Package 'lymphclon'

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Title Estimating the Clonality Score, a Measure of Conincidences with
Replicated Abundances, with Applications in the Study of Lymphocytes

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Depends R (>= 2.15.0), VGAM, MASS, expm, Matrix, corpcor

Imports VGAM, MASS, expm, Matrix, corpcor

Suggests VGAM, MASS, expm, Matrix, corpcor

Description We provide a clonality score estimator that takes full advantage of the multi-biological-
replicate structure of modern sequencing experiments; it specifically takes into account the real-
ity that, typically, the clonal coverage is well below 0.1%.

License LGPL-2

URL http://www.r-project.org, http://www.another.url

BugReports http://pkgname.bugtracker.url

R topics documented:

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lymphclon-package   *Estimates the clonality score from replicate of abundances data*

Description

There are an enormous number of clones(species) distributed in a highly unequal distribution. The experimenters collect a small number of very coarse samplings, and perform noisy measurements on the samplings, leading to abundance estimations for the indiviudal biological replicates. The goal of this package is to estimate the probability that two random cells belong to the same clone. Clonality estimation arises as a naturally interesting question when trying to understand the diversity of B cell populations, T cell populations, microbial populations, cancer cell subclones, and artificial biologicl libraries, and also broader ecological settings.

This package provides two primary functions; one computes the clonality score estimate (probability that two random individuals belong to the same clone), given replicate of abundances; it also infers the underlying clonal distribution, which may be of interest in diagnostic and scientific settings.

The other function generates reasonable simulation data, for evaluation purposes. The default behavior of this function generates a very large number of classes, which is suitable for B and T cell settings. It can be easily repurposed for other applications. The simulation assumes random sampling, amplifying, and sequencing of individual cells; this is implemented by introducing sparse sampling of individual cells, followed by introduction of log-normal error, and finally unbiased "rounding" by use of a poisson distribution.

Details

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Author(s)

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References

~~ Literature or other references for background information ~~

See Also

<vegan>

Examples

```
my.data <- simulate.clonality.data(n=2e3)
# n ~ 2e7 is more appropriate for a realistic B cell repertoire
```

```
my.lymphclon.results <- infer.clonality(my.data$read.count.matrix)
# a consistently improved estimate of clonality (the squared 2-norm of the underlying multinomial probabil
```

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infer.clonality	*infer.clonality (part of lymphclon package)*

Description

Clonality score, a useful metric used in immunology, refers to the probability that two random lymphocyte receptor chain reads drawn with replacement (makes no difference in the immunology context) from an individual corresponded to the same clone, within some given repertoire of either B cells or T cells. This package implements ane estimator which understands the multi-replicate-with-PCR structure of thes sequencing experiments.

Usage

```
infer.clonality(
  read.count.matrix,
  variance.method = 'fpc.1',
  estimate.abundances = F,
  num.iterations = 1,
  internal.parameters = list())
```

Arguments

read.count.matrix

A matrix of read frequences, where each row corresponds to a distinct clone, and each column corresponds to a particular biological (rather than technical) replicate. All biological replicates should be drawn from the same person. Reads from technical replicates of the same underlying templates should be merged into a single column.

variance.method

The method is a code defaulting to "loo.2". usr.1: argument use.squared.err.est specifies 1st order variances mle.1: use maximum likelihood estimate of 1st order variances loo.1: use leave-one-out estimate of 1st order variances corpcor.1: use shrinkage-based estimate of 1st order variances (see package corpcor)

estimate.abundances

A boolean value defaulting to false. If set to true, then the return value will be in the form of a list, and include an additional item named "estiamted.abundances". The estimated abundances are computed as the (conditional) precision weighted average of the read.count.matrix.

num.iterations   An integer specifying the number of iterations in estimation; applicable only if the variance method is set to one of the loo or mle methods. Note that the ue.zr.half setting provides the most consistent improvement against the naive simple clonality score, in terms of MSE reduction.

internal.parameters

A named list of internal parameters used primarily to speed up evaluation of MSE performance across a large number of simulations. The entries are named "replicates", "rep.grahm.matrix", "simple.precision.clonality", and "use.squared.err.est". "replicates" refer to a column normalized (to 1) matrix of read.count.matrix.

"rep.grahm.matrix" refers to t(replicates) "simple.precision.clonality" refers to the unweighted averaging of all n-choose-2 estimators of clonality. "use.squared.err.est" refers to a user-provided set of squared error estimates corresponding to each of the replicates; this parameter is active iff the variance method is set to 'usr.1'.

Value

simple.precision.clonality

This is a base line estimator of the clonality score based on simple modeling. Briefly, for each pairing of reads possible, where the two reads arise from different biological replicates – this pairing is considered as an observation from a single share undelrying bernoulli distribution with parameter equal to the clonality score. This estimator computes maximum likelihood estimate of the underlying clonality score. This estimator can be thought of as a baseline estimate. Unlike the Gini-Simpson-Estimator, this baseline does not suffer from any convexity-based bias.

lymphclon.clonality

This is an estimator is a weighted average of n-choose-2 individually unbiased estimators that arise from comparing the provided n biological replicates pairwise. The weighting is determined by the covariance between these estimators. This has much lower variance than the simple.precision.clonality. This is the value returned by the ue.zr.half regularization setting

estimated.abundances

If the estimate.abundances parameter was set to True, then return a probability vector indicating the fractional contributions of each individual clone to the overall multinomial repertoire.

esimated.squared.errs

A numerical measure of the estimated squared 2-norm error of each given replicate.

estimated.precisions

A numerical measure of the estimated precisions of each given replicate.

variance.method

The method code provided in the input, determining the method by which the replicate-level covariances are computed.

fpc.iter.estimates

Specifies the intermediate clonality score estimates across iterations, when num.iterations is greater than 1. Note that, in empirical simulations, it is best to use a num.iterations value of 1. Additional iterations occasionally, but usually do not help in improving the mean squared error of the clonality measures.

regularized.estimates

Under a variety of regularization settings on the n-choose-2 by n-choose-2 covariance matrix for the n-choose-2 individually unbiased clonality estimators, return the respectively weighted clonality measures for each regularization setting.

Examples

```
my.data <- simulate.clonality.data(n=2e3)
# n ~ 2e7 is more appropriate for a realistic B cell repertoire
my.lymphclon.results <- infer.clonality(my.data$read.count.matrix)
# a consistently improved estimate of clonality (the squared 2-norm of the underlying multinomial probabil:
my.lymphclon.results$lymphclon.clonality
```

```
simulate.clonality.data
```
simulate.clonality.data (part of lymphclon package)

Description

This function generates simulated data, for evaluation purposes. We start with an underlying multinomial population with entries proportional to rank^-power distribution, where power is fixed. Next, we draw multinomially from this distribution, a fixed number of cells, to generate each desired replicate. Then, this distribution is subject to log-normal error, and subsequently scaled up to the expected number of reads. To round into integers, the expected number of reads for each clone is finally pushed through a poisson process to generate integer read counts. The poisson "rounding" process is why the resulting read counts are not exactly as specified.

Usage

```
simulate.clonality.data(
  n = 2e+07,
  num.cells.taken.vector = c(2000, 5000, 10000, 20000, 50000, 50000),
  read.count.per.replicate.vector = rep(20000, length(num.cells.taken.vector)),
  clonal.distribution.power = -sqrt(2))
```

Arguments

n
: The true number of distinct clones in the underlying assemblage

num.cells.taken.vector
: A vector specifying the number of cells taken in each independent biological replicate

read.count.per.replicate.vector
: A vector of the same length as num.cells.taken.vector, specifying the number of reads generated from each biological replicate, of the same corresponding indices

clonal.distribution.power
: The true underlying clonal multinomial distribution is proportional to $(1:n)^-$clonal.distribution.power

Value

read.count.matrix
: This is a matrix of simulated counts, with rows corresponding to clones (classes, or species), and columns corresponding to biological replicates

true.clone.prob
: This is the underlying simulated assemblage multinomial distribution used to generate read.count.matrix

true.clonality
: This is the true clonality score of the underlying simulated assemblage

Examples

```
my.data <- simulate.clonality.data(n=2e3)
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