EXCHANGEABLE MODEL FOR MULTINOMIAL DATA

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Abstract. We implement parameter estimation for exchangeable multinomial data, including estimation under marginal compatibility.

1. Preliminaries

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

We will also need to load support libraries.

```
"..\R\ExchMultinomial.R" 1≡
```

```
#'@importFrom combinat hcube
```

◇

File defined by 1, 2, 4b, 5, 6g, 8b, 9ab, 10abc, 12, 14b.

2. Exchangeable multinomial model

2.1. **Definitions.** Let $\mathbf{R} = (R_1, \ldots, R_K)^T$ follow an exchangeable multinomial distribution with $K+1$ categories. We parameterize it by

$$\tau_{r_1,\ldots,r_k|n} = \mathrm{P}\left[\mathcal{X}_{\{1,\ldots,r_1\}}(O_1), \ldots, \mathcal{X}_{\{\sum_{i=1}^{k-1} r_i+1,\ldots,\sum_{i=1}^{k} r_i\}}(O_k)\right] \quad (k = 1, \ldots, K), \tag{1}$$

where $r_i \geq 0$ and $r_1 + \cdots + r_k \leq n$. For notational convenience, also let $\tau_{0,\ldots,0} = 1$.

2.2. **Estimation.** Consider $\tau_{r_1,\ldots,r_K|n}$ and its unconditional counterpart

$$\theta_{r_1,\ldots,r_K} = \mathrm{P}\left[\mathcal{X}_{\{1,\ldots,r_1\}}(O_1), \ldots, \mathcal{X}_{\{\sum_{i=1}^{K-1} r_i+1,\ldots,\sum_{i=1}^{K} r_i\}}(O_K)\right] = \sum_{n=\sum r_i}^{C} \tau_{r_1,\ldots,r_K|n}\, \mathrm{P}(N = n).$$

If $A_{r_1,\ldots,r_K|n}$ denotes the number of clusters of size n with response vector $(r_1, \ldots, r_K)$, then their non-parametric estimates are

$$\hat{\tau}_{r_1,\ldots,r_K|n} = \sum_{s_1,\ldots,s_K} \frac{\binom{n-\sum r_i}{s_1,\ldots,s_K}}{\binom{n}{r_1+s_1,\ldots,r_K+s_K}} \frac{A_{r_1,\ldots,r_K|n}}{M_n}, \tag{2}$$

and

$$\hat{\theta}_{r_1,\ldots,r_K} = \sum_{n=1}^{M} \sum_{s_1,\ldots,s_K} \frac{\binom{n-\sum r_i}{s_1,\ldots,s_K}}{\binom{n}{r_1+s_1,\ldots,r_K+s_K}} \frac{A_{r_1+s_1,\ldots,r_K+s_K|n}}{M}. \tag{3}$$

The function `tau` creates a "look-up table" for the MLEs. It returns either a list by treatment group of either $K+1$ or K dimensional arrays, depending on whether cluster-size specific estimates (τ's) or averaged estimates (θ's) are requested. For the cluster-size specific estimates the first dimension is the cluster size. The calculation of θ's is done separately for each dose level, and thus each dose level uses a different sample-size distribution for averaging.

Date: August 28, 2024.

"..\R\ExchMultinomial.R" 2≡

```
#'@rdname CorrBin-internal
⟨ Define function for multinomial coefficient 14a ⟩
#' Estimate joint event probabilities for multinomial data
#'
#' An exchangeable multinomial distribution with \eqn{K+1} categories \eqn{O_1,\ldots,O_{K+1}}, can be
#' parameterized by the joint probabilities of events
#'\deqn{\tau_{r_1,\ldots,r_{K}|n} = P\big[X_1=\cdots=X_{r_1}=O_1,\ldots, X_{\sum_{i=1}^{K-1}r_i+1} =\cdot
#'where \eqn{r_i \geq 0} and \eqn{r_1+\cdots +r_K\leq n}.
#'The \code{jointprobs} function estimates these probabilities under various settings.
#'Note that when some of the \eqn{r_i}'s equal zero, then no restriction on the number of outcomes of the
#' corresponding type are imposed, so the resulting probabilities are marginal.
#'
#'@param cmdata a \code{CMData} object
#'@param type character string describing the desired type of estimate:
#' \itemize{
#'  \item{"averaged"}{ - averaged over the observed cluster-size distribution within each treatment}
#'  \item{"cluster"}{ - separately for each cluster size within each treatment}
#'  \item{"mc"}{ - assuming marginal compatibility, ie that \eqn{\tau} does not depend on the cluster-siz
#' }
#'@return a list with an array of estimates for each treatment. For a multinomial distribution with
#' \eqn{K+1} categories the arrays will have either \eqn{K+1} or {K} dimensions, depending on whether
#' cluster-size specific estimates (\code{type="cluster"}) or pooled estimates
#' (\code{type="averaged"} or \code{type="mc"}) are requested. For the cluster-size specific estimates
#' the first dimension is the cluster-size. Each additional dimension is a possible outcome.
#'
#'@seealso \code{\link{mc.est}} for estimating the distribution under marginal compatibility,
#'\code{\link{uniprobs}} and \code{\link{multi.corr}} for extracting the univariate marginal event
#'probabilities, and the within-multinomial correlations from the joint probabilities.
#'@examples
#'data(dehp)
#'# averaged over cluster-sizes
#'tau.ave <- jointprobs(dehp, type="ave")
#'# averaged P(X1=X2=O1, X3=O2) in the 1500 dose group
#'tau.ave[["1500"]]["2","1"]  # there are two type-1, and one type-2 outcome
#'
#'#plot P(X1=O1) - the marginal probability of a type-1 event over cluster-sizes
#'tau <- jointprobs(dehp, type="cluster")
#'ests <- as.data.frame(lapply(tau, function(x)x[,"1","0"]))
#'matplot(ests, type="b")
#'@export
#'@importFrom stats xtabs

jointprobs <- function(cmdata, type=c("averaged","cluster","mc")){
  type <- match.arg(type)

  ⟨ Extract info from cmdata into variables 3a ⟩
  # multinomial lookup table
  mctab <- mChooseTable(M, nc, log=FALSE)

  res <- list()
  for (trt in levels(cmdata$Trt)){
    cm1 <- cmdata[cmdata$Trt==trt,]
    # observed freq lookup table
    atab <- array(0, dim=rep(M+1, nc))
    a.idx <- data.matrix(cm1[,nrespvars])
    atab[a.idx + 1] <- atab[a.idx + 1] + cm1$Freq

    if (type=="averaged"){
      Mn <- sum(cm1$Freq)
      ⟨ Calculate averaged thetas 3b ⟩
    } else if (type=="cluster") {
      Mn <- xtabs(Freq ~ factor(ClusterSize, levels=1:M), data=cm1)
      ⟨ Calculate cluster-specific taus 3k ⟩
    } else if (type=="mc") {
```

⟨ *Extract info from cmdata into variables* 3a ⟩ ≡

```
nc <- attr(cmdata, "ncat")
nrespvars <- paste("NResp", 1:nc, sep=".")
M <- max(cmdata$ClusterSize)
```

◇

Fragment referenced in 2, 6g.

First, we define the MLE averaged over cluster sizes. The `Calculate averaged thetas` macro creates a K-dimensional array of $\theta_{r_1,\ldots,r_K}(d)$ values. The implementation is based on combining the two summations of the definition into one using $n = \sum_{i=1}^{K} r_i + \sum_{i=1}^{K} s_i + s_{K+1}$:

$$\hat{\theta}_{r_1,\ldots,r_K} = \sum_{n=1}^{M} \sum_{s_1,\ldots,s_K} \frac{\binom{n-\sum r_i}{s_1,\ldots,s_K}}{\binom{n}{r_1+s_1,\ldots,r_K+s_K}} \frac{A_{r_1+s_1,\ldots,r_K+s_K|n}}{M}$$

$$= \sum_{s_1,\ldots,s_{K+1}} \frac{\binom{\sum s_i}{s_1,\ldots,s_K}}{\binom{\sum r_i + \sum s_i}{r_1+s_1,\ldots,r_K+s_K}} \frac{A_{r_1+s_1,\ldots,r_K+s_K|\sum r_i+\sum s_i}}{M}. \quad (4)$$

⟨ *Calculate averaged thetas* 3b ⟩ ≡

```
res.trt <- array(NA, dim=rep(M+1, nc-1))
dimnames(res.trt) <- rep.int(list(0:M), nc-1)
names(dimnames(res.trt)) <- paste("R", 1:(nc-1), sep="")
# indices for possible values of r
⟨ Simplex with sums (3c idx ,3d M ,3e nc-1 ,3f idxsum ) 13 ⟩
#indices for possible values of s
# (one more column than for r - ensures summation over all n's)
⟨ Simplex with sums (3g sidx ,3h M ,3i nc ,3j sidxsum ) 13 ⟩
for (i in 1:nrow(idx)){
  r <- idx[i,]
  s.idx <- which(sidxsum <= M-sum(r))
  lower.idx <- sidx[s.idx, , drop=FALSE]
  upper.idx <- lower.idx + rep(c(r,0), each=nrow(lower.idx))
  res.trt[rbind(r)+1] <-
    sum(mctab[lower.idx+1] / mctab[upper.idx+1] * atab[upper.idx+1]) / Mn
}
```

◇

Fragment referenced in 2.

Next, we define the MLEs specific for each cluster size. The macro `Calculate cluster-specific taus` creates a $K+1$ dimensional array, with the cluster size as the first dimension.

⟨ *Calculate cluster-specific taus* 3k ⟩ ≡

```
res.trt <- array(NA, dim=c(M, rep(M+1, nc-1))) #first dimension is 'n'
dimnames(res.trt) <- c(list(1:M), rep.int(list(0:M), nc-1))
names(dimnames(res.trt)) <- c("N",paste("R", 1:(nc-1), sep=""))
for (n in which(Mn > 0)){
  # indices for possible values of r
  ⟨ Simplex with sums (3l idx ,3m n ,3n nc-1 ,3o idxsum ) 13 ⟩
  for (i in 1:nrow(idx)){
    r <- idx[i,]
```

```
      s.idx <- which(idxsum <= n-sum(r))
      lower.idx <- idx[s.idx, , drop=FALSE]
      upper.idx <- lower.idx + rep(r, each=nrow(lower.idx))
      lower.idx <- cbind(lower.idx, n-sum(r)-idxsum[s.idx])   #add implied last column
      upper.idx <- cbind(upper.idx, n-sum(r)-idxsum[s.idx])   #add implied last column
      res.trt[cbind(n,rbind(r)+1)] <-
        sum(mctab[lower.idx+1] / mctab[upper.idx+1] * atab[upper.idx+1]) / Mn[n]
    }
  }
  ◇
```

Fragment referenced in 2.

The code for calculating marginally-compatible *tau*'s is described in the next section.

⟨ *Calculate MC taus* 4a ⟩ ≡

```
  pim <- mc.estraw(cm1)[[1]]  #only one treatment group
  res.trt <- tau.from.pi(pim)
◇
```

Fragment referenced in 2.
Uses: `mc.estraw` 6g, `tau` 2, `tau.from.pi` 8b.

3. Marginal compatibility

Under marginal compatibility,

$$\pi_{\mathbf{r}|n} = \sum_{\mathbf{t}\in\mathcal{V}_M} h(\mathbf{r},\mathbf{t},n)\pi_{\mathbf{t}|M}, \tag{5}$$

where $h(\mathbf{r},\mathbf{t},n) = \binom{\mathbf{t}}{\mathbf{r}}\binom{M-\sum t_i}{n-\sum r_i}\Big/\binom{M}{n} = \prod_{i=1}^K \binom{t_i}{r_i}\binom{M-\sum t_i}{n-\sum r_i}\Big/\binom{M}{n}$ and $\mathcal{V}_n = \{(v_1,\ldots,v_K) \in \mathbb{N}^K \mid v_i \geq 0, \sum v_i \leq n\}$ is a K-dimensional simplex lattice with maximum sum n.

3.1. **Estimation.** The following code implements the EM-algorithm for estimating the probabilities of response assuming marginal compatibility. Let $(\mathbf{r}_i, n_i)$, $i = 1,\ldots N$ denote the observed data for a given dose level, where i iterates through the clusters, n_i is the cluster size and $\mathbf{r}_i = (r_1,\ldots,r_K)$ is the observed number of responses of each type.

$$\pi^{(t+1)}_{\mathbf{t}|M} = \frac{1}{N}\sum_{i=1}^N h(\mathbf{r}_i,\mathbf{t},n_i)\frac{\pi^{(t)}_{\mathbf{t}|M}}{\pi^{(t)}_{\mathbf{r}_i|n_i}}, \tag{6}$$

The `mc.est.CMData` function implements the `mc.est` S3 method for `CMData` objects, returning a data frame with all $\pi^{(g)}_{\mathbf{r}|n}, n = 1,\ldots,M$ probabilities. The 'hard' work is done by the `mc.estraw` function, which returns a list of matrices with $\pi^{(g)}_{\mathbf{r}|M}$ values.

`"..\R\ExchMultinomial.R"` 4b≡

```
#'@rdname mc.est
#'@method mc.est CMData
#'@export
#'@param eps numeric; EM iterations proceed until the sum of squared changes fall below \code{eps}
#'@return For \code{CMData}: 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.1 - NResp.K}{numeric, the number of responses of each type}
```

```
#'
#'@note
#'For multinomial data, the implementation is currently written in R, so it is not very fast.
#'
#'@references George EO, Cheon K, Yuan Y, Szabo A (2016)  On Exchangeable Multinomial Distributions. #'\e
#'@examples
#'data(dehp)
#'dehp.mc <- mc.est(subset(dehp, Trt=="0"))
#'subset(dehp.mc, ClusterSize==2)

mc.est.CMData <- function(object, eps=1E-6, ...){

    nc <- attr(object, "ncat")
    resp.vars1 <- paste("NResp", 1:(nc-1), sep=".")

    res <- mc.estraw(object=object, eps=eps, ...)
    margres <- lapply(res, Marginals)  # has only NResp.1 - NResp.K

    mat.to.df <- function(idx, alist){
        dd <- as.data.frame.table(alist[[idx]], responseName="Prob")
        dd[c("N", resp.vars1)] <- lapply(dd[c("N", resp.vars1)], function(x)as.numeric(as.character(x)))
        dd$Trt <- names(alist)[idx]
        dd
    }
    margres <- lapply(1:length(margres), mat.to.df, alist=margres)
    fin <- do.call(rbind, margres)
    names(fin)[1] <- "ClusterSize"
    last.resp <- paste("NResp", nc, sep=".")
    fin[last.resp] <- fin$ClusterSize - rowSums(fin[resp.vars1]) # calculated omitted frequency
    fin$Trt <- factor(fin$Trt)
    fin <- fin[fin[last.resp] >= 0,]  #remove impossible clusters
    fin[c("Trt","ClusterSize", resp.vars1, last.resp, "Prob")]
}
```

◇

File defined by 1, 2, 4b, 5, 6g, 8b, 9ab, 10abc, 12, 14b.
Defines: `mc.est.CMData` Never used.
Uses: `Marginals` 5, `mc.estraw` 6g.

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

$$\pi_{\mathbf{r}|n} = \sum_{i=1}^{K} \frac{r_i + 1}{n+1} \pi_{\mathbf{r}+\mathbf{d}_i|n+1} + \frac{n - \sum_i r_i + 1}{n+1} \pi_{\mathbf{r}|n+1}, \tag{7}$$

where $\mathbf{d}_i$ is the ith coordinate basis vector (i.e. all its elements are 0, except the ith, which is 1).

The input for `Marginals` is a K-dimensional array of $\pi_{\mathbf{r}|M}$, and the output is a $(K+1)$-dimensional array with the values of $\pi_{\mathbf{r}|n}$, $n = 1, \ldots, M$ with cluster size as the first dimension

"..\R\ExchMultinomial.R" 5≡

```
#'@rdname CorrBin-internal
Marginals <- function(theta){
  K <- length(dim(theta))
  M <- dim(theta)[1]-1

  res <- array(0, dim=c(M, rep(M+1, K)))
  dimnames(res) <- c(N=list(1:M), dimnames(theta))

  # indices for possible values of r
```

```
⟨ Simplex with sums (6a idx ,6b  M ,6c  K+1 ,6d  clustersize  ) 13 ⟩
idx <- idx[ , -1, drop=FALSE]  #remove (K+1)st category

⟨ Initialize for cluster size M 6e ⟩
for (cs in seq.int(M-1,1)){
  ⟨ Calculate values for cluster size cs given values for size cs+1 6f ⟩
}

res
}
◇
```

File defined by 1, 2, 4b, 5, 6g, 8b, 9ab, 10abc, 12, 14b.

The initialization just copies over the values from `theta` to the appropriate dimension. Note that when indexing the arrays, a "+1" is necessary since `idx` is 0-based.

⟨ *Initialize for cluster size M* 6e ⟩ ≡

```
curridx <- idx[clustersize==M, ,drop=FALSE]
res[cbind(M, curridx+1)] <- theta[curridx+1]
◇
```

Fragment referenced in 5.

The iterative step initializes with the last term (with $\pi_{\mathbf{r}|n+1}$) and loops over the basis vectors.

⟨ *Calculate values for cluster size cs given values for size cs+1* 6f ⟩ ≡

```
curridx <- idx[clustersize==cs, , drop=FALSE]
res[cbind(cs, curridx+1)] <- (cs+1- rowSums(curridx))/(cs+1) * res[cbind(cs+1, curridx+1)]
for (j in 1:K){
  lookidx <- curridx
  lookidx[ ,j] <- lookidx[ ,j] + 1   #add 1 to the j-th coordinate
  res[cbind(cs, curridx+1)] <- res[cbind(cs, curridx+1)] +
                               lookidx[,j]/(cs+1) * res[cbind(cs+1, lookidx+1)]
}
◇
```

Fragment referenced in 5.

The actual EM iterations are performed in `mc.estraw`.

"..\R\ExchMultinomial.R" 6g≡

```
#'@rdname CorrBin-internal
#'@name mc.estraw
mc.estraw <- function(object, ...) UseMethod("mc.estraw")

#'@rdname CorrBin-internal
#'@method mc.estraw CMData
mc.estraw.CMData <- function(object, eps=1E-6, ...){
  cmdata <- object
  ⟨ Extract info from cmdata into variables 3a ⟩

  # indices for possible values of r with clustersize = M
  ⟨ Simplex with sums (6h idx ,6i  M ,6j  nc-1 ,6k  idxsum  ) 13 ⟩

  res <- list()
  for (trt in levels(cmdata$Trt)){
    cm1 <- cmdata[cmdata$Trt==trt,]
```

```
  if (nrow(cm1) > 0){
    # observed freq lookup table
    atab <- array(0, dim=rep(M+1, nc))
    a.idx <- data.matrix(cm1[,nrespvars])
    atab[a.idx + 1] <- atab[a.idx + 1] + cm1$Freq
    Mn <- sum(cm1$Freq)

    ⟨ MC estimates for given dose group 7 ⟩

    # append treatment-specific result to result list
    dimnames(res.trt) <- rep.int(list(0:M), nc-1)
    names(dimnames(res.trt)) <- paste("NResp", 1:(nc-1), sep=".")
    res.trt <- list(res.trt)
  } else {
    res.trt <- list(c())
  }
  res <- c(res, res.trt)
}
names(res) <- levels(cmdata$Trt)
res
}◇
```

File defined by 1, 2, 4b, 5, 6g, 8b, 9ab, 10abc, 12, 14b.

Within each dose group, the algorithm iterates until the sum of squared changes of the parameters is smaller than the selected threshold `eps`.

⟨ *MC estimates for given dose group* 7 ⟩ ≡

```
res.trt <- array(NA, dim=rep(M+1, nc-1))

#starting values
res.trt[idx + 1] <- 1/nrow(idx)

sqerror <- 1
#EM update
while (sqerror > eps){
      sqerror <- 0
      marg <- Marginals(res.trt)
  res.new <- array(NA, dim=rep(M+1, nc-1))
  res.new[idx + 1] <- 0

  ⟨ Calculate res.new - the value of res.trt for next iteration 8a ⟩

  sqerror <- sum((res.new[idx+1] - res.trt[idx+1])^2)
      res.trt <- res.new
}
◇
```

Fragment referenced in 6g.
Uses: `Marginals` 5.

The update of the $\pi_{\mathbf{t}|M}$ is performed based on (6) rewritten to combine clusters of the same type:

$$\pi_{\mathbf{t}|M}^{(t+1)} = \frac{1}{N} \sum_{(\mathbf{r},n)} \frac{A_{\mathbf{r},n}}{\pi_{\mathbf{r}|n}^{(t)}} h(\mathbf{r},\mathbf{t},n) \pi_{\mathbf{t}|M}^{(t)}, \tag{8}$$

looping through each cluster type $(\mathbf{r}, n)$, and updating all $\pi_{\mathbf{t}|M}$ values compatible with this type. The compatible $\mathbf{t}$ vectors have $t_i \geq r_i$, so they can be written in the form $\mathbf{t} = \mathbf{r} + \mathbf{s}$, where $s_i \geq 0$ and $\sum s_i \leq M - \sum r_i$.

⟨ *Calculate res.new - the value of res.trt for next iteration* 8a ⟩ ≡

```
for (i in 1:nrow(cm1)){
  rlong <- data.matrix(cm1[,nrespvars])[i,]    #nc elements
  r <- rlong[-nc]              #without the last category
  n <- cm1$ClusterSize[i]
  # indices to which this cluster type contributes
  s.idx <- which(idxsum <= M-sum(r))
  tidx <- idx[s.idx, , drop=FALSE] + rep(r, each=length(s.idx))

  hvals <- apply(tidx, 1, function(tvec)prod(choose(tvec, r)) * choose(M-sum(tvec), n-sum(r)))
  hvals <- hvals / choose(M, n)
  res.new[tidx+1] <- res.new[tidx+1] + atab[rbind(rlong)+1] / marg[rbind(c(n,r+1))] / Mn *
                                       hvals * res.trt[tidx+1]
}
```

◇

Fragment referenced in 7.

3.2. **Manipulating estimates.** It is helpful to have functions that can convert the marginally compatible estimates from the π-based form obtained in the estimates to the τ's and to extract the variance-covariance matrix and the correlation parameters.

The `tau.from.pi` function takes a K-dimensional array of $\pi_{\mathbf{r}}$ values, and returns a K-dimensional array of $\tau_{\mathbf{r}}$ values using

$$\tau_{\mathbf{r}} = \sum_{\mathbf{s}} \frac{\binom{n-\sum r_i}{\mathbf{s}}}{\binom{n}{\mathbf{r}+\mathbf{s}}} \pi_{\mathbf{r}+\mathbf{s}}. \tag{9}$$

"..\R\ExchMultinomial.R" 8b≡

```
#'@rdname CorrBin-internal
tau.from.pi <- function(pimat){
  K <- length(dim(pimat))
  n <- dim(pimat)[1] - 1
  res <- array(NA, dim=rep(n+1, K))
  dimnames(res) <- rep.int(list(0:n), K)
  names(dimnames(res)) <- paste("R", 1:K, sep="")

  # multinomial lookup table
  mctab <- mChooseTable(n, K+1, log=FALSE)

  # indices for possible values of r
  ⟨ Simplex with sums (8c idx ,8d n ,8e K ,8f idxsum ) 13 ⟩
  for (i in 1:nrow(idx)){
    r <- idx[i,]
    s.idx <- which(idxsum <= n-sum(r))
    lower.idx <- idx[s.idx, , drop=FALSE]
    upper.idx <- lower.idx + rep(r, each=nrow(lower.idx))
    lower.mc.idx <- cbind(lower.idx, n-sum(r)-idxsum[s.idx])   #add implied last column
    upper.mc.idx <- cbind(upper.idx, n-sum(r)-idxsum[s.idx])   #add implied last column
    res[rbind(r)+1] <-
      sum(mctab[lower.mc.idx+1] / mctab[upper.mc.idx+1] * pimat[upper.idx+1])
  }
  res
}
```

◇

File defined by 1, 2, 4b, 5, 6g, 8b, 9ab, 10abc, 12, 14b.

The `p.from.tau` function function takes a K-dimensional array of $\tau_{\mathbf{r}}$ values, and returns a vector of marginal probabilities of success $\tau_{\mathbf{d}_i}$.

"..\R\ExchMultinomial.R" 9a≡

```
#'@rdname CorrBin-internal
p.from.tau <- function(taumat){
  K <- length(dim(taumat))
  idx <- diag(nrow=K)
  taumat[rbind(idx+1)]
}
```

◇

File defined by 1, 2, 4b, 5, 6g, 8b, 9ab, 10abc, 12, 14b.
Uses: `tau` 2.

The `uniprobs` function provides a wrapper to `p.from.tau` so that it works with the list output of the `jointprobs` function.

"..\R\ExchMultinomial.R" 9b≡

```
#'Extract univariate marginal probabilities from joint probability arrays
#'
#'Calculates the marginal probability of each event type for exchangeable correlated multinomial
#'data based on joint probability estimates calculated by the \code{\link{jointprobs}} function.
#'@param jp the output of \code{\link{jointprobs}} - a list of joint probability arrays by treatment
#'@param type one of c("averaged","cluster","mc") - the type of joint probability. By default,
#'the \code{type} attribute of \code{jp} is used.
#'@return a list of estimated probability of each outcome by treatment group. The elements are either
#'matrices or vectors depending on whether cluster-size specific estimates were requested
#' (\code{type="cluster"}) or not.
#'@export
#'@seealso \code{\link{jointprobs}} for calculating the joint probability arrays
#'@examples
#'data(dehp)
#'tau <- jointprobs(dehp, type="averaged")
#'uniprobs(tau)
#'
#'#separately for each cluster size
#'tau2 <- jointprobs(dehp, type="cluster")
#'uniprobs(tau2)

uniprobs <- function(jp, type=attr(jp, "type")){
  type <- match.arg(type, c("averaged","cluster","mc"))

  get.probs <- function(tt){
    p <- p.from.tau(tt)
    c(p, 1-sum(p)) #add probability of last event type
  }

  if (type=="cluster") {
    res <- lapply(jp, function(x)apply(x, 1, get.probs))
  } else {
    res <- lapply(jp, get.probs)
  }
  res
}
```

◇
File defined by 1, 2, 4b, 5, 6g, 8b, 9ab, 10abc, 12, 14b.
Defines: `uniprobs` 2.
Uses: `tau` 2.

The function `corr.from.pi` calculates the within- and between-outcome correlation coefficients for the exchangeable model. It takes a K-dimensional array of $\pi_{\mathbf{r}}$ values, and returns a 2-dimensional matrix of ϕ_{ij}, $i, j = 1, \ldots, K$ values using

$$\phi_{ij} = \begin{cases} \left[\tau_{(2\mathbf{d}_i)} - \tau^2_{(\mathbf{d}_i)}\right] \Big/ \left[\tau_{(\mathbf{d}_i)}(1 - \tau_{(\mathbf{d}_i)})\right] & i = j \\ -\left[\tau_{(\mathbf{d}_i+\mathbf{d}_j)} - \tau_{(\mathbf{d}_i)}\tau_{(\mathbf{d}_j)}\right] \Big/ \left[\tau_{(\mathbf{d}_i)}\tau_{(\mathbf{d}_j)}\right] & i \neq j, \end{cases} \tag{10}$$

where $\mathbf{d}_i = (0, \ldots, 0, \overbrace{1}^{i}, 0, \ldots, 0)$.

The function `corr.from.tau` does the same calculation, except it starts with τ's.

"..\R\ExchMultinomial.R" 10a≡

```
#'@rdname CorrBin-internal
corr.from.tau <- function(taumat){
  K <- length(dim(taumat))

  idx <- diag(nrow=K)
  numerator <- outer(1:K, 1:K, function(i,j){
     taumat[idx[i,]+idx[j,]+1] - taumat[idx[i,]+1] * taumat[idx[j,]+1]})
  denominator <- outer(1:K, 1:K, function(i,j){
     taumat[idx[i,]+1] * ifelse(i==j, 1-taumat[idx[i,]+1], -taumat[idx[j,]+1])})
  res <- numerator / denominator    #the negative sign is in the denominator
  res
}
```

◇
File defined by 1, 2, 4b, 5, 6g, 8b, 9ab, 10abc, 12, 14b.
Defines: `corr.from.tau` 10bc, 12.
Uses: `tau` 2.

"..\R\ExchMultinomial.R" 10b≡

```
#'@rdname CorrBin-internal
corr.from.pi <- function(pimat){
  tt <- tau.from.pi(pimat)
  res <- corr.from.tau(tt)
  res
}
```

◇
File defined by 1, 2, 4b, 5, 6g, 8b, 9ab, 10abc, 12, 14b.
Defines: `corr.from.pi` Never used.
Uses: `corr.from.tau` 10a, `tau` 2, `tau.from.pi` 8b.

Finally, `multi.corr` wraps these into an exported function useable on the list output of the `jointprobs` function.

"..\R\ExchMultinomial.R" 10c≡

```
#'Extract correlation coefficients from joint probability arrays
#'
```

```
#'Calculates the within- and between-outcome correlation coefficients for exchangeable correlated
#'multinomial data based on joint probability estimates calculated by the \code{\link{jointprobs}}
#'function. These determine the variance inflation due the cluster structure.
#'
#'If \eqn{R_i} and \eqn{R_j} is the number of events of type \eqn{i} and \eqn{j}, respectively, in a clus
#'size \eqn{n}, then
#'\deqn{Var(R_i)= n p_i (1-p_i)(1 + (n-1)\phi_{ii})}
#'\deqn{Cov(R_i,R_j)= -n p_i p_j (1 + (n-1)\phi_{ij})}
#'where \eqn{p_i} and \eqn{p_j} are the marginal event probabilities and \eqn{\phi_{ij}} are the correlat
#' coefficients computed by \code{multi.corr}.
#'@param jp the output of \code{\link{jointprobs}} - a list of joint probability arrays by treatment
#'@param type one of c("averaged","cluster","mc") - the type of joint probability. By default,
#'the \code{type} attribute of \code{jp} is used.
#'@return a list of estimated correlation matrices by treatment group. If cluster-size specific
#' estimates were requested (\code{(type="cluster")}), then each list elements are a list of
#' these matrices for each cluster size.
#'@export
#'@seealso \code{\link{jointprobs}} for calculating the joint probability arrays
#'@examples
#'data(dehp)
#'tau <- jointprobs(dehp, type="averaged")
#'multi.corr(tau)
#'

multi.corr <- function(jp, type=attr(jp, "type")){
  type <- match.arg(type, c("averaged","cluster","mc"))

  if (type=="cluster") {
    K <- length(dim(jp[[1]])) - 1
    resmat <- lapply(jp, function(x)apply(x, 1, corr.from.tau))
    res <- lapply(resmat, function(x){
                  lapply(1:ncol(x), function(idx)matrix(x[,idx], nrow=K))})
  } else {
    res <- lapply(jp, corr.from.tau)
  }
  res
}
```

◇

File defined by 1, 2, 4b, 5, 6g, 8b, 9ab, 10abc, 12, 14b.
Defines: `multi.corr` 2.
Uses: `corr.from.tau` 10a, `tau` 2.

3.3. **Testing marginal compatibility.** The `mc.test.chisq` function implements a generalization of the Cochran-Armitage trend test for correlated multinomial data to test for marginal compatibility. Note that it only tests that the marginal probability of response p_i does not depend on the cluster size for any category.

First, we define the test statistic for one group, and then add the resulting χ^2_K-distributed test statistics over the G groups for an overall GK degree of freedom test.

As above, let $(\mathbf{r}_i, n_i)$, $i = 1, \ldots N$ denote the observed data for a given dose level, where i iterates through the clusters, n_i is the cluster size and $\mathbf{r}_i = (r_{i1}, \ldots, r_{iK})$ is the observed number of responses of each type. Define the raw trend statistic for response j as

$$X_j = \sum_{i=1}^{N} r_{ij}(c_{n_i} - \bar{c}), \quad j = 1, \ldots, K, \tag{11}$$

where c_n are the scores for the Cochran-Armitage test usually chosen as $c_n = n - (M+1)/2$, and $\bar{c}_g = \left(\sum_{i=1}^{N} n_i c_{n_i}\right)/\left(\sum_{i=1}^{N} n_i\right) = \sum_{n=1}^{M} M_n n c_n / \sum_{n=1}^{M} n M_n$ is the weighted average of the scores (M_n is the number of clusters of size n).

The covariance of two of these test statistics is

$$\sigma_{jk} = \mathrm{Cov}(X_j, X_k) = \begin{cases} \sum_{i=1}^{N} (c_{n_i} - \bar{c})^2 n_i p_{j|n}(1 - p_{j|n})[1 + (n_i - 1)\phi_{jj|n_i}], & j = k; \\ -\sum_{i=1}^{N} (c_{n_i} - \bar{c})^2 n_i p_{j|n} p_{k|n}[1 + (n_i - 1)\phi_{jk|n_i}], & j \neq k, \end{cases} \tag{12}$$

where $p_{j|n} = \tau_{\mathbf{d}_j|n}$ is the probability of event type O_j in clusters of size n. Under the null hypothesis of marginal compatibility, the dependence of $p_{j|n}$ and $\phi_{jk|n}$ on n can be removed:

$$\sigma_{jk} = \begin{cases} p_j(1 - p_j) \sum_{i=1}^{N} (c_{n_i} - \bar{c})^2 n_i [1 + (n_i - 1)\phi_{jj}] = p_j(1 - p_j) \sum_{n=1}^{M} n M_n (c_n - \bar{c})^2 [1 + (n - 1)\phi_{jj}], & j = k; \\ -p_j p_k \sum_{i=1}^{N} (c_{n_i} - \bar{c})^2 n_i [1 + (n_i - 1)\phi_{jk}] = -p_j p_k \sum_{n=1}^{M} n M_n (c_n - \bar{c})^2 [1 + (n - 1)\phi_{jk}], & j \neq k, \end{cases} \tag{13}$$

The combined test statistic for the given dose group g is

$$T_g^2 = X_g' \Sigma_g^{-1} X_g \sim \chi^2_K \text{ under } H_0, \tag{14}$$

where $X_g' = (X_{g1}, \ldots, X_{gK})$, and $\Sigma_g = (\sigma_{gjk})_{K \times K}$ is its variance-covariance matrix defined by (11) and (13). The unknown values of p_j and ϕ_{jk} will be replaced by their estimates under marginal compatibility $\hat{\tau}_{g\mathbf{d}_j}$ and $\hat{\phi}_{gjk}$.

The final test statistic is an independent combination of the statistics for each dose group:

$$T^2 = \sum_{g=1}^{G} T_g^2 \sim \chi^2_{G\,K} \text{ under } H_0. \tag{15}$$

"..\R\ExchMultinomial.R" 12≡

```
#'@rdname mc.test.chisq
#'@method mc.test.chisq CMData
#'@export
#'@importFrom stats weighted.mean pchisq
#'@examples
#'
#'data(dehp)
#'mc.test.chisq(dehp)
#'

mc.test.chisq.CMData <- function(object, ...){
  cmdata <- object[object$Freq > 0, ]
  K <- attr(object, "ncat")-1
  nrespvars <- paste("NResp", 1:K, sep=".")

  get.T <- function(x){
      x$Trt <- factor(x$Trt)  #remove unused levels
      tt <- jointprobs(x, type="mc")[[1]] #only one treatment group
      p <- p.from.tau(tt)
      phi <- corr.from.tau(tt)
      xx <- x[rep(1:nrow(x), x$Freq),]
      xx$Freq <- 1

      M <- max(x$ClusterSize)
      Mn <- table(factor(xx$ClusterSize, levels=1:M))

      scores <- (1:M) - (M+1)/2

      Rmat <- data.matrix(xx[,nrespvars,drop=FALSE])
```

```
    nvec <- xx$ClusterSize
    cvec <- scores[nvec]
    c.bar <- weighted.mean(cvec, w=nvec)
    cvec <- cvec - c.bar

    X <- t(Rmat) %*% cvec
    Sigma <- diag(p, nrow=length(p)) - outer(p,p)  #multinomial vcov
    od.matrix <- matrix(0, nrow=K, ncol=K)  #over-dispersion matrix
    for (n in 1:M){
      od.matrix <- od.matrix + n * Mn[n] * (scores[n]-c.bar)^2 * (1+(n-1)*phi)
    }
    Sigma <- Sigma * od.matrix

    Tstat <- t(X) %*% solve(Sigma) %*% X
    Tstat
  }

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

File defined by 1, 2, 4b, 5, 6g, 8b, 9ab, 10abc, 12, 14b.
Defines: `mc.test.chisq` Never used.
Uses: `corr.from.tau` 10a, `tau` 2.

4. Support functions

The `Simplex with sums` macro creates a matrix (parameter 1) with rows containing the coordinates of an integer lattice within a d-dimensional (parameter 3) simplex of size n (parameter 2). That is all d-dimensional vectors with non-negative elements with sum not exceeding n are listed. The actual sums are saved in a vector (parameter 4). Since this is a parametrized macro, it will expand to code, so no actual function calls will be made by the program. This should reduce copying of the potentially large matrices.

⟨ *Simplex with sums* 13 ⟩ ≡

```
@1 <- hcube(rep(@2+1, @3))-1
@4 <- rowSums(@1)
@1 <- @1[@4 <= @2, ,drop=FALSE]  #remove impossible indices
@4 <- @4[@4 <= @2]
◇
```

Fragment referenced in 3bk, 5, 6g, 8b.

The `mChoose` function calculates the multinomial coefficient $\binom{n}{r_1,\ldots,r_K}$. The lower part of the expression is passed as a vector. If its values add up to less than n, an additional value is added. The function is not vectorized.

⟨ *Define function for multinomial coefficient* 14a ⟩ ≡

```
mChoose <- function(n, rvec, log=FALSE){
  rlast <- n - sum(rvec)
  rveclong <- c(rvec, rlast)
  if (any(rveclong < 0)) return(0)

  res <- lgamma(n + 1) - sum(lgamma(rveclong + 1))
  if (log) res else exp(res)
}
```

◇

Fragment referenced in 2.
Defines: `mChoose` 14b.

The `mChooseTable` function creates a lookup table of the multinomial coefficients with the number of categories k and $n = \max \sum r_i$ given. The results is a k-dimensional array, with element `[r1,...,rK]` corresponding to $\binom{\sum(r_i-1)}{r_1-1,\ldots,r_k-1}$ (because the array is 1-indexed, while r_i can go from 0). The values in the array with coordinate sum exceeding n are missing.

`"..\R\ExchMultinomial.R"` 14b≡

```
#'@rdname CorrBin-internal
  mChooseTable <- function(n, k, log=FALSE){
    res <- array(NA, dim=rep.int(n+1, k))
    dimnames(res) <- rep.int(list(0:n), k)

    idx <- hcube(rep.int(n+1, k)) - 1
    idx <- idx[rowSums(idx) <= n, ,drop=FALSE]
    for (i in 1:nrow(idx)){
        r <- idx[i, ]
        res[rbind(r)+1] <- mChoose(n=sum(r), rvec=r, log=log)
    }
    res
  }
```

◇

File defined by 1, 2, 4b, 5, 6g, 8b, 9ab, 10abc, 12, 14b.
Uses: `mChoose` 14a.

5. Files

`"..\R\ExchMultinomial.R"` Defined by 1, 2, 4b, 5, 6g, 8b, 9ab, 10abc, 12, 14b.

6. Macros

⟨ Calculate averaged thetas 3b ⟩ Referenced in 2.
⟨ Calculate cluster-specific taus 3k ⟩ Referenced in 2.
⟨ Calculate MC taus 4a ⟩ Referenced in 2.
⟨ Calculate res.new - the value of res.trt for next iteration 8a ⟩ Referenced in 7.
⟨ Calculate values for cluster size cs given values for size cs+1 6f ⟩ Referenced in 5.
⟨ Define function for multinomial coefficient 14a ⟩ Referenced in 2.
⟨ Extract info from cmdata into variables 3a ⟩ Referenced in 2, 6g.
⟨ Initialize for cluster size M 6e ⟩ Referenced in 5.
⟨ MC estimates for given dose group 7 ⟩ Referenced in 6g.
⟨ Simplex with sums 13 ⟩ Referenced in 3bk, 5, 6g, 8b.

7. Identifiers

`corr.from.pi`: 10b.
`corr.from.tau`: 10a, 10bc, 12.

`Marginals`: 4b, 5, 7.
`mc.est.CMData`: 4b.
`mc.estraw`: 4ab, 6g.
`mc.test.chisq`: 12.
`mChoose`: 14a, 14b.
`multi.corr`: 2, 10c.
`tau`: 2, 4a, 8b, 9ab, 10abc, 12.
`tau.from.pi`: 4a, 8b, 10b.
`uniprobs`: 2, 9b.