

Package ‘hsrecombi’

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Type Package

Title Estimation of Recombination Rate and Maternal LD in Half-Sibs

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Description Paternal recombination rate and maternal linkage disequilibrium (LD) are estimated for pairs of biallelic markers such as single nucleotide polymorphisms (SNPs) from progeny genotypes and sire haplotypes. At least one sire has to be double heterozygous at the investigated pairs of SNPs. The implementation relies on paternal half-sib families. If maternal half-sib families are used, the roles of sire/dam are swapped. Multiple families can be considered.

Hampel, Teuscher, Gomez-Raya, Doschoris, Wittenburg (2018) ``Estimation of recombination rate and maternal linkage disequilibrium in half-sibs" <doi:10.3389/fgene.2018.00186>.

Gomez-Raya (2012) ``Maximum likelihood estimation of linkage disequilibrium in half-sib families" <doi:10.1534/genetics.111.137521>.

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License GPL (>= 2)

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| | |
|-----------------|------------------------------------|
| checkCandidates | <i>Candidates for misplacement</i> |
|-----------------|------------------------------------|

Description

Search for SNPs with unusually large estimates of recombination rate

Usage

```
checkCandidates(final, win = 30, quant = 0.99)
```

Arguments

| | |
|-------|--|
| final | table of results produced by editraw with pairwise estimates of recombination rate between p SNPs within chromosome; minimum required data frame with columns SNP1, SNP2 and theta |
| win | optional value for window size; default value 30 |
| quant | optional value; default value 0.99, see details |

Details

Markers with unusually large estimates of recombination rate to close SNPs are candidates for misplacements in the underlying assembly. The mean of recombination rate estimates with win subsequent or preceding markers is calculated and those SNPs with mean value exceeding the quant quantile are denoted as candidates which have to be manually curated! This can be done, for instance, by visual inspection of a correlation plot containing estimates of recombination rate in a selected region.

Value

vector of SNP indices for further verification

Examples

```
### test data
data(targetregion)
### make list for paternal half-sib families
hap <- makehaplist(daughterSire, hapSire)
### parameter estimates on a chromosome
res <- hsrecombi(hap, genotype.chr, map.chr$SNP)
### post-processing to achieve final and valid set of estimates
final <- editraw(res, map.chr)
### check for candidates of misplacement
snp <- checkCandidates(final)
```

countNumbers

Count genotype combinations at 2 SNPs

Description

Count genotype combinations at 2 SNPs

Arguments

X numeric matrix of genotypes

Value

count vector of counts of 9 possible genotypes at SNP pair

daughterSire

targetregion: allocation of paternal half-sib families

Description

Vector of sire ID for each progeny

Usage

daughterSire

Format

An object of class integer of length 265.

editraw

Editing results of hsrecombi

Description

Process raw results from `hsrecombi`, decide which out of two sets of estimates is more likely and prepare list of final results

Usage

```
editraw(Roh, map1)
```

Arguments

| | |
|------|--|
| Roh | list of raw results from <code>hsrecombi</code> |
| map1 | data.frame containing information on physical map, at least: SNP SNP ID locus_Mb physical position in Mbp of SNP on chromosomes Chr chromosome of SNP |

Value

final table of results

SNP1 index 1. SNP

SNP2 index 2. SNP

D maternal LD

fAA frequency of maternal haplotype 1-1

fAB frequency of maternal haplotype 1-0

fBA frequency of maternal haplotype 0-1

fBB frequency of maternal haplotype 0-0

p1 Maternal allele frequency (allele 1) SNP1

p2 Maternal allele frequency (allele 1) SNP2

nfam1 size of genomic family 1

nfam2 size of genomic family 2

error 0 if computations were without error; 1 if EM algorithm did not converge

iteration number of EM iterations

theta paternal recombination rate

r2 r^2 of maternal LD

logL value of log likelihood function

unimodal 1 if likelihood is unimodal; 0 if likelihood is bimodal

critical 0 if parameter estimates were unique; 1 if parameter estimates were obtained via decision process

locus_Mb physical distance between SNPs in Mbp

Examples

```
### test data
data(targetregion)
### make list for paternal half-sib families
hap <- makehaplist(daughterSire, hapSire)
### parameter estimates on a chromosome
res <- hsrecombi(hap, genotype.chr, map.chr$SNP)
### post-processing to achieve final and valid set of estimates
final <- editraw(res, map.chr)
```

geneticPosition *Estimation of genetic position*

Description

Estimation of genetic positions (in centi Morgan)

Usage

```
geneticPosition(final, exclude = NULL, threshold = 0.05)
```

Arguments

| | |
|-----------|--|
| final | table of results produced by editraw with pairwise estimates of recombination rate between p SNPs within chromosome; minimum required data frame with columns SNP1, SNP2 and theta |
| exclude | optional vector (LEN q) of SNPs to be excluded (e.g., candidates of misplaced SNPs) |
| threshold | optional value; recombination rates \leq threshold are considered for smoothing |

Details

Smoothing of recombination rates (θ) ≤ 0.05 via quadratic optimization provides an approximation of genetic distances (in Morgan) between SNPs. The cumulative sum * 100 yields the genetic positions in cM.

The minimization problem $(\theta - D d)^2$ is solved s.t. $d > 0$ where d is the vector of genetic distances between adjacent markers but θ is not restricted to adjacent markers. The incidence matrix D contains 1's for those intervals contributing to the total distance relevant for each θ .

Estimates of $\theta = 1e-6$ are neglected as these values coincide with start values and indicate that (because of a very flat likelihood surface) no meaningful estimate of recombination rate has been obtained.

Value

vector (LEN p) of genetic positions of SNPs (in cM)

Examples

```

### test data
data(targetregion)
### make list for paternal half-sib families
hap <- makehaplist(daughterSire, hapSire)
### parameter estimates on a chromosome
res <- hsrecombi(hap, genotype.chr, map.chr$SNP)
### post-processing to achieve final and valid set of estimates
final <- editraw(res, map.chr)
### approximation of genetic positions
pos <- geneticPosition(final)

```

| | |
|--------------|--|
| genotype.chr | <i>targetregion: progeny genotypes</i> |
|--------------|--|

Description

matrix of progeny genotypes in target region on chromosome BTA1

Usage

genotype.chr

Format

An object of class `matrix` with 265 rows and 300 columns.

| | |
|---------|--------------------------------------|
| hapSire | <i>targetregion: sire haplotypes</i> |
|---------|--------------------------------------|

Description

matrix of sire haplotypes in target region on chromosome BTA1

Usage

hapSire

Format

An object of class `matrix` with 10 rows and 301 columns.

hsrecombi

*Estimation of recombination rate and maternal LD***Description**

Wrapper function for estimating recombination rate and maternal linkage disequilibrium between intra-chromosomal SNP pairs by calling EM algorithm

Usage

```
hsrecombi(hap, genotype.chr, snp.chr, only.adj = FALSE, prec = 1e-06)
```

Arguments

| | |
|--------------|---|
| hap | list (LEN 2) of lists famID list (LEN number of sires) of vectors (LEN n.progeny) of progeny indices relating to lines in genotype matrix sireHap list (LEN number of sires) of matrices (DIM 2 x p) of sire haplotypes (0, 1) on investigated chromosome |
| genotype.chr | matrix (DIM n x p) of all progeny genotypes (0, 1, 2) on a chromosome with p SNPs |
| snp.chr | vector(LEN p) of SNP indices as in physical map |
| only.adj | logical; if TRUE, recombination rate is calculated only between neighbouring markers |
| prec | scalar; precision of estimation |

Details

Paternal recombination rate and maternal linkage disequilibrium (LD) are estimated for pairs of biallelic markers (such as single nucleotide polymorphisms; SNPs) from progeny genotypes and sire haplotypes. At least one sire has to be double heterozygous at the investigated pairs of SNPs. All progeny are merged in two genomic families: (1) coupling phase family if sires are double heterozygous 0-0/1-1 and (2) repulsion phase family if sires are double heterozygous 0-1/1-0. So far it is recommended processing the chromosomes separately. If maternal half-sib families are used, the roles of sire/dam are swapped. Multiple families can be considered.

Value

list (LEN p - 1) of data.frames; for each SNP, parameters are estimated with all following SNPs; two solutions (prefix sln1 and sln2) are obtained for two runs of the EM algorithm

SNP1 index 1. SNP

SNP2 index 2. SNP

D maternal LD

fAA frequency of maternal haplotype 1-1

fAB frequency of maternal haplotype 1-0
 fBA frequency of maternal haplotype 0-1
 fBB frequency of maternal haplotype 0-0
 p1 Maternal allele frequency (allele 1)
 p2 Maternal allele frequency (allele 0)
 nfam1 size of genomic family 1
 nfam2 size of genomic family 2
 error 0 if computations were without error; 1 if EM algorithm did not converge
 iteration number of EM iterations
 theta paternal recombination rate
 r2 r^2 of maternal LD
 logL value of log likelihood function
 unimodal 1 if likelihood is unimodal; 0 if likelihood is bimodal
 critical 0 if parameter estimates are unique; 1 if parameter estimates at both solutions are valid,
 then decision process follows in post-processing function "editraw"

Afterwards, solutions are compared and processed with function `editraw`, yielding the final estimates for each valid pair of SNPs.

References

- Hampel, A., Teuscher, F., Gomez-Raya, L., Doschoris, M. & Wittenburg, D. (2018) Estimation of recombination rate and maternal linkage disequilibrium in half-sibs. *Frontiers in Genetics* 9:186. <https://doi.org/10.3389/fgene.2018.00186>
- Gomez-Raya, L. (2012) Maximum likelihood estimation of linkage disequilibrium in half-sib families. *Genetics* 191:195-213.

Examples

```

### test data
data(targetregion)
### make list for paternal half-sib families
hap <- makehaplist(daughterSire, hapSire)
### parameter estimates on a chromosome
res <- hsrecombi(hap, genotype.chr, map.chr$SNP)
### post-processing to achieve final and valid set of estimates
final <- editraw(res, map.chr)

```


LDHScpp

*Expectation Maximisation (EM) algorithm***Description**

Expectation Maximisation (EM) algorithm

Usage

LDHScpp(XGF1, XGF2, fAA, fAB, fBA, theta, display, threshold)

Arguments

| | |
|-----------|---|
| XGF1 | numeric matrix of progeny genotypes in genomic family 1 |
| XGF2 | numeric matrix of progeny genotypes in genomic family 2 |
| fAA | frequency of maternal haplotype 1-1 |
| fAB | frequency of maternal haplotype 1-0 |
| fBA | frequency of maternal haplotype 0-1 |
| theta | paternal recombination rate |
| display | logical for displaying additional information |
| threshold | convergence criterion |

Value

list of parameter estimates

D maternal LD

fAA frequency of maternal haplotype 1-1

fAB frequency of maternal haplotype 1-0

fBA frequency of maternal haplotype 0-1

fBB frequency of maternal haplotype 0-0

p1 Maternal allele frequency (allele 1)

p2 Maternal allele frequency (allele 0)

nfam1 size of genomic family 1

nfam2 size of genomic family 2

error 0 if computations were without error; 1 if EM algorithm did not converge

iteration number of EM iterations

theta paternal recombination rate

r2 r^2 of maternal LD

logL value of log likelihood function

| | |
|-----------|--|
| loglikfun | <i>Calculate log-likelihood function</i> |
|-----------|--|

Description

Calculate log-likelihood function

Arguments

| | |
|--------|---|
| counts | integer vector of observed 2-locus genotype |
| fAA | frequency of maternal haplotype 1-1 |
| fAB | frequency of maternal haplotype 1-0 |
| fBA | frequency of maternal haplotype 0-1 |
| fBB | frequency of maternal haplotype 0-0 |
| theta | paternal recombination rate |

Value

lik value of log likelihood at parameter estimates

| | |
|---------|---|
| makehap | <i>Make list of imputed sire haplotypes</i> |
|---------|---|

Description

List of sire haplotypes is set up in the format required for hsrecombi. Sire haplotypes are imputed from progeny genotypes using R package hspbase.

Usage

```
makehap(sireID, daughterSire, genotype.chr, nmin = 30)
```

Arguments

| | |
|--------------|--|
| sireID | vector (LEN N) of IDs of all sires |
| daughterSire | vector (LEN n) of sire ID for each progeny |
| genotype.chr | matrix (DIM n x p) of progeny genotypes on a single chromosome with p SNPs |
| nmin | scalar, minimum required number of progeny for proper imputation, default 30 |

Value

list (LEN 2) of lists. For each sire:

famID list (LEN N) of vectors (LEN n.progeny) of progeny indices relating to lines in genotype matrix

sireHap list (LEN N) of matrices (DIM 2 x p) of sire haplotypes (0, 1) on investigated chromosome

References

Ferdosi, M., Kinghorn, B., van der Werf, J., Lee, S. & Gondro, C. (2014) hsphase: an R package for pedigree reconstruction, detection of recombination events, phasing and imputation of half-sib family groups BMC Bioinformatics 15:172. <https://CRAN.R-project.org/package=hsphase>

Examples

```
data(targetregion)
hap <- makehap(unique(daughterSire), daughterSire, genotype.chr)
```

| | |
|-------------|-------------------------------------|
| makehaplist | <i>Make list of sire haplotypes</i> |
|-------------|-------------------------------------|

Description

List of sire haplotypes is set up in the format required for hsrecombi. Haplotypes (obtained by external software) are provided.

Usage

```
makehaplist(daughterSire, hapSire, nmin = 1)
```

Arguments

| | |
|--------------|--|
| daughterSire | vector (LEN n) of sire ID for each progeny |
| hapSire | matrix (DIM 2N x p + 1) of sire haplotype at p SNPs; 2 lines per sire, 1. columns contains sire ID |
| nmin | scalar, minimum number of progeny required, default 1 |

Value

hap list (LEN 2) of lists. For each sire:

famID list (LEN N) of vectors (LEN n.progeny) of progeny indices relating to lines in genotype matrix

sireHap list (LEN N) of matrices (DIM 2 x p) of sire haplotypes (0, 1) on investigated chromosome

Examples

```
data(targetregion)
hap <- makehaplist(daughterSire, hapSire)
```

 makehappm

Make list of imputed haplotypes and recombination rate

Description

List of sire haplotypes is set up in the format required for hsrecombi. Sire haplotypes are imputed from progeny genotypes using R package hsphase. Furthermore, recombination rate estimates between adjacent SNPs from hsphase are reported.

Usage

```
makehappm(sireID, daughterSire, genotype.chr, nmin = 30)
```

Arguments

| | |
|--------------|--|
| sireID | vector (LEN N) of IDs of all sires |
| daughterSire | vector (LEN n) of sire ID for each progeny |
| genotype.chr | matrix (DIM n x p) of progeny genotypes on a single chromosome with p SNPs |
| nmin | scalar, minimum number of progeny required, default 1 |

Value

hap list (LEN 2) of lists. For each sire:

famID list (LEN N) of vectors (LEN n.progeny) of progeny indices relating to lines in genotype matrix

sireHap list (LEN N) of matrices (DIM 2 x p) of sire haplotypes (0, 1) on investigated chromosome

probRec vector (LEN p - 1) of proportion of recombinant progeny over all families between adjacent SNPs

numberRec list (LEN N) of vectors (LEN n.progeny) of number of recombination events per animal

References

Ferdosi, M., Kinghorn, B., van der Werf, J., Lee, S. & Gondro, C. (2014) hsphase: an R package for pedigree reconstruction, detection of recombination events, phasing and imputation of half-sib family groups BMC Bioinformatics 15:172. <https://CRAN.R-project.org/package=hsphase>

Examples

```
data(targetregion)
hap <- makehappm(unique(daughterSire), daughterSire, genotype.chr)
```

| | |
|---------|-----------------------------------|
| map.chr | <i>targetregion: physical map</i> |
|---------|-----------------------------------|

Description

SNP marker map in target region on chromosome BTA1 according to ARS-UCD1.2

Usage

map.chr

Arguments

| | |
|---------|---|
| map.chr | data frame |
| | SNP SNP index |
| | Chr chromosome of SNP |
| | locus_bp physical position of SNP in bp |
| | locus_Mb physical position of SNP in Mbp |
| | markername official SNP name |

Format

An object of class `data.frame` with 300 rows and 5 columns.

| | |
|------------|--|
| startvalue | <i>Start value for maternal allele and haplotype frequencies</i> |
|------------|--|

Description

Determine default start values for Expectation Maximisation (EM) algorithm that is used to estimate paternal recombination rate and maternal haplotype frequencies

Usage

startvalue(Fam1, Fam2, Dd = 0, prec = 1e-06)

Arguments

| | |
|------|--|
| Fam1 | matrix (DIM n.progeny x 2) of progeny genotypes of genomic family with coupling phase sires (1) at SNP pair |
| Fam2 | matrix (DIM n.progeny x 2) of progeny genotypes of genomic family with repulsion phase sires (2) at SNP pair |
| Dd | maternal LD, default 0 |
| prec | minimum accepted start value for fAA, fAB, fBA; default 1e-6 |

Value

list (LEN 8)

fAA.start frequency of maternal haplotype 1-1

fAB.start frequency of maternal haplotype 1-0

fBA.start frequency of maternal haplotype 0-1

p1 estimate of maternal allele frequency (allele 1) when sire is heterozygous at SNP1

p2 estimate of maternal allele frequency (allele 1) when sire is heterozygous at SNP2

L1 lower bound of maternal LD

L2 upper bound for maternal LD

critical 0 if parameter estimates are unique; 1 if parameter estimates at both solutions are valid

Examples

```
n1 <- 100
n2 <- 20
G1 <- matrix(ncol = 2, nrow = n1, sample(c(0:2), replace = TRUE,
  size = 2 * n1))
G2 <- matrix(ncol = 2, nrow = n2, sample(c(0:2), replace = TRUE,
  size = 2 * n2))
startvalue(G1, G2)
```

| | |
|--------------|---|
| targetregion | <i>Description of the targetregion data set</i> |
|--------------|---|

Description

The data set contains sire haplotypes, assignment of progeny to sire, progeny genotypes and physical map information in a target region

The raw data can be downloaded at the source given below. Then, executing the following R code leads to the data provided in targetregion.RData.

hapSire matrix of sire haplotypes of each sire; 2 lines per sire; 1. column contains sireID

daughterSire vector of sire ID for each progeny

genotype.chr matrix of progeny genotypes

map.chr SNP marker map in target region

Source

The data are available from the RADAR repository <https://dx.doi.org/10.22000/280>

Examples

```
## list of haplotypes of sires for each chromosome
load('sire_haplotypes.RData')
## assign progeny to sire
daughterSire <- read.table('assign_to_family.txt')[, 1]
## progeny genotypes
X <- as.matrix(read.table('XFam-ARS.txt'))
## physical and approximated genetic map
map <- read.table('map50K_ARS_reordered.txt', header = T)
## select target region
chr <- 1
window <- 301:600
## map information of target region
map.chr <- map[map$Chr == chr, ][window, 1:5]
## matrix of sire haplotypes in target region
hapSire <- rlist::list.rbind(haps[[chr]])
sireID <- 1:length(unique(daughterSire))
hapSire <- cbind(rep(sireID, each = 2), hapSire[, window])
## matrix of progeny genotypes
genotype.chr <- X[, map.chr$SNP]
```

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