Package: simtrait (via r-universe)

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Title Simulate Complex Traits from Genotypes

Version 1.1.4.9000

Description Simulate complex traits given a SNP genotype matrix and model parameters (the desired heritability, optional environment group effects, number of causal loci, and either the true ancestral allele frequencies used to generate the genotypes or the mean kinship for a real dataset). Emphasis is on avoiding common biases due to the use of estimated allele frequencies. The code selects random loci to be causal, constructs coefficients for these loci and random independent non-genetic effects, and can optionally generate random group effects. Traits can follow three models: random coefficients, fixed effect sizes, and infinitesimal (multivariate normal). GWAS method benchmarking functions are also provided. Described in Yao and Ochoa (2023) [<doi:10.7554/eLife.79238>](https://doi.org/10.7554/eLife.79238).

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Imports PRROC

Suggests popkin, testthat, knitr, rmarkdown, bnpsd, BEDMatrix

VignetteBuilder knitr

URL <https://github.com/OchoaLab/simtrait>

BugReports <https://github.com/OchoaLab/simtrait/issues>

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Contents

allele_freqs *Compute locus allele frequencies*

Description

On a regular matrix, this is essentially a wrapper for [colMeans\(\)](#page-0-0) or [rowMeans\(\)](#page-0-0) depending on loci_on_cols. On a BEDMatrix object, the locus allele frequencies are computed keeping memory usage low.

Usage

```
allele_freqs(
  X,
  loci_on_cols = FALSE,
  fold = FALSE,
  m_{\text{c}}hunk_max = 1000,
  subset_ind = NULL
\mathcal{L}
```
Arguments

cov_trait 3

Value

The vector of allele frequencies, one per locus. Names are set to the locus names, if present.

Examples

```
# Construct toy data
X <- matrix(
    c(0, 1, 2,1, 0, 1,
     1, NA, 2),
    nrow = 3,
    byrow = TRUE
)
# row means
allele_freqs(X)
c(1/2, 1/3, 3/4)
# row means, in minor allele frequencies
allele_freqs(X, fold = TRUE)
c(1/2, 1/3, 1/4)
# col means
allele_freqs(X, loci_on_cols = TRUE)
c(1/3, 1/4, 5/6)
```


The model covariance matrix of the trait

Description

This function returns the expected covariance matrix of trait vectors simulated via [sim_trait\(\)](#page-13-1) and [sim_trait_mvn\(\)](#page-16-1). Below there are n individuals.

Usage

```
cov_trait(kinship, herit, sigma_sq = 1, labs = NULL, labs_sigma_sq = NULL)
```
Arguments

Value

The n-by-n trait covariance matrix, which under no environment effects equals sigma_sq \star (herit * 2 * kinship + sigma_sq_residual * I), where I is the n-by-n identity matrix and sigma_sq_residual = 1 - herit. If there are labels, covariance will include the specified block diagonal effects and sigma_sq_residual = 1 - herit - sum(labs_sigma_sq).

See Also

[sim_trait\(\)](#page-13-1), [sim_trait_mvn\(\)](#page-16-1)

```
# create a dummy kinship matrix
kinship <- matrix(
    data = c(0.6, 0.1, 0.0,
        0.1, 0.6, 0.1,
        0.0, 0.1, 0.6
    ),
    nrow = 3,
    byrow = TRUE
)
# covariance of simulated traits
V \leq -\text{cov\_trait}(kinship = kinship, herit = 0.8)
```
Calculates the vector of per-locus heritability values, with each causal locus i calculated as $h_1 \hat{i}^2 =$ $2 \times p_i \times (1 - p_i) \times \beta$ beta_i^2 / sigma_sq, where p_i is the ancestral allele frequency, beta_i is the causal coefficient, and sigma_sq is the trait variance scale. These are all assumed to be true parameters (not estimated). These per-locus heritabilities equal per-locus effect sizes divided by sigma_sq.

Usage

```
herit_loci(p_anc, causal_coeffs, causal_indexes = NULL, sigma_sq = 1)
```
Arguments

Value

The vector of per-locus heritability contributions. The sum of these values gives the overall heritability. This value can be greater than one (or wrong, more generally) if sigma_sq is misspecified.

See Also

[sim_trait\(\)](#page-13-1) generates random traits by drawing causal loci and their coefficients to fit a desired heritability. $cov_trait()$ calculates the covariance structure of the random traits.

```
# create toy random data
m_loci <- 10
# ancestral allele frequencies
p_anc <- runif( m_loci )
# causal loci
causal_coeffs <- rnorm( m_loci ) / m_loci
# resulting heritability contributions vector
```

```
herit_loci( p_anc, causal_coeffs )
```
pval_aucpr *Area under the precision-recall curve*

Description

Calculates the Precision-Recall (PR) Area Under the Curve (AUC) given a vector of p-values and the true classes (causal (alternative) vs non-causal (null)). This is a wrapper around [PRROC::pr.curve\(\)](#page-0-0), which actually calculates the AUC (see that for details).

Usage

pval_aucpr(pvals, causal_indexes, curve = FALSE)

Arguments

Value

If curve = FALSE, returns the PR AUC scalar value. If curve = TRUE, returns the PRROC object as returned by [PRROC::pr.curve\(\)](#page-0-0), which can be plotted directly, and which contains the AUC under the named value auc.integral.

However, if the input pvals is NULL (taken for case of singular association test, which is rare but may happen), then the returned value is NA.

See Also

PRROC:: pr. curve(), which is used internally by this function.

[pval_power_calib\(\)](#page-7-1) for calibrated power estimates.

pval_infl 7 7

Examples

```
# simulate truly null p-values, which should be uniform
pvals <- runif(10)
# for toy example, take the first two p-values to be truly causal
causal indexes \leq -1:2# calculate desired measure
pval_aucpr( pvals, causal_indexes )
```
pval_infl *Calculate inflation factor from p-values*

Description

The inflation factor is defined as the median association test statistic divided by the expected median under the null hypothesis, which is typically assumed to have a chi-squared distribution. This function takes a p-value distribution and maps its median back to the chi-squared value (using the quantile function) in order to compute the inflation factor in the chi-squared scale. The full p-value distribution (a mix of null and alternative cases) is used to calculate the desired median value (the true causal_loci is not needed, unlike [pval_srmsd\(\)](#page-8-1)).

Usage

pval_infl(pvals, df = 1)

Arguments

Value

The inflation factor

See Also

[pval_srmsd\(\)](#page-8-1), a more robust measure of null p-value accuracy, but which requires knowing the true causal loci.

[pval_type_1_err\(\)](#page-9-1) for classical type I error rate estimates.

```
# simulate truly null p-values, which should be uniform
pvals <- runif(10)
# calculate desired measure
pval_infl( pvals )
```
Given a significance level alpha and p-values with known causal status, this function estimates the calibrated power. First it estimates the p-value threshold at which the desired type I error of alpha is achieved, then it uses this p-value threshold (not alpha) to estimate statistical power. Note that these simple empirical estimates are likely to be inaccurate unless the number of p-values is much larger than 1/alpha.

Usage

pval_power_calib(pvals, causal_indexes, alpha = 0.05)

Arguments

Value

The calibrated power estimates at each alpha

See Also

[pval_aucpr\(\)](#page-5-1), a robust proxy for calibrated power that integrates across significance thresholds.

```
# simulate truly null p-values, which should be uniform
pvals <- runif(10)
# for toy example, take the first two p-values to be truly causal
causal_indexes <- 1:2
# estimate desired measure
pval_power_calib( pvals, causal_indexes )
```
pval_srmsd *Signed RMSD measure of null p-value uniformity*

Description

Quantifies null p-value uniformity by computing the RMSD (root mean square deviation) between the sorted observed null (truly non-causal) p-values and their expected quantiles under a uniform distribution. Meant as a more robust alternative to the "inflation factor" common in the GWAS literature, which compares median values only and uses all p-values (not just null p-values). Our signed RMSD, to correspond with the inflation factor, includes a sign that depends on the median null p-value: positive if this median is <= 0.5 (corresponds with test statistic inflation), negative otherwise (test statistic deflation). Zero corresponds to uniform null p-values, which arises in expectation only if test statistics have their assumed null distribution (there is no misspecification, including inflation).

Usage

pval_srmsd(pvals, causal_indexes, detailed = FALSE)

Arguments

Value

If detailed is FALSE, returns the signed RMSD between the observed p-value order statistics and their expectation under true uniformity. If detailed is TRUE, returns data useful for plots, a named list containing:

- srmsd: The signed RMSD between the observed p-value order statistics and their expectation under true uniformity.
- pvals_null: Sorted null p-values (observed order statistics). If any input null p-values were NA, these have been removed here (removed by $sort()$).
- pvals_unif: Expected order statistics assuming uniform distribution, same length as pvals_null.

If the input pvals is NULL (taken for case of singular association test, which is rare but may happen), then the returned value is NA if detailed was FALSE, or otherwise the list contains NA, NULL and NULL for the above three items.

See Also

[rmsd\(\)](#page-10-1) for the generic root-mean-square deviation function.

[pval_infl\(\)](#page-6-1) for the more traditional inflation factor, which focuses on the median of the full distribution (combination of causal and null cases).

[pval_type_1_err\(\)](#page-9-1) for classical type I error rate estimates.

Examples

```
# simulate truly null p-values, which should be uniform
pvals <- runif(10)
# for toy example, take the first p-value to be truly causal (will be ignored below)
causal_indexes <- 1
# calculate desired measure
pval_srmsd( pvals, causal_indexes )
```
pval_type_1_err *Estimate type I error rate*

Description

Given a significance level and p-values with known causal status, this function estimates the type I error rate, defined as the proportion of null p-values that are below or equal to the threshold. Note that these simple empirical estimates are likely to be zero unless the number of p-values is much larger than 1/alpha.

Usage

```
pval_type_1_err(pvals, causal_indexes, alpha = 0.05)
```
Arguments

Value

The type I error rate estimates at each alpha

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See Also

[pval_srmsd\(\)](#page-8-1) to directly quantify null p-value uniformity, a more robust alternative to type I error rate.

[pval_infl\(\)](#page-6-1) for the more traditional inflation factor, which focuses on the median of the full distribution (combination of causal and null cases).

Examples

```
# simulate truly null p-values, which should be uniform
pvals <- runif(10)
# for toy example, take the first p-value to be truly causal (will be ignored below)
causal_indexes <- 1
# estimate desired measure
pval_type_1_err( pvals, causal_indexes )
```
rmsd *Root mean square deviation*

Description

Calculates the euclidean distance between two vectors x and y divided by the square root of the lengths of the vectors. NA values are ignored by default when calculating the mean squares (so the denominator is the number of non-NA differences).

Usage

 $rmsd(x, y, na.rm = TRUE)$

Arguments

Value

the square root of the mean square difference between x and y , after removing NA comparisons (cases where either is NA).

```
x \leftarrow \text{norm}(10)y \le - rnorm(10)
rmsd( x, y )
```
This package enables simulation of complex (polygenic and continuous) traits from a simulated or real genotype matrix. The focus is on constructing the mean and covariance structure of the data to yield the desired heritability. The main function is $sim_train()$, which returns the simulated trait and the vector of causal loci (randomly selected) and their coefficients. The causal coefficients are constructed under two models: *random coefficients* (RC) and *fixed effect sizes* (FES). The function [cov_trait\(\)](#page-2-1) computes the expected covariance matrix of the trait given the model parameters (namely the desired heritability and the true kinship matrix). Infinitesimal traits (without causal loci) can also be simulated using [sim_trait_mvn\(\)](#page-16-1).

Details

Package also provides some functions for evaluating genetic association approaches. [pval_srmsd\(\)](#page-8-1) and [pval_infl\(\)](#page-6-1) quantify null p-value accuracy, while [pval_aucpr\(\)](#page-5-1) quantifies predictive power.

The recommended inputs are simulated genotypes with known ancestral allele frequencies. The bnpsd package simulates genotypes for admixed individuals, resulting in a complex population structure.

For real data it is necessary to estimate the kinship matrix. [popkin::popkin\(\)](#page-0-0)' provides highaccuracy kinship estimates.

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See Also

Useful links:

- <https://github.com/OchoaLab/simtrait>
- Report bugs at <https://github.com/OchoaLab/simtrait/issues>

```
# construct a dummy genotype matrix
X \leftarrow matrix(
    data = c(0, 1, 2,
        1, 2, 1,
        0, 0, 1
    ),
    nrow = 3,
    byrow = TRUE
\lambda# made up ancestral allele frequency vector for example
```
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```
p_{anc} < -c(0.5, 0.6, 0.2)# desired heritability
herit <-0.8# create a dummy kinship matrix for example
# make sure it is positive definite!
kinship <- matrix(
    data = c(0.6, 0.1, 0.0,
        0.1, 0.5, 0.0,
        0.0, 0.0, 0.5
    ),
   nrow = 3)
# create simulated trait and associated data
# default is *random coefficients* (RC) model
obj \le sim_trait(X = X, m_causal = 2, herit = herit, p_anc = p_anc)
# trait vector
obj$trait
# randomly-picked causal locus indeces
obj$causal_indexes
# regression coefficient vector
obj$causal_coeffs
# *fixed effect sizes* (FES) model
obj \le sim_trait(X = X, m_causal = 2, herit = herit, p_anc = p_anc, fes = TRUE)
# either model, can apply to real data by replacing `p_anc` with `kinship`
obj \le sim_trait(X = X, m_causal = 2, herit = herit, kinship = kinship)
# covariance of simulated traits
V \leftarrow cov_{\text{train}}(kinship = kinship, herit = herit)# draw simulated traits (matrix of replicates) from infinitesimal model
traits \le sim_trait_mvn( rep = 10, kinship = kinship, herit = herit )
traits
# Metrics for genetic association approaches
# simulate truly null p-values, which should be uniform
pvals <- runif(10)
# for toy example, take these p-value to be truly causal
causal_indexes <- c(1, 5, 7)
# calculate desired measures
# this one quantifies p-value uniformity
pval_srmsd( pvals, causal_indexes )
# related, calculates inflation factors
pval_infl( pvals )
# this one quantifies predictive power
pval_aucpr( pvals, causal_indexes )
```


Simulate a complex trait given a SNP genotype matrix and model parameters, which are minimally: the number of causal loci, the heritability, and either the true ancestral allele frequencies used to generate the genotypes or the mean kinship of all individuals. An optional minimum marginal allele frequency for the causal loci can be set. The output traits have by default a zero mean and unit variance (for outbred individuals), but those parameters can be modified. The code selects random loci to be causal, constructs coefficients for these loci (scaled appropriately) and random Normal independent non-genetic effects and random environment group effects if specified. There are two models for constructing causal coefficients: random coefficients (RC; default) and fixed effect sizes (FES; i.e., coefficients roughly inversely proportional to allele frequency; use fes = TRUE). Suppose there are m loci and n individuals.

Usage

```
sim_trait(
  X,
  m_causal,
  herit,
  p_anc = NULL,
  kinship = NULL,
  mu = 0,
  signa_sq = 1,
  \text{labels} = \text{NULL},
  labs_sigma_sq = NULL,
  maf_cut = NA,
  loci_on_cols = FALSE,
  m_{\text{L}}chunk\text{max} = 1000,
  fes = FALSE
)
```
Arguments

Details

To center and scale the trait and locus coefficients vector correctly to the desired parameters (mean, variance, heritability), the parametric ancestral allele frequencies (p_anc) must be known. This is necessary since in the heritability model the genotypes are random variables (with means given by p_anc and a covariance structure given by p_anc and the kinship matrix), so these genotype distribution parameters are required. If p_anc are known (true for simulated genotypes), then the trait will have the specified mean and covariance matrix in agreement with $cov_trait()$. To simulate traits using real genotypes, where p_anc is unknown, a compromise that works well in practice is possible if the mean kinship is known (see package vignette). We recommend estimating the mean kinship using the popkin package!

Value

A named list containing:

- • trait: length-n vector of the simulated trait
- causal_indexes: length-m_causal vector of causal locus indexes
- causal_coeffs: length-m_causal vector of coefficients at the causal loci
- group_effects: length-n vector of simulated environment group effects, or 0 (scalar) if not simulated

However, if herit = 0 then causal_indexes and causal_coeffs will have zero length regardless of m_causal.

See Also

```
cov_trait(), sim_trait_mvn()
```

```
# construct a dummy genotype matrix
X \leftarrow matrix(data = c(0, 1, 2,
         1, 2, 1,
         0, 0, 1
    ),
    nrow = 3,
    byrow = TRUE
\lambda# made up ancestral allele frequency vector for example
p_anc <- c(0.5, 0.6, 0.2)
# made up mean kinship
kinship <-0.2# desired heritability
herit <-0.8# create simulated trait and associated data
# default is *random coefficients* (RC) model
obj \le sim_trait(X = X, m_causal = 2, herit = herit, p_anc = p_anc)
# trait vector
obj$trait
# randomly-picked causal locus indexes
obj$causal_indexes
# regression coefficients vector
obj$causal_coeffs
# *fixed effect sizes* (FES) model
obj <- sim_trait(X = X, m_causal = 2, herit = herit, p_anc = p_anc, fes = TRUE)
# *fixed effect sizes* (FES) model<br>obj <- sim_trait(X = X, m_causal = 2, herit = herit, p_anc = p_anc, fes = <sup>.</sup><br># either model, can apply to real data by replacing `p_anc` with `kinship`
obj \le sim_trait(X = X, m_causal = 2, herit = herit, kinship = kinship)
```
Simulate matrix of trait replicates given a kinship matrix and model parameters (the desired heritability, group effects, total variance scale, and mean). Although these traits have the covariance structure of genetic traits, and have heritabilities that can be estimated, they do not have causal loci (an association test against any locus should fail). Below n is the number of individuals.

Usage

```
sim_trait_mvn(
  rep,
  kinship,
  herit,
  mu = 0,
  signa_sq = 1,
  \text{labels} = \text{NULL},
  labs_sigma_sq = NULL,
  tol = 1e-06)
```
Arguments

tol Tolerance factor for an internal test of positive semi-definiteness of the trait covariance matrix. Procedure fails if any eigenvalues are smaller than -tol times the absolute value of the largest eigenvalue. Increase this value only if you are getting errors but you're sure your covariance matrix (the output of [cov_trait\(\)](#page-2-1)) is positive semi-definite.

Value

A rep-by-n matrix containing the simulated traits along the rows, individuals along the columns.

See Also

```
cov_trait(), sim_trait()
```

```
# create a dummy kinship matrix
# make sure it is positive definite!
kinship <- matrix(
    data = c(0.6, 0.1, 0.0,
       0.1, 0.5, 0.0,
       0.0, 0.0, 0.5
   ),
   nrow = 3)
# draw simulated traits (matrix)
traits \le sim_trait_mvn( rep = 10, kinship = kinship, herit = 0.8 )
traits
```
Index

allele_freqs, [2](#page-1-0) colMeans(), *[2](#page-1-0)* cov_trait, [3](#page-2-0) cov_trait(), *[5](#page-4-0)*, *[12](#page-11-0)*, *[15,](#page-14-0) [16](#page-15-0)*, *[18](#page-17-0)* herit_loci, [5](#page-4-0) mean(), *[11](#page-10-0)* popkin::popkin(), *[12](#page-11-0)* PRROC::pr.curve(), *[6](#page-5-0)* pval_aucpr, [6](#page-5-0) pval_aucpr(), *[8](#page-7-0)*, *[12](#page-11-0)* pval_infl, [7](#page-6-0) pval_infl(), *[10](#page-9-0)[–12](#page-11-0)* pval_power_calib, [8](#page-7-0) pval_power_calib(), *[6](#page-5-0)* pval_srmsd, [9](#page-8-0) pval_srmsd(), *[7](#page-6-0)*, *[11,](#page-10-0) [12](#page-11-0)* pval_type_1_err, [10](#page-9-0) pval_type_1_err(), *[7](#page-6-0)*, *[10](#page-9-0)* rmsd, [11](#page-10-0) rmsd(), *[10](#page-9-0)* rowMeans(), *[2](#page-1-0)* sim_trait, [14](#page-13-0) sim_trait(), *[3](#page-2-0)[–5](#page-4-0)*, *[12](#page-11-0)*, *[18](#page-17-0)* sim_trait_mvn, [17](#page-16-0) sim_trait_mvn(), *[3,](#page-2-0) [4](#page-3-0)*, *[12](#page-11-0)*, *[16](#page-15-0)* simtrait, [12](#page-11-0) simtrait-package *(*simtrait*)*, [12](#page-11-0) sort(), *[9](#page-8-0)*