sequence and insert into 'res' [11a](#) ⟩ Referenced in [10b](#).

⟨ Declare global variables [20a](#) ⟩ Referenced in [17](#).

⟨ Generate non-decreasing sequences of length `ntrt`-turn with values between `sq` and size [12c](#) ⟩ Referenced in [12a](#).

⟨ Generate non-increasing sequences of length `turn` with values  $\leq$  size [12b](#) ⟩ Referenced in [12a](#).

⟨ Take care of `turn=1` and `turn=ntrt` [13a](#) ⟩ Referenced in [12a](#).

## 7. IDENTIFIERS

`CalcMarginals`: [14b](#), [20b](#), [23](#), [24](#).

`CalcTopD`: [16b](#), [20b](#).

`Comb`: [10b](#), [11b](#).

`DownUpMatrix`: [8](#), [11c](#), [12a](#).

`HyperTable`: [13c](#), [14b](#), [20b](#), [24](#).

`IndexVectorC`: [14a](#), [20b](#).

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