

Package ‘MADPop’

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Type Package

Title MHC Allele-Based Differencing Between Populations

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Description Tools for the analysis of population differences using the Major Histocompatibility Complex (MHC) genotypes of samples having a variable number of alleles (1-4) recorded for each individual. A hierarchical Dirichlet-Multinomial model on the genotype counts is used to pool small samples from multiple populations for pairwise tests of equality. Bayesian inference is implemented via the 'rstan' package. Bootstrapped and posterior p-values are provided for chi-squared and likelihood ratio tests of equal genotype probabilities.

URL <https://github.com/mlysy/MADPop>

BugReports <https://github.com/mlysy/MADPop/issues>

License GPL-3

Depends R (>= 3.4.0), rstan (>= 2.26.0)

Imports methods, Rcpp (>= 0.12.0), stats, rstantools

Suggests knitr, rmarkdown, testthat

LinkingTo BH (>= 1.66.0), Rcpp (>= 0.12.0), RcppEigen (>= 0.3.3.3.0), rstan (>= 2.26.0), StanHeaders (>= 2.26.0), RcppParallel (>= 5.0.1)

VignetteBuilder knitr

SystemRequirements GNU make

Encoding UTF-8

LazyData true

RoxygenNote 7.2.3

NeedsCompilation yes

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MADPop-package	<i>(M)HC (A)llele-Based (D)ifferencing between (Pop)ulations</i>
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Description

Tools for the analysis of population differences using the Major Histocompatibility Complex (MHC) genotypes of samples having a variable number of alleles (1-4) recorded for each individual.

Details

For a full tutorial see package vignette: vignette("MADPop-quick tut").

Author(s)

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See Also

Useful links:

- <https://github.com/mlysy/MADPop>
- Report bugs at <https://github.com/mlysy/MADPop/issues>

Examples

```

# typical dataset
head(fish215[sample(nrow(fish215)),])
table(fish215$Lake) # number of samples per lake

# contingency table on two lakes
iLakes <- c("Michipicoten", "Simcoe")
Xsuff <- UM.suff(X = fish215[fish215$Lake %in% iLakes,])
ctab <- Xsuff$stab
ctab

# bootstrapped p-value calculation for chi^2 and LR tests
p.MLE <- colSums(ctab)/sum(ctab)
N1 <- sum(ctab[1,])
N2 <- sum(ctab[2,])
# bootstrapped test statistics (chi^2 and LRT)
T.boot <- UM.eqtest(N1 = N1, N2 = N2, p0 = p.MLE, nreps = 1e3)

# observed test statistics
T.obs <- c(chi2 = chi2.stat(ctab), LRT = LRT.stat(ctab))
# p-values
rowMeans(t(T.boot) > T.obs)

# posterior sampler for hierarchical model

# output posterior probability for each genotype in lake Simcoe
rhoId <- "Simcoe"
nsamples <- 500
hUM.fit <- hUM.post(nsamples = nsamples, X = fish215,
                   rhoId = rhoId, chains = 1)

# first 20 genotype posterior probabilities in lake Simcoe
rho.post <- hUM.fit$rho[,1,]
boxplot(rho.post[,1:20], las = 2,
        xlab = "Genotype", ylab = "Posterior Probability",
        pch = ".", col = "grey")

```

chi2.stat

*Chi-squared test statistic for contingency tables***Description**

Calculates the chi-squared test statistic for a two-way contingency table.

Usage

```
chi2.stat(tab)
```

Arguments

tab A $K \times C$ matrix (contingency table) of counts. See details.

Details

Suppose that **tab** consists of counts from K populations (rows) in C categories. The chi-squared test statistic is computed as

$$\sum_{i=1}^K \sum_{j=1}^C (E_{ij} - O_{ij})^2 / E_{ij},$$

where O_{ij} is the observed number of counts in the i th row and j th column of **tab**, and E_{ij} is the expected number of counts under H_0 that the populations have identical proportions in each category:

$$E_{ij} = \frac{1}{N} \sum_{i=1}^K O_{ij} \times \sum_{j=1}^C O_{ij}.$$

where N is the total number of counts in **tab**.

Value

The calculated value of the chi-squared statistic.

Examples

```
# simple contingency table
ctab <- rbind(pop1 = c(5, 3, 0, 3),
              pop2 = c(4, 10, 2, 5))
colnames(ctab) <- LETTERS[1:4]
ctab
chi2.stat(ctab) # chi^2 test statistic
```

fish215

Genotypes of lake trout from Ontario, Canada

Description

Observable genotypes (up to possibly duplicated alleles) of 215 lake trout (*Salvelinus namaycush*) collected from 11 lakes in Ontario, Canada.

Format

A data.frame with 215 rows and 5 columns. The first column is an (optional) vector of population identifiers. The next four columns contain the recorded genotype for each observation (row). Each row contains up to four distinct allele identifiers in any order. Missing alleles should be denoted by NA, or "", but not both.

Details

This `data.frame` is how a typical spreadsheet of genotype data gets imported into **R**. Data must adhere to this format to be correctly processed by the functions in **MADPop**.

Source

Kuntz, S. (2014). *Population Differentiation of Ontario Lake trout (*Salvelinus namaycush*) using the Major Histocompatibility Complex class II β gene* ([URL](#)).

Examples

```
head(fish215)
```

hUM.post	<i>Posterior sampling from a hierarchical Unconstrained-Multinomial model</i>
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Description

MCMC sampling from a Dirichlet-Multinomial model using [stan](#).

Usage

```
hUM.post(nsamples, X, popId, rhoId, full.stan.out = FALSE, ...)
```

Arguments

<code>nsamples</code>	Number of posterior samples
<code>X</code>	4-column or 5-column matrix of observations in the correct format. See UM.suff .
<code>popId</code>	Optional vector of population identifiers. See UM.suff .
<code>rhoId</code>	Populations for which posterior samples of the genotype probability vector <code>rho</code> are desired. Defaults to all populations. Set <code>rhoId = NULL</code> not to output these for any populations.
<code>full.stan.out</code>	Logical. Whether or not to return the full <code>stan</code> output. For monitoring convergence of the MCMC sampling.
<code>...</code>	Further arguments to be passed to the sampling function in rstan .

Details

The hierarchical Dirichlet-Multinomial model is given by

$$Y_k \mid \rho_k \sim_{\text{ind}} \text{Multinomial}(\rho_k, N_k),$$

$$\rho_k \sim_{\text{iid}} \text{Dirichlet}(\alpha).$$

where $\alpha_0 = \sum_{i=1}^C \alpha_i$ and $\bar{\alpha} = \alpha/\alpha_0$. MCMC sampling is achieved with the **rstan** package, which is listed as a dependency for **MADPop** so as to expose **rstan**'s sophisticated tuning mechanism and convergence diagnostics.

Value

A list with elements

- A: The unique allele names.
- G: The 4-column matrix Package libcurl was not found in the pkg-config search path.of unique genotype combinations.
- rho: A matrix with $\text{ncol}(\text{rho}) == \text{nrow}(G)$, where each row is a draw from the posterior distribution of inheritance probabilities.
- sfit: If `full.stan.out = TRUE`, the fitted stan object.

Examples

```
# fit hierarchical model to fish215 data

# only output posterior samples for lake Simcoe
rhoId <- "Simcoe"
nsamples <- 500
hUM.fit <- hUM.post(nsamples = nsamples, X = fish215,
                    rhoId = rhoId,
                    chains = 1) # number of MCMC chains

# plot first 20 posterior probabilities in lake Simcoe
rho.post <- hUM.fit$rho[,1,]
boxplot(rho.post[,1:20], las = 2,
        xlab = "Genotype", ylab = "Posterior Probability",
        pch = ".", col = "grey")
```

LRT.stat

Likelihood ratio test statistic for contingency tables

Description

Calculate the likelihood ratio test statistic for general two-way contingency tables.

Usage

```
LRT.stat(tab)
```

Arguments

tab A $K \times C$ matrix (contingency table) of counts. See details.

Details

Suppose that `tab` consists of counts from K populations (rows) in C categories. The likelihood ratio test statistic is computed as

$$2 \sum_{i=1}^K \sum_{j=1}^C O_{ij} \log(p_{ij}^A / p_j^0),$$

where O_{ij} is the observed number of counts in the i th row and j th column of `tab`, $p_{ij}^A = O_{ij} / \sum_{j=1}^C O_{ij}$ is the unconstrained estimate of the proportion of category j in population i , and $p_j^0 = \sum_{i=1}^K O_{ij} / \sum_{i=1}^K \sum_{j=1}^C O_{ij}$ is the estimate of this proportion under H_0 that the populations have identical proportions in each category. If any column has only zeros it is removed before calculating the LRT statistic.

Value

The calculated value of the LRT statistic.

Examples

```
# simple contingency table
ctab <- rbind(pop1 = c(5, 3, 0, 3),
              pop2 = c(4, 10, 2, 5))
colnames(ctab) <- LETTERS[1:4]
ctab
LRT.stat(ctab) # likelihood ratio statistic
```

UM.eqtest

Equality tests for two multinomial samples

Description

Generate multinomial samples from a common probability vector and calculate the Chi-square and Likelihood Ratio test statistics.

Usage

```
UM.eqtest(N1, N2, p0, nreps, verbose = TRUE)
```

Arguments

N1	Size of sample 1.
N2	Size of sample 2.
p0	Common probability vector from which to draw the multinomial samples. Can also be a matrix, in which case each simulation randomly draws with replacement from the rows of <code>p0</code> .
nreps	Number of replications of the simulation.
verbose	Logical. If TRUE prints message every 5000 replications.

Details

The chi-squared and likelihood ratio test statistics are calculated from multinomial samples $(Y_1^1, Y_2^1), \dots, (Y_1^M, Y_2^M)$, where

$$Y_k^m \stackrel{\text{ind}}{\sim} \text{Multinomial}(N_k, p_0^m),$$

where p_0^m is the m th row of p_0 .

Value

An $n\text{reps} \times 2$ matrix with the simulated chi-squared and LR values.

Examples

```
# bootstrapped p-value calculation against equal genotype proportions
# in lakes Michipicoten and Simcoe

# contingency table
popId <- c("Michipicoten", "Simcoe")
ctab <- UM.suff(fish215[fish215$Lake %in% popId,])$tab
ctab

# MLE of probability vector
p.MLE <- colSums(ctab)/sum(ctab)
# sample sizes
N1 <- sum(ctab[1,]) # Michipicoten
N2 <- sum(ctab[2,]) # Simcoe

# bootstrapped test statistics (chi^2 and LRT)
T.boot <- UM.eqtest(N1 = N1, N2 = N2, p0 = p.MLE, nreps = 1e3)

# observed test statistics
T.obs <- c(chi2 = chi2.stat(ctab), LRT = LRT.stat(ctab))
# p-values
rowMeans(t(T.boot) > T.obs)
```

UM.suff

Sufficient statistics for the Unconstrained-Multinomial model

Description

Converts a matrix or data.frame of genotype data into the sufficient statistics required to fit a Dirichlet-Multinomial hierarchical model.

Usage

```
UM.suff(X, popId)
```


Arguments

X	Genotype adata. Either a N x 4 matrix with NA's indicating duplicates or a N x 5 column data.frame with the first column being the popId.
popId	grouping variable for X. Must be supplied if X has 4 columns.

Value

A list with elements:

- A: Vector of unique alleles names. The allele numbers in the following quantities correspond to the indices of A.
- G: 4-column matrix of unique genotype combinations. The presence of 0's indicates that less than four alleles were amplified indicating that a given genotype either has less than 4 distinct alleles or that some alleles are duplicated.
- tab: Observed data in a simplified numerical format. This is a contingency table with rows given by the unique elements of popId and columns given by each row of G.

Examples

```
# sufficient statistics in 3 lakes

X <- fish215[fish215$Lake %in% c("Hogan", "Manitou", "Simcoe"),]
suff <- UM.suff(X)

suff$A # allele names
suff$G # unique genotypes
suff$tab # contingency table
```

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