Package ‘stochprofML’

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Title Stochastic Profiling using Maximum Likelihood Estimation

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Imports MASS, numDeriv

Description New Version of the R package originally accompanying the paper
``Parameterizing cell-to-cell regulatory heterogeneities via stochastic transcriptional profiles``
by Sameer S Bajikar, Christiane Fuchs, Andreas Roller, Fabian J Theis and Kevin A Janes
(PNAS 2014, 111(5), E626-635 <doi:10.1073/pnas.1311647111>). In this paper, we measure expression profiles
from small heterogeneous populations of cells, where each cell is assumed to be from a mixture of
lognormal distributions. We perform maximum likelihood estimation in order to infer the mixture ratio and
the parameters of these lognormal distributions from the cumulated expression measurements.
The main difference of this new package version to the previous one is that it is now possible to use
different n's, i.e. a dataset where each tissue sample originates from a different number of cells.
We used this on pheno-seq data, see: Tirier, S.M., Park, J., Preussner, F. et al. Pheno-seq -
linking visual
features and gene expression in 3D cell culture systems. Sci Rep 9, 12367 (2019)

License GPL (>= 2)

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stochprofML-package  Stochastic Profiling using Maximum Likelihood Estimation

Description

This package accompanies the paper "Parameterizing cell-to-cell regulatory heterogeneities via stochastic transcriptional profiles" by Sameer S Bajikar, Christiane Fuchs, Andreas Roller, Fabian J Theis and Kevin A Janes (PNAS 2014, 111(5), E626-635). In that work, we measure expression profiles from small heterogeneous populations of cells. Each cell is assumed to be from a mixture of lognormal and exponential distributions (see details). We perform maximum likelihood estimation in order to infer the mixture ratio and the parameters of the lognormal/exponential distributions from the cumulated expression measurements.
There are three stochastic profiling models: The lognormal-lognormal (LN-LN) model assumes that each cell is from a mixture of one or more lognormal distributions with different log-means but identical log-standard deviations. In the relaxed lognormal-lognormal (rLN-LN) model, the log-standard deviations are not necessarily identical. The exponential-lognormal (EXP-LN) model considers the mixture of zero, one or more lognormal distributions and one exponential distribution.

The user can immediately start with data generation and model estimation using the two functions `stochasticProfilingData` and `stochasticProfilingML`, respectively. These functions prompt the user to input the settings/data. Typical analyses are then performed without the user having to delve into the structure of this package.

When not using one of the above two functions, parameters can be estimated calling `stochprof.loop`, which again utilizes three other functions: `stochprof.search.LNLN`, `stochprof.search.rLN LN`/`stochprof.search.EXP LN` in order to calculate and locally optimize the likelihood function; `stochprof.results.LNLN`, `stochprof.results.rLN LN`/`stochprof.results.EXP LN` for evaluating these results; and `calculate.ci.LNLN`, `calculate.ci.rLN LN`/`calculate.ci.EXP LN` for calculating confidence intervals.

Two essential functions are `r.sum.of.mixtures.LNLN`/`r.sum.of.mixtures.rLN LN`/`r.sum.of.mixtures.EXP LN` and `d.sum.of.mixtures.LNLN`/`d.sum.of.mixtures.rLN LN`/`d.sum.of.mixtures.EXP LN` for the density and random number generation of the distribution assumed for all measurements in the stochastic profiling model.

Version 2.0 shows one significant extension to previous versions: The number of cells n in the input data does no longer need to be the same over all samples.

The package provides four datasets: `sod2`, containing real measurements for one gene, and `toycluster.LNLN`/`toycluster.rLN LN`/`toycluster.EXP LN`, containing artificial data for 12 genes generated with the three stochastic profiling models.

Examples for typical analyses are given below.

**Author(s)**

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**References**


Examples

```r
## Not run:
# Generate synthetic data. The user is prompted to input all settings.
stochasticProfilingData()

# Estimate a stochastic profiling model. The user is prompted to input the data
# and other parameters.
stochasticProfilingML()

# Generate a synthetic dataset (without measurement error) for one gene
# and estimate the parameters from this data.
generate.toydata()

# Estimate the model parameters for the SOD2 dataset.
analyze.sod2()

# Estimate the model parameters for the 12-gene toycluster.
analyze.toycluster()

## End(Not run)
```

---

**analyze.sod2**

**Analysis of SOD2 data in stochastic profiling model**

**Description**

Estimation of the model parameters for the SOD2 dataset provided in this package.

**Usage**

```r
analyze.sod2(model = "LN-LN", TY = 2, use.constraints = F)
```

**Arguments**

- `model`  
  model for which one wishes to estimate the parameters: "LN-LN", "rLN-LN" or "EXP-LN"

- `TY`  
  number of types of cells that is assumed in the stochastic model

- `use.constraints`  
  if TRUE, constraints on the individual population densities are applied; see `penalty.constraint.LNLN`, `penalty.constraint.rLNLN` and `penalty.constraint.EXPLN` for details.
Details

The sod2 dataset contains real 10-cell samplings from the detoxifying enzyme, SOD2. This function estimates the parameters of the stochastic profiling models for this data. At the end, it graphically represents a histogram of the SOD2 data together with the estimated probability density function.

Value

A list as returned by stochprof.loop, i.e. the following components:

- mle: maximum likelihood estimate
- neg-loglikeli: value of the negative log-likelihood function at maximum likelihood estimate
- ci: approximate marginal maximum likelihood confidence intervals for the maximum likelihood estimate
- pargrid: matrix containing parameter combinations and according values of the target function
- bic: Bayesian information criterion value
- adj.bic: adjusted Bayesian information criterion value which takes into account the numbers of parameters that were estimated during the preanalysis of a gene cluster (not applicable here, hence NULL)
- pen: penalization for densities not fulfilling required constraints. If use.constraints is FALSE, this has no practical meaning. If use.constraints is TRUE, this value is included in loglikeli.

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References


Description

Estimation of the model parameters for the 12-gene toyclusters provided in this package. This is done in three steps: an optional preanalysis of the single genes, an analysis of three 4-gene subclusters, and finally the analysis of the entire 12-gene cluster.

Usage

```r
analyze.toycluster(model = "LN-LN", data.model = "LN-LN", TY = 2,
preanalyze = T, show.plots = T, use.constraints = F)
```

Arguments

- `model`: model for which one wishes to estimate the parameters: "LN-LN", "rLN-LN" or "EXP-LN"
- `data.model`: model which has generated the 12-gene dataset: "LN-LN", "rLN-LN" or "EXP-LN"
- `TY`: number of types of cells that is assumed in the stochastic model
- `preanalyze`: if TRUE, the single-gene preanalysis as described below is carried out
- `show.plots`: if TRUE, interim results are graphically displayed. This requires the user to confirm each new plot.
- `use.constraints`: if TRUE, constraints on the individual population densities are applied; see `penalty.constraint.LNLN`, `penalty.constraint.rLNLN` and `penalty.constraint.EXPLN` for details.

Details

This function carries out estimation of the model parameters for the toycluster.LNLN, toycluster.rLNLN or toycluster.EXPLN dataset. This contains perfectly observed measurements for 12 genes and 16 tissue samples, assuming 10-cell samplings and two different types of cells. The true underlying parameters are given on the help page for the datasets.

The estimation is performed in three steps:

In an optional preanalysis (carried out if preanalyze is TRUE), each gene is considered individually, i.e. for each gene the parameters are estimated (these are p, mu_1, mu_2 and sigma for LN-LN, p, mu_1, mu_2, sigma_1 and sigma_2 for rLN-LN, and p, mu, sigma and lambda for EXP-LN). This gives a rough idea about the location of the parameters at computationally low cost. This might speed up the analysis of the larger clusters. From the confidence intervals of the single-gene estimates, one can construct appropriate parameter ranges for the following step.

In the main step of the estimation procedure, the 12 genes are divided into three groups of size four. This is because the stochastic profiling model for 12 genes involves 48 (LN-LN and EXP-LN) to 49 (rLN-LN) parameters, which is computationally expensive and sometimes unreliable. Simulation
studies showed that datasets comprising four genes are sufficient to estimate the log-means when there is data from 16 experiments available. For each of these 4-gene clusters, 10 (LN-LN and EXP-LN) or 11 (rLN-LN) parameters are estimated. The three groups result from a hierarchical clustering of the entire dataset. The genes numbers are (7,5,2,8), (1,3,4,10) and (9,6,12,11) for the LN-LN model, (12,9,6,11), (4,10,5,3) and (1,7,8,2) for the rLN-LN model and (11,1,10,9), (3,5,8,7) and (4,2,12,6) for the EXP-LN model.

In the final step, the log-means mu are fixed to the maximum likelihood estimates that resulted from the main step. Then there remain only p, sigma and possibly lambda to be estimated. These are inferred now.

Throughout the whole estimation process, interim results are printed into the console and, if show.plots is TRUE, graphically displayed.

Value

The final result for the chosen 12-gene cluster. That is a list as returned by stochprof.loop, i.e. the following components:

- mle maximum likelihood estimate
- neg-loglikeli value of the negative log-likelihood function at maximum likelihood estimate
- ci approximate marginal maximum likelihood confidence intervals for the maximum likelihood estimate
- pargrid matrix containing parameter combinations and according values of the target function
- bic Bayesian information criterion value
- adj.bic adjusted Bayesian information criterion value which takes into account the numbers of parameters that were estimated during the preanalysis of the gene cluster
- pen penalization for densities not fulfilling required constraints. If use.constraints is FALSE, this has no practical meaning. If use.constraints is TRUE, this value is included in loglikeli.

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References


calculate.ci.EXPLN  Maximum likelihood confidence intervals for EXP-LN model

Description
Calculates approximate marginal maximum likelihood confidence intervals with significance level alpha for all parameters in the EXP-LN model.

Usage
```r
calculate.ci.EXPLN(alpha, parameter, prev.result, dataset, n, TY,
                 fix.mu = F, fixed.mu)
```

Arguments
- **alpha**: the significance level
- **parameter**: the maximum likelihood estimate around which the confidence interval is centered; if this value is missing, it is determined from prev.result. This parameter has to be on the original scale, not on the logit-/log-transformed scale as used during the estimation procedure. It has to be TY*(m+1)-dimensional (or m-dimensional, if TY=1), even for fix.mu==T.
- **prev.result**: a list of previous results as returned by stochprof.results. This variable is only used when ‘parameter’ is missing.
- **dataset**: a matrix which contains the cumulated expression data over all cells in a tissue sample. Columns represent different genes, rows represent different tissue samples.
- **n**: number of cells taken from each tissue sample. This can also be a vector stating how many cells are in each sample separately.
- **TY**: the number of types of cells that is assumed in the stochastic model
- **fix.mu**: if TRUE, the log-means of the lognormal distributions are kept fixed in the estimation procedure. Otherwise, they are to be estimated.
- **fixed.mu**: a vector containing the values to which the log-means should be fixed if fix.mu==T. The order of components is as follows:
  (mu_type_1_gene_1, mu_type_1_gene_2, ..., mu_type_2_gene_1, mu_type_2_gene_2, ...).
  The parameter needs to be specified only when fix.mu==T.

Details
The intervals are approximate because the function uses the formula
```
[ theta_i +/- q_(1-alpha/2) * sqrt(H_ii) ],
```
where theta_i is the estimate of the i.th parameter, q_(1-alpha/2) is the 1-alpha/2 quantile of the standard normal distribution, H is the inverse Hessian of the negative log likelihood function evaluated at the maximum likelihood estimate; H_ii is the i.th diagonal element of H. This approximation
implicitly assumes that the log likelihood function is unimodal. The confidence interval is first calculated on the transformed, unrestricted parameter space and then back-transformed to the original one.

Value

Approximate marginal maximum likelihood confidence intervals for all parameter components:
Each row corresponds to one parameter (in the same order as always used in the stochastic profiling model). The first column contains lower bounds, the second column upper bounds.

Author(s)

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References


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**calculate.ci.LNLN**

*Maximum likelihood confidence intervals for LN-LN model*

**Description**

Calculates approximate marginal maximum likelihood confidence intervals with significance level alpha for all parameters in the LN-LN model.

**Usage**

```r
calculate.ci.LNLN(alpha, parameter, prev.result, dataset, n, TY, 
fix.mu = F, fixed.mu)
```

**Arguments**

- `alpha`: the significance level
- `parameter`: the maximum likelihood estimate around which the confidence interval is centered; if this value is missing, it is determined from `prev.result`. This parameter has to be on the original scale, not on the logit-/log-transformed scale as used during the estimation procedure. It has to be `TY*(m+1)`-dimensional, even for `fix.mu==T`. 
prev.result  a list of previous results as returned by stochprof.results. This variable is only used when ’parameter’ is missing.

dataset  a matrix which contains the cumulated expression data over all cells in a tissue sample. Columns represent different genes, rows represent different tissue samples.

n  number of cells taken from each tissue sample. This can also be a vector stating how many cells are in each sample separately.

TY  the number of types of cells that is assumed in the stochastic model

fix.mu  if TRUE, the log-means are kept fixed in the estimation procedure. Otherwise, they are to be estimated.

fixed.mu  a vector containing the values to which the log-means should be fixed if fix.mu==T. The order of components is as follows:

(mu_type_1_gene_1, mu_type_1_gene_2, ..., mu_type_2_gene_1, mu_type_2_gene_2, ...).

The parameter needs to be specified only when fix.mu==T.

Details

The intervals are approximate because the function uses the formula

\[
theta_i \pm \alpha_{(1-\alpha/2)} \times \sqrt{H_{ii}},
\]

where \(\theta_i\) is the estimate of the i.th parameter, \(\alpha_{(1-\alpha/2)}\) is the 1-alpha/2 quantile of the standard normal distribution, \(H\) is the inverse Hessian of the negative log likelihood function evaluated at the maximum likelihood estimate; \(H_{ii}\) is the i.th diagonal element of \(H\). This approximation implicitly assumes that the log likelihood function is unimodal. The confidence interval is first calculated on the transformed, unrestricted parameter space and then back-transformed to the original one.

Value

Approximate marginal maximum likelihood confidence intervals for all parameter components: Each row corresponds to one parameter (in the same order as always used in the stochastic profiling model). The first column contains lower bounds, the second column upper bounds.

Author(s)

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References


"Pheno-seq - linking visual features and gene expression in 3D cell culture systems" by Stephan M. Tirier, Jeongbin Park, Friedrich Preusser, Lisa Amrhein, Zuguang Gu, Simon Steiger, Jan-Philipp Mallm, Teresa Krieger, Marcel Waschow, Björn Eismann, Marta Gut, Ivo G. Gut, Karsten Rippe,
The R function `calculate.ci.rLNLN` is used to calculate approximate marginal maximum likelihood confidence intervals with significance level $\alpha$ for all parameters in the rLN-LN model. The function takes the following arguments:

- `alpha`: the significance level
- `parameter`: the maximum likelihood estimate around which the confidence interval is centered. It should be on the original scale, not on the logit-/log-transformed scale as used during the estimation procedure.
- `prev.result`: a list of previous results as returned by the `stochprof.results` function. This variable is only used when `parameter` is missing.
- `dataset`: a matrix which contains the cumulated expression data over all cells in a tissue sample. Columns represent different genes, rows represent different tissue samples.
- `n`: number of cells taken from each tissue sample. This can also be a vector stating how many cells are in each sample separately.
- `TY`: the number of types of cells that is assumed in the stochastic model.
- `fix.mu`: if TRUE, the log-means are kept fixed in the estimation procedure. Otherwise, they are to be estimated.
- `fixed.mu`: a vector containing the values to which the log-means should be fixed if `fix.mu`==T. The order of components is as follows:
  - (mu_type_1_gene_1, mu_type_1_gene_2, ..., mu_type_2_gene_1, mu_type_2_gene_2, ...).

The parameter needs to be specified only when `fix.mu`==T.
Details

The intervals are approximate because the function uses the formula

\[ \theta_i \pm q_{(1-\alpha/2)} \times \sqrt{H_{ii}} \],

where \( \theta_i \) is the estimate of the i.th parameter, \( q_{(1-\alpha/2)} \) is the 1-\( \alpha/2 \) quantile of the standard normal distribution, \( H \) is the inverse Hessian of the negative log likelihood function evaluated at the maximum likelihood estimate; \( H_{ii} \) is the i.th diagonal element of \( H \). This approximation implicitly assumes that the log likelihood function is unimodal. The confidence interval is first calculated on the transformed, unrestricted parameter space and then back-transformed to the original one.

Value

Approximate marginal maximum likelihood confidence intervals for all parameter components: Each row corresponds to one parameter (in the same order as always used in the stochastic profiling model). The first column contains lower bounds, the second column upper bounds.

Author(s)

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References


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**comb.summands**

Combinations of fixed number of summands with pre-defined sum.

Description

Returns all combinations of \( k \) numbers between 0 and \( n \) whose sum equals \( n \).

Usage

\[ \text{comb.summands}(n, k) \]

Arguments

- \( n \) the sum of the \( k \) summands
- \( k \) the number of summands
Details

Returns all combinations of k numbers (non-negative integers) between 0 and n whose sum equals n. The order of the summands matters, i.e. 2+3=5 and 3+2=5 would count as two different combinations.

Value

A matrix with k columns. Each row contains a different combination of k non-negative integers which sum up to n.

Author(s)

Christoph Kurz

References


d.sum.of.mixtures.EXPLN

Sums of mixtures of zero, one or more lognormal random variables and one exponential random variable

Description

Density and random generation of a sum of i.i.d. random variables, where each random variable is from the following mixture distribution: With probability p_i, it is of type i. For all but the largest i, it is lognormally distributed with log-mean mu_i and log-standard deviation sigma_i. Otherwise it is exponentially distributed with rate lambda.

Usage

d.sum.of.mixtures.EXPLN(y, n, p.vector, mu.vector, sigma.vector, lambda, logdens = T)
r.sum.of.mixtures.EXPLN(k, n, p.vector, mu.vector, sigma.vector, lambda, N.matrix)
Arguments

- y: the argument at which the density is evaluated
- k: number of i.i.d. random variables returned by this function (in the considered application: number of tissue samples)
- n: the number of random variables entering each sum (in the considered application: number of cells per tissue sample). This can also be a vector stating how many cells are in each sample separately.

- p.vector: vector (mu1,mu2,...,mu(T-1)) containing the log-means for each lognormal type (types 1 to T-1)
- mu.vector: vector (sigma1,...,sigma(T-1)) containing the log-standard deviations sigma for each lognormal type (types 1 to T-1)
- lambda: the rate for the exponential type (type T)
- logdens: if TRUE, the log of the density is returned
- N.matrix: optional. Matrix, that shows the decomposition of samples to be generated. Each row stands for a future sample and the columns show the decomposition of types for the specific sample such that the row sum should be n (either a value, i.e. all the same or a vector).

Details

The lengths of mu.vector and sigma.vector have to be identical. p.vector has to have one component more. Its length automatically determines the number of different types. lambda has to be a scalar.

Value

'd.sum.of.mixtures.EXPLN' gives the density, and 'r.sum.of.mixtures.EXPLN' generates random variables.

Author(s)

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References


Examples

```r
# generate random variables
p <- c(0.25, 0.75)
mu <- 2
sigma <- 0.3
lambda <- 5
set.model.functions("EXP-LN")

r <- r.sum.of.mixtures.EXPLN(10^4, 10, p, mu, sigma, lambda)
hist(r, xlab="Sum of mixtures of lognormals", freq=FALSE, breaks=100, ylim=c(0, 0.2))

# plot according theoretical density function
x <- seq(round(min(r)), round(max(r)), (round(max(r)) - round(min(r)))/500)
y <- d.sum.of.mixtures.EXPLN(x, 10, p, mu, sigma, lambda, logdens=FALSE)
lines(x, y, col="blue", lwd=3)
```

---

d.sum.of.mixtures.LNLN

**Sums of mixtures of lognormal random variables**

Description

Density and random generation of a sum of i.i.d. random variables, where each random variable is from the following mixture distribution: With probability $p_i$, it is of type $i$. In that case, it is lognormally distributed with log-mean $\mu_i$ and log-standard deviation $\sigma_i$.

Usage

```r
d.sum.of.mixtures.LNLN(y, n, p.vector, mu.vector, sigma.vector, logdens = T)
r.sum.of.mixtures.LNLN(k, n, p.vector, mu.vector, sigma.vector, N.matrix)
```

Arguments

- `y` the argument at which the density is evaluated
- `k` number of i.i.d. random variables returned by this function (in the considered application: number of tissue samples)
- `n` the number of random variables entering each sum (in the considered application: number of cells per tissue sample). This can also be a vector stating how many cells are in each sample separately.
- `p.vector` vector ($p_1, p_2, \ldots, p_T$) containing the probabilities for each type of cell. Its elements have to sum up to one
- `mu.vector` vector ($\mu_1, \mu_2, \ldots, \mu_T$) containing the log-means for each type
- `sigma.vector` vector ($\sigma_1, \sigma_2, \ldots, \sigma_T$) containing the log-standard deviations $\sigma_i$ for each type
- `logdens` if TRUE, the log of the density is returned
N.matrix
optional. Matrix, that shows the decomposition of samples to be generated. Each row stands for a future sample and the columns show the decomposition of types for the specific sample such that the row sum should be n (either a value, i.e. all the same or a vector).

Details
The lengths of p.vector, mu.vector and sigma.vector have to be identical. Their lengths automatically determine the number of different types.

Value
'd.sum.of.mixtures.LNLN' gives the density, and 'r.sum.of.mixtures.LNLN' generates random variables.

Author(s)
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References


Examples
# generate random variables
p <- c(0.25,0.75)
mu <- c(2,-1)
sigma <- c(0.3,0.1)

set.model.functions("LN-LN")

r <- r.sum.of.mixtures.LNLN(10^4,10,p,mu,sigma)
hist(r,xlab="Sum of mixtures of lognormals",freq=FALSE,breaks=100,ylim=c(0,0.2))

# plot according theoretical density function
x <- seq(round(min(r)),round(max(r)),(round(max(r))-round(min(r)))/500)
y <- d.sum.of.mixtures.LNLN(x,10,p,mu,sigma,logdens=FALSE)
lines(x,y,col="blue",lwd=3)
**Description**

Density and random generation of a sum of i.i.d. random variables, where each random variable is from the following mixture distribution: With probability \( p_i \), it is of type \( i \). In that case, it is lognormally distributed with log-mean \( \mu_i \) and log-standard deviation \( \sigma_i \).

**Usage**

```R
d.sum.of.mixtures.rLNLN(y, n, p.vector, mu.vector, sigma.vector, logdens = T)
r.sum.of.mixtures.rLNLN(k, n, p.vector, mu.vector, sigma.vector, N.matrix)
```

**Arguments**

- `y`: the argument at which the density is evaluated
- `k`: number of i.i.d. random variables returned by this function (in the considered application: number of tissue samples)
- `n`: the number of random variables entering each sum (in the considered application: number of cells per tissue sample). This can also be a vector stating how many cells are in each sample separately.
- `p.vector`: vector \((p_1,p_2,...,p_T)\) containing the probabilities for each type of cell. Its elements have to sum up to one
- `mu.vector`: vector \((\mu_1,\mu_2,...,\mu_T)\) containing the log-means for each type
- `sigma.vector`: vector \((\sigma_1,...,\sigma_T)\) containing the log-standard deviations \( \sigma \) for each type
- `logdens`: if TRUE, the log of the density is returned
- `N.matrix`: optional. Matrix, that shows the decomposition of samples to be generated. Each row stands for a future sample and the columns show the decomposition of types for the specific sample such that the row sum should be \( n \) (either a value, i.e. all the same or a vector).

**Details**

The lengths of `p.vector`, `mu.vector` and `sigma.vector` have to be identical. Their lengths automatically determine the number of different types.

**Value**

`d.sum.of.mixtures.rLNLN` gives the density, and `r.sum.of.mixtures.rLNLN` generates random variables.
Author(s)

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References


Examples

# generate random variables
p <- c(0.25,0.75)
mu <- c(2,-1)
sigma <- c(0.3,0.1)

set.model.functions("rLN-LN")

r <- r.sum.of.mixtures.rLNLN(10^4,10,p,mu,sigma)
hist(r,xlab="Sum of mixtures of lognormals",freq=FALSE,breaks=100,ylim=c(0,0.2))

# plot according theoretical density function
x <- seq(round(min(r)),round(max(r)),(round(max(r))-round(min(r)))/500)
y <- d.sum.of.mixtures.rLNLN(x,10,p,mu,sigma,logdens=FALSE)
lines(x,y,col="blue",lwd=3)

---

**generate.toydata**

*Generation and analysis of synthetic data in stochastic profiling model*

Description

Generation of a dataset of 500 i.i.d measurements as considered in the stochastic profiling model. Afterwards estimation of the model parameters and comparison of the estimates with the true value.

Usage

`generate.toydata(model = "LN-LN")`

Arguments

- **model**: the chosen stochastic profiling model: "LN-LN", "rLN-LN" or "EXP-LN"
generate.toydata

Details

This function first generates a dataset of 500 i.i.d. 10-cell samplings as considered in the stochastic profiling models "LN-LN", "rLN-LN" and "EXP-LN". The employed parameters are TY=2 (i.e. two different types of cells are assumed) and p=c(0.2,0.8) for all models. Furthermore, mu=c(1.5,-1.5) and sigma=0.2 for the LN-LN model, mu=c(1.5,-1.5) and sigma=(0.2,0.6) for the rLN-LN model, and mu=1.5, sigma=0.2 and lambda=0.5 for the EXP-LN model. The generated data is displayed in a histogram together with the theoretical probability density function. At the end of the estimation procedure, the profile log-likelihood plots are shown. Finally, the true and the estimated probability density functions are compared and the estimation results are printed.

Value

A list as returned by stochprof.loop, i.e. the following components:

mle maximum likelihood estimate
neg-loglikeli value of the negative log-likelihood function at maximum likelihood estimate
ci approximate marginal maximum likelihood confidence intervals for the maximum likelihood estimate
pargrid matrix containing parameter combinations and according values of the target function
bic Bayesian information criterion value
adj.bic adjusted Bayesian information criterion value which takes into account the numbers of parameters that were estimated during the preanalysis of a gene cluster. Is only calculated if parameter subgroups is given, otherwise set to NULL.
pen penalization for densities not fulfilling required constraints. If use.constraints is FALSE, this has no practical meaning. If use.constraints is TRUE, this value is included in loglikeli.

Author(s)

Lisa Amrhein, Christiane Fuchs

Maintainer: Lisa Amrhein <amrheinlisa@gmail.com>

References


Density of the sum of mixtures of zero, one or more lognormal random variables and one exponential random variable weighted by all possible summands

Description

Density of a sum of i.i.d. random variables, where each random variable is from the following mixture distribution: With probability p_i, it is of type i. For all but the largest i, it is lognormally distributed with log-mean mu_i and log-standard deviation sigma_i. Otherwise it is exponentially distributed with rate lambda. The density is somehow a "mixed" one, as for all values in n the density of the random variable is calculated and the weighted average is taken to be the density of this specific value.

Usage

mix.d.sum.of.mixtures.EXPLN(y, n.vector, p.vector, mu.vector, sigma.vector, lambda)

Arguments

y the argument at which the density is evaluated
n.vector the number of random variables entering each sum (in the considered application: number of cells per tissue sample). This can also be a vector stating how many cells are in each sample separately
p.vector vector (p1,p2,...,pT) containing the probabilities for each type of cell. Its elements have to sum up to one
mu.vector vector (mu1,mu2,...,mu(T-1)) containing the log-means for each lognormal type (types 1 to T-1)
sigma.vector vector (sigma1,...,sigma(T-1)) containing the log-standard deviations sigma for each lognormal type (types 1 to T-1)
lambda the rate for the exponential type (type T)

Details

The lengths of mu.vector and sigma.vector have to be identical. p.vector has to have one component more. Its length automatically determines the number of different types. lambda has to be a scalar.

Value

'mix.d.sum.of.mixtures.EXPLN' gives the density of a random variable originating from one of the tissue samples in the mixed n-vector.

Author(s)

Lisa Amrhein, Christiane Fuchs
Maintainer: Lisa Amrhein <amrheinlisa@gmail.com>
Density of the sum of mixtures of lognormal random variables weighted by all possible summands

Description

Density of a random variable that is the sum of i.i.d. random variables, where each random variable is from the following mixture distribution: With probability $p_i$, it is of type $i$. In that case, it is lognormally distributed with log-mean $\mu_i$ and log-standard deviation $\sigma_i$. The density is somehow a "mixed" one, as for all values in $n$ the density of the random variable is calculated and the weighted average is taken to be the density of this specific value.

Usage

mix.d.sum.of.mixtures.LNLN(y, n.vector, p.vector, mu.vector, sigma.vector)

Arguments

- **y**: the argument at which the density is evaluated
- **n.vector**: the number of random variables entering each sum (in the considered application: number of cells per tissue sample). This can also be a vector stating how many cells are in each sample separately
- **p.vector**: vector ($p1, p2, ..., pT$) containing the probabilities for each type of cell. Its elements have to sum up to one
- **mu.vector**: vector ($\mu1, \mu2, ..., \muT$) containing the log-means for each type
- **sigma.vector**: vector ($\sigma1, ..., \sigmaT$) containing the log-standard deviations $\sigma$ for each type

Details

The lengths of p.vector, mu.vector and sigma.vector have to be identical. Their lengths automatically determine the number of different types.
Value

'mix.d.sum.of.mixtures.LNLN' gives the density of a random variable originating from one of the tissue samples in the mixed n-vector.

Author(s)

Lisa Amrhein, Christiane Fuchs
Maintainer: Lisa Amrhein <amrheinlisa@gmail.com>

References


mix.d.sum.of.mixtures.rLNLN

Density of the sum of mixtures of lognormal random variables weighted by all possible summands

Description

Density and random generation of a sum of i.i.d. random variables, where each random variable is from the following mixture distribution: With probability p_i, it is of type i. In that case, it is lognormally distributed with log-mean mu_i and log-standard deviation sigma_i. The density is somehow a "mixed" one, as for all values in n the density of the random variable is calculated and the weighted average is taken to be the density of this specific value.

Usage

mix.d.sum.of.mixtures.rLNLN(y, n.vector, p.vector, mu.vector, sigma.vector)

Arguments

y the argument at which the density is evaluated

n.vector the number of random variables entering each sum (in the considered application: number of cells per tissue sample). This can also be a vector stating how many cells are in each sample separately

p.vector vector (p1, p2, ..., pT) containing the probabilities for each type of cell. Its elements have to sum up to one
penalty.constraint.EXPLN

mu.vector vector (μ1,μ2,...,μT) containing the log-means for each type
sigma.vector vector (σ1,...,σT) containing the log-standard deviations σ for each type

Details

The lengths of p.vector, mu.vector and sigma.vector have to be identical. Their lengths automatically determine the number of different types.

Value

'mix.d.sum.of.mixtures.LNLN' gives the density of a random variable originating from one of the tissue samples in the mixed n-vector.

Author(s)

Lisa Amrhein, Christiane Fuchs
Maintainer: Lisa Amrhein <amrheinlisa@gmail.com>

References


penalty.constraint.EXPLN

Penalization for population densities that do not fulfill certain constraints for the EXP-LN model

Description

In order to force the individual populations to be sufficiently distinct from each other, one can perform penalized optimization. To this end, constraints on the densities are introduced (see details). If the constraints are not fulfilled, a penalization term is added to the negative log-likelihood (which is to be minimized).

Usage

penalty.constraint.EXPLN(dataset, parameter, smoothingpar = 10^5)
Arguments

dataset matrix which contains the cumulated expression data over all cells in a tissue sample. Columns represent different genes, rows represent different tissue samples.

parameter parameter for which the penalization term is calculated. This is a vector containing p, mu, sigma and lambda.

smoothingpar weight with which the penalization term is multiplied.

Details

The constraints are as follows: There are TY densities for the TY distinct populations. For each i=1,...,(TY-1), one considers the density of population i (the higher regulatory state) and the density of population i+1 (the lower regulatory state). The density of the higher regulatory state is constrained to be greater than the density of the lower regulatory state in the domain between the mode of the high state and the largest observation in the dataset.

Introduction of this penalization term does not mean that the constraints will automatically be fulfilled. The parameter estimate will be a trade-off between a maximizer of the unconstrained likelihood function and a minimizer of the penalization function. The higher the parameter smoothingpar, the more importance is on fulfilling the constraints.

Value

The population densities are compared on the above described domains. Wherever the constraint is not fulfilled, the difference between the larger and the lower density is calculated. The squares of all such differences are summed up and multiplied with smoothingpar. This value is returned.

Author(s)

Lisa Amrhein, Christiane Fuchs

Maintainer: Lisa Amrhein <amrheinlisa@gmail.com>

References


penalty.constraint.LNLN

*Penalization for population densities that do not fulfill certain constraints for the LN-LN model*

**Description**

In order to force the individual populations to be sufficiently distinct from each other, one can perform penalized optimization. To this end, constraints on the densities are introduced (see details). If the constraints are not fulfilled, a penalization term is added to the negative log-likelihood (which is to be minimized).

**Usage**

```r
penalty.constraint.LNLN(dataset, parameter, smoothingpar = 10^5)
```

**Arguments**

- `dataset` matrix which contains the cumulated expression data over all cells in a tissue sample. Columns represent different genes, rows represent different tissue samples.
- `parameter` parameter for which the penalization term is calculated. This is a vector containing p, mu and sigma.
- `smoothingpar` weight with which the penalization term is multiplied.

**Details**

The constraints are as follows: There are TY densities for the TY distinct populations. For each i=1,...,(TY-1), one considers the density of population i (the higher regulatory state) and the density of population i+1 (the lower regulatory state). The density of the higher regulatory state is constrained to be greater than the density of the lower regulatory state in the domain between the mode of the high state and the largest observation in the dataset.

Introduction of this penalization term does not mean that the constraints will automatically be fulfilled. The parameter estimate will be a trade-off between a maximizer of the unconstrained likelihood function and a minimizer of the penalization function. The higher the parameter `smoothingpar`, the more importance is on fulfilling the constraints.

**Value**

The population densities are compared on the above described domains. Wherever the constraint is not fulfilled, the difference between the larger and the lower density is calculated. The squares of all such differences are summed up and multiplied with `smoothingpar`. This value is returned.

**Author(s)**

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Maintainer: Lisa Amrhein <amrheinlisa@gmail.com>
penalty.constraint.rLNLN

Penalization for population densities that do not fulfil certain constraints for the rLN-LN model

Description
In order to force the individual populations to be sufficiently distinct from each other, one can perform penalized optimization. To this end, constraints on the densities are introduced (see details). If the constraints are not fulfilled, a penalization term is added to the negative log-likelihood (which is to be minimized).

Usage
penalty.constraint.rLNLN(dataset, parameter, smoothingpar = 10^5)

Arguments

- **dataset**: matrix which contains the cumulated expression data over all cells in a tissue sample. Columns represent different genes, rows represent different tissue samples.
- **parameter**: parameter for which the penalization term is calculated. This is a vector containing p, mu and sigma.
- **smoothingpar**: weight with which the penalization term is multiplied.

Details
The constraints are as follows: There are TY densities for the TY distinct populations. For each i=1,...,(TY-1), one considers the density of population i (the higher regulatory state) and the density of population i+1 (the lower regulatory state). The density of the higher regulatory state is constrained to be greater than the density of the lower regulatory state in the domain between the mode of the high state and the largest observation in the dataset.

Introduction of this penalization term does not mean that the constraints will automatically be fulfilled. The parameter estimate will be a trade-off between a maximizer of the unconstrained likelihood function and a minimizer of the penalization function. The higher the parameter smoothingpar, the more importance is on fulfilling the constraints.

References

The population densities are compared on the above described domains. Wherever the constraint is not fulfilled, the difference between the larger and the lower density is calculated. The squares of all such differences are summed up and multiplied with smoothingpar. This value is returned.

Author(s)
Lisa Amrhein, Christiane Fuchs
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References

sod2  

Measurements from the detoxifying enzyme, SOD2

Description

Real 10-cell samplings from the detoxifying enzyme, SOD2. The dataset contains the measurements of SOD2 expression by qPCR in 81 random samplings of 10 ECM-attached cells.

Usage

data(sod2)

Format

The format is: num [1:81] 0.603 0.873 0.204 1 3.001 ...

Source

"Parameterizing cell-to-cell regulatory heterogeneities via stochastic transcriptional profiles" by Sameer S Bajikar*, Christiane Fuchs*, Andreas Roller, Fabian J Theis^ and Kevin A Janes^: PNAS 2014, 111(5), E626-635 (* joint first authors, ^ joint last authors)

References

"Parameterizing cell-to-cell regulatory heterogeneities via stochastic transcriptional profiles" by Sameer S Bajikar*, Christiane Fuchs*, Andreas Roller, Fabian J Theis^ and Kevin A Janes^: PNAS 2014, 111(5), E626-635 (* joint first authors, ^ joint last authors)

Examples

data(sod2)
hist(sod2,breaks=seq(0,7,0.5),col="grey")

stochasticProfilingData

User prompt for generation and visualization of synthetic data in stochastic profiling model

Description

Generation of a dataset of i.i.d measurements as considered in the stochastic profiling model. The user is prompted to input all required settings. He or she hence does not have to delve into the structure of this package.

Usage

stochasticProfilingData()
Details

This function generates a dataset of i.i.d synthetic measurements as considered in the stochastic profiling model. The user is prompted to input all required settings, e.g. the exact model (LN-LN, rLN-LN or EXP-LN), the number of samples, the number of populations etc. The dataset is returned as a matrix and visualized in histograms together with the data generating probability density function (pdf).

Value

A matrix containing the synthetic data. Columns stand for different genes, rows for samples.

Author(s)

Lisa Amrhein, Christiane Fuchs
Maintainer: Lisa Amrhein <amrheinlisa@gmail.com>

References


Value

A list as returned by `stochprof.loop`, i.e. the following components:

- **mle**: maximum likelihood estimate
- **neg-loglikeli**: value of the negative log-likelihood function at maximum likelihood estimate
- **ci**: approximate marginal maximum likelihood confidence intervals for the maximum likelihood estimate
- **pargrid**: matrix containing parameter combinations and according values of the target function
- **bic**: Bayesian information criterion value
- **adj.bic**: adjusted Bayesian information criterion value which takes into account the numbers of parameters that were estimated during the preanalysis of a gene cluster. Is only calculated if parameter subgroups is given, otherwise set to NULL.
- **pen**: penalization for densities not fulfilling required constraints. If `use.constraints` is FALSE, this has no practical meaning. If `use.constraints` is TRUE, this value is included in `loglikeli`.

Author(s)

Lisa Amrhein, Christiane Fuchs

Maintainer: Lisa Amrhein <amrheinlisa@gmail.com>

References


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**stochprof.loop**

Maximum likelihood estimation for the parameters in the stochastic profiling model

---

Description

Maximum likelihood estimation for the parameters in the stochastic profiling model. Because the log-likelihood function is potentially multimodal, no straightforward use of gradient-based approaches for finding globally optimal parameter combinations is possible. To tackle this challenge, this function performs a two-step estimation procedure.
Usage

stochprof.loop(model, dataset, n, TY, genenames = NULL, fix.mu = F, fixed.mu, par.range = NULL, prev.result = NULL, loops = 5, until.convergence = T, print.output = T, show.plots = T, plot.title = "", pdf.file, use.constraints = F, subgroups)

Arguments

model            model for which one wishes to estimate the parameters: "LN-LN", "rLN-LN" or "EXP-LN"
dataset          matrix which contains the cumulated expression data over all cells in a tissue sample. Columns represent different genes, rows represent different tissue samples.
n               number of cells taken from each tissue sample. This can also be a vector stating how many cells are in each sample separately.
TY               number of types of cells that is assumed in the stochastic model
genenames        names of the genes in the dataset. For genenames==NULL, the genes will simply be enumerated according to the column numbers in the dataset.
fix.mu           if TRUE, the log-means of the lognormal distributions are kept fixed in the estimation procedure. Otherwise, they are to be estimated.
fixed.mu         vector containing the values to which the log-means should be fixed if fix.mu==T. The order of components is as follows:
                 (mu_type_1_gene_1, mu_type_1_gene_2, ..., mu_type_2_gene_1, mu_type_2_gene_2, ...).
                 This argument needs to be specified only when fix.mu==T.
par.range        range from which the parameter values should be randomly drawn if there is no knowledge from previous iterations of the search algorithm available. This is a matrix with the number of rows being equal to the number of model parameters. The first column contains the lower bound, the second column the upper bound. If par.range==NULL, some rather large range is defined.
prev.result      can contain results from former calls of this function
loops            maximal number of loops carried out in the estimation procedure. Each loops involves various methods to determine the high-likelihood region.
until.convergence if TRUE, the estimation process is terminated if there had been no improvement concerning the value of the target function between two consecutive loops. Otherwise, the estimation procedure is terminated according to the parameter "loops".
print.output     if TRUE, interim results of the grid search and numerical optimization are printed into the console throughout the estimation procedure
show.plots       if TRUE, profile log-likelihood plots are displayed at the end of the estimation procedure
plot.title       title of each plot if show.plots==T
pdf.file: optional filename. If this is not missing and showplots=T, the profile log-likelihoods will be plotted into this file.

use.constraints: if TRUE, constraints on the individual population densities are applied; see penalty.constraint.LNLN, penalty.constraint.rLNLN and penalty.constraint.EXPLN for details.

subgroups: list of sets of gene numbers. This parameter should be given only when the present call of stochprof.loop is based on a subanalysis of the subgroups of genes with non-fixed mu. The parameter is used only for calculation of the adjusted BIC which takes into account the number of parameters that had to be estimated during the whole estimation procedure: First, for each of the subclusters, and then for the final analysis.

Details

This function carries out maximum likelihood estimation for the parameters of the stochastic profiling model. Because the log-likelihood function is potentially multimodal, no straightforward use of gradient-based approaches for finding globally optimal parameter combinations is possible. To tackle this challenge, this function performs a two-step estimation procedure: First, it computes the log-likelihood function at randomly drawn parameter combinations to identify high-likelihood regions in parameter space at computationally low cost. Then, it uses the Nelder-Mead algorithm to identify local maxima of the likelihood function. The starting values for this algorithm are randomly drawn from the high-likelihood regions determined in the first step. To further localize the global optimum, the function again performs grid searches of the parameter space, this time around the optimum identified by the Nelder-Mead algorithm. This search creates another space to identify high-likelihood regions, which are then used to seed another Nelder-Mead optimization.

Value

A list with the following components:

mle: maximum likelihood estimate

neg-loglikeli: value of the negative log-likelihood function at maximum likelihood estimate

neg-loglikeli: approximate marginal maximum likelihood confidence intervals for the maximum likelihood estimate

pargrid: matrix containing parameter combinations and according values of the target function

bic: Bayesian information criterion value

adj.bic: adjusted Bayesian information criterion value which takes into account the numbers of parameters that were estimated during the preanalysis of a gene cluster. Is only calculated if parameter subgroups is given, otherwise set to NULL.

pen: penalization for densities not fulfilling required constraints. If use.constraints is FALSE, this has no practical meaning. If use.constraints is TRUE, this value is included in loglikeli.
stochprof.results.EXPLN

Evaluation of results from estimation of EXP-LN model

Description
Evaluates the set of results that are passed to this function. That means, it removes entries where the target function is equal to infinity, it removes double entries, it removes unlikely parameter combinations (if there are too many) etc., and it sorts the data. When show.plots==T, the results are graphically displayed.

Usage
stochprof.results.EXPLN(prev.result, TY, show.plots = T, plot.title = "", pdf.file, fix.mu = F)

Arguments
prev.result contains parameter combinations and the respective value of the target function. It is typically the output of `stochprof.search.EXPLN`.
TY number of types of cells assumed in the model
show.plots if TRUE, the results are plotted. In particular, one plot is produced for each parameter, with the value of the parameter plotted against the value of the target function. This is not exactly the profile log-likelihood function because there is no conditioning on the other parameters being equal to the ML estimate. If the estimation procedure has converged, however, one can recognize the shape of the profile log-likelihood from these plots. A red bar indicates the position of the maximum likelihood estimator.
plot.title title of each plot if show.plots==T
Description

Evaluates the set of results that are passed to this function. That means, it removes entries where the target function is equal to infinity, it removes double entries, it removes unlikely parameter combinations (if there are too many) etc., and it sorts the data. When show.plots==T, the results are graphically displayed.

Usage

```
stochprof.results.LNLN(prev.result, TY, show.plots = T, plot.title = "", pdf.file, fix.mu = F)
```
Arguments

prev.result: contains parameter combinations and the respective value of the target function. It is typically the output of 'stochprof.search.LNLN'.

TY: number of types of cells assumed in the model

show.plots: if TRUE, the results are plotted. In particular, one plot is produced for each parameter, with the value of the parameter plotted against the value of the target function. This is not exactly the profile log-likelihood function because there is no conditioning on the other parameters being equal to the ML estimate. If the estimation procedure has converged, however, one can recognize the shape of the profile log-likelihood from these plots. A red bar indicates the position of the maximum likelihood estimator.

plot.title: title of each plot if show.plots==T

pdf.file: plots will be written into this file when this argument is not missing. The file has to include the entire path.

fix.mu: if TRUE, the log-mean of the lognormal distributions has been kept fixed. In that case, no plots will be produced for these parameters.

Value

Matrix with sorted and evaluated results. The columns are exactly the same as those in 'prev.result'. The first row contains the best estimate.

Author(s)

Lisa Amrhein, Christiane Fuchs

Maintainer: Lisa Amrhein <amrheinlisa@gmail.com>

References


Description

Evaluates the set of results that are passed to this function. That means, it removes entries where the target function is equal to infinity, it removes double entries, it removes unlikely parameter combinations (if there are too many) etc., and it sorts the data. When show.plots==T, the results are graphically displayed.

Usage

stochprof.results.rLNLN(prev.result, TY, show.plots = T, plot.title = "", pdf.file, fix.mu = F)

Arguments

prev.result  contains parameter combinations and the respective value of the target function. It is typically the output of 'stochprof.search.rLNLN'.

TY  number of types of cells assumed in the model

show.plots  if TRUE, the results are plotted. In particular, one plot is produced for each parameter, with the value of the parameter plotted against the value of the target function. This is not exactly the profile log-likelihood function because there is no conditioning on the other parameters being equal to the ML estimate. If the estimation procedure has converged, however, one can recognize the shape of the profile log-likelihood from these plots. A red bar indicates the position of the maximum likelihood estimator.

plot.title  title of each plot if show.plots==T

pdf.file  plots will be written into this file when this argument is not missing. The file has to include the entire path.

fix.mu  if TRUE, the log-mean of the lognormal distributions has been kept fixed. In that case, no plots will be produced for these parameters.

Value

Matrix with sorted and evaluated results. The columns are exactly the same as those in 'prev.result'. The first row contains the best estimate.

Author(s)

Lisa Amrhein, Christiane Fuchs

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stochprof.search.EXPLN

Calculation of the log likelihood function of the EXP-LN model

Description

Calculates the log likelihood function of the parameters of the EXP-LN model for a given dataset at certain parameter values.

Usage

stochprof.search.EXPLN(dataset, n, TY, method = "grid", M = 10,
par.range = NULL, prev.result = NULL, fix.mu = F, fixed.mu,
genenames = NULL, print.output = F, use.constraints = F)

Arguments

dataset matrix which contains the cumulated expression data over all cells in a tissue sample. Columns represent genes, rows represent tissue samples.
n number of cells taken from each tissue sample. This can also be a vector stating how many cells are in each sample separately
TY number of types of cells that is assumed in the stochastic model
method determines whether a grid search or the Nelder-Mead algorithm should be applied: If method=="grid", the log likelihood function is simply evaluated at certain parameter values that are randomly drawn. If method=="optim", a Nelder-Mead search starts at a randomly drawn set of parameter values in order to find a local maximum. The resulting locally optimal parameter is stored in the results matrix as one row.
M number of randomly drawn parameter combinations
par.range range from which the parameter values should be randomly drawn. This is a matrix with the number of rows being equal to the number of model parameters. The first columns contains the lower bound, the second column the upper bound. If par.range==NULL, some rather large range is defined.
prev.result can contain results from former calls of this function
if TRUE, the log-means are kept fixed in the estimation procedure. Otherwise, they are to be estimated.

vector containing the values to which the log-means should be fixed if fix.mu==T. The order of components is as follows:

(mu_type_1_gene_1, mu_type_1_gene_2, ..., mu_type_2_gene_1, mu_type_2_gene_2, ...).

This argument needs to be specified only when fix.mu==T.

names of the genes in the dataset. For genenames==NULL, the genes will simply be enumerated according to the column numbers in the dataset.

if TRUE, interim results of the grid search and numerical optimization are printed into the console throughout the estimation procedure

if TRUE, constraints on the individual population densities are applied; see penalty.constraint.EXPLN for details.

The values at which the target function is calculated are randomly drawn from some range specified by "par.range". If method=="grid", the target function is simply evaluated at such a randomly drawn parameter vector. If method=="optim", this randomly drawn vector is passed to the Nelder-Mead algorithm as a starting value in order to search for a local maximum around it.

A matrix with the following entries: Each row corresponds to one parameter combination. All columns but the last one contain the parameter values at which the log likelihood function has been computed. The column names are the parameter names. The last column ("target") is the negative log likelihood function computed at the respective parameter vector. For numerical reasons, this target value is set to the minimum of 10^7 and the actual value.

Lisa Amrhein, Christiane Fuchs

Maintainer: Lisa Amrhein <amrheinlisa@gmail.com>


Description

Calculates the log likelihood function of the parameters of the LN-LN model for a given dataset at certain parameter values.

Usage

```r
stochprof.search.LNLN(dataset, n, TY, method = "grid", M = 10,
                      par.range = NULL, prev.result = NULL, fix.mu = F, fixed.mu,
                      genenames = NULL, print.output = F, use.constraints = F)
```

Arguments

dataset: matrix which contains the cumulated expression data over all cells in a tissue sample. Columns represent genes, rows represent tissue samples.

n: number of cells taken from each tissue sample. This can also be a vector stating how many cells are in each sample separately.

TY: number of types of cells that is assumed in the stochastic model.

method: determines whether a grid search or the Nelder-Mead algorithm should be applied: If method="grid", the log likelihood function is simply evaluated at certain parameter values that are randomly drawn. If method="optim", a Nelder-Mead search starts at a randomly drawn set of parameter values in order to find a local maximum. The resulting locally optimal parameter is stored in the results matrix as one row.

M: number of randomly drawn parameter combinations.

par.range: range from which the parameter values should be randomly drawn. This is a matrix with the number of rows being equal to the number of model parameters. The first columns contains the lower bound, the second column the upper bound. If par.range==NULL, some rather large range is defined.

prev.result: can contain results from former calls of this function.

fix.mu: if TRUE, the log-means are kept fixed in the estimation procedure. Otherwise, they are to be estimated.

fixed.mu: vector containing the values to which the log-means should be fixed if fix.mu==T. The order of components is as follows:

\[
(mu_{type\_1\_gene\_1}, mu_{type\_1\_gene\_2}, ..., \\
mu_{type\_2\_gene\_1}, mu_{type\_2\_gene\_2}, ...).
\]

This argument needs to be specified only when fix.mu==T.

genenames: names of the genes in the dataset. For genenames==NULL, the genes will simply be enumerated according to the column numbers in the dataset.

print.output: if TRUE, interim results of the grid search and numerical optimization are printed into the console throughout the estimation procedure.
use.constraints

if TRUE, constraints on the individual population densities are applied; see
penalty.constraint.LNLN for details.

Details

The values at which the target function is calculated are randomly drawn from some range specified
by "par.range". If method="grid", the target function is simply evaluated at such a randomly drawn
parameter vector. If method="optim", this randomly drawn vector is passed to the Nelder-Mead
algorithm as a starting value in order to search for a local maximum around it.

Value

A matrix with the following entries: Each row corresponds to one parameter combination. All
columns but the last one contain the parameter values at which the log likelihood function has been
computed. The column names are the parameter names. The last column ("target") is the negative
log likelihood function computed at the respective parameter vector. For numerical reasons, this
target value is set to the minimum of \(10^7\) and the actual value.

Author(s)

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Maintainer: Lisa Amrhein <amrheinlisa@gmail.com>

References

"Parameterizing cell-to-cell regulatory heterogeneities via stochastic transcriptional profiles" by
2014, 111(5), E626-635 (* joint first authors, ^ joint last authors) <doi:10.1073/pnas.1311647111>

"Pheno-seq - linking visual features and gene expression in 3D cell culture systems" by Stephan M.
Tirier, Jeongbin Park, Friedrich Preusser, Lisa Amrhein, Zuguang Gu, Simon Steiger, Jan-Philipp
Mallm, Teresa Krieger, Marcel Waschow, Bjoern Eismann, Marta Gut, Ivo G. Gut, Karsten Rippe,
Matthias Schlesner, Fabian Theis, Christiane Fuchs, Claudia R. Ball, Hanno Glimm, Roland Eils &

stochprof.search.rLNLN

Calculation of the log likelihood function of the rLN-LN model

Description

Calculates the log likelihood function of the parameters of the rLN-LN model for a given dataset at
certain parameter values.

Usage

stochprof.search.rLNLN(dataset, n, TY, method = "grid", M = 10,
par.range = NULL, prev.result = NULL, fix.mu = F, fixed.mu,
genenames = NULL, print.output = F, use.constraints = F)
stochprof.search.rLNLN

Arguments

dataset
t matrix which contains the cumulated expression data over all cells in a tissue sample. Columns represent genes, rows represent tissue samples.

n
number of cells taken from each tissue sample. This can also be a vector stating how many cells are in each sample separately.

TY
t number of types of cells that is assumed in the stochastic model.

method
determines whether a grid search or the Nelder-Mead algorithm should be applied: If method=="grid", the log likelihood function is simply evaluated at certain parameter values that are randomly drawn. If method=="optim", a Nelder-Mead search starts at a randomly drawn set of parameter values in order to find a local maximum. The resulting locally optimal parameter is stored in the results matrix as one row.

M
number of randomly drawn parameter combinations.

par.range
range from which the parameter values should be randomly drawn. This is a matrix with the number of rows being equal to the number of model parameters. The first columns contain the lower bound, the second column the upper bound. If par.range==NULL, some rather large range is defined.

prev.result
can contain results from former calls of this function.

fix.mu
if TRUE, the log-means are kept fixed in the estimation procedure. Otherwise, they are to be estimated.

fixed.mu
vector containing the values to which the log-means should be fixed if fix.mu==T. The order of components is as follows:

(mu_type_1_gene_1, mu_type_1_gene_2, ..., mu_type_2_gene_1, mu_type_2_gene_2, ...).
This argument needs to be specified only when fix.mu==T.

genenames
names of the genes in the dataset. For genenames==NULL, the genes will simply be enumerated according to the column numbers in the dataset.

print.output
if TRUE, interim results of the grid search and numerical optimization are printed into the console throughout the estimation procedure.

use.constraints
if TRUE, constraints on the individual population densities are applied; see penalty.constraint.rLNLN for details.

Details

The values at which the target function is calculated are randomly drawn from some range specified by "par.range". If method=="grid", the target function is simply evaluated at such a randomly drawn parameter vector. If method=="optim", this randomly drawn vector is passed to the Nelder-Mead algorithm as a starting value in order to search for a local maximum around it.

Value

A matrix with the following entries: Each row corresponds to one parameter combination. All columns but the last one contain the parameter values at which the log likelihood function has been computed. The column names are the parameter names. The last column ("target") is the negative
log likelihood function computed at the respective parameter vector. For numerical reasons, this target value is set to the minimum of $10^{-7}$ and the actual value.

**Author(s)**
Lisa Amrhein, Christiane Fuchs
Maintainer: Lisa Amrhein <amrheinlisa@gmail.com>

**References**

**toycluster.EXPLN**
* Synthetic data from the EXP-LN model

**Description**
A matrix containing synthetic measurements from the stochastic profiling EXP-LN model. There is data for 12 genes (columns) and 16 tissue samples (rows). Each measurement is the sum of 10 i.i.d. random variables from a mixture of one lognormal and one exponential distribution.

**Usage**
data(toycluster.EXPLN)

**Format**
The format is: num [1:16, 1:12] 3.77 4.87 5.05 4.45 5.35 ... - attr(*, "dimnames")=List of 2 ..$ : chr [1:16] "V1" "V2" "V3" "V4" ...

**Details**
The true underlying parameters are:
TY = 2, i.e. there are two types of cells
p = (0.225, 0.775), that is the probability for cell type I and II, respectively
mu = (0.1223, 0.2705, 2.1457, 2.2899, 1.6791, 1.1558, 2.4035, 0.1998, 0.9648, 0.0411, 1.4798, 1.4206), that is the log-mean for cell type I for genes 1 to 12
sigma = 0.225, that is the log-standard deviation for type I
lambda = (5.5522, 31.5412, 21.2097, 6.1446, 49.0361, 10.9487, 29.7759, 43.8547, 35.7143, 6.5736, 24.8089, 24.7922), that is the exponential rate for cell type II for genes 1 to 12
**Source**

"Parameterizing cell-to-cell regulatory heterogeneities via stochastic transcriptional profiles" by Sameer S Bajikar*, Christiane Fuchs*, Andreas Roller, Fabian J Theis^ and Kevin A Janes^: PNAS 2014, 111(5), E626-635 (* joint first authors, ^ joint last authors)

**References**

"Parameterizing cell-to-cell regulatory heterogeneities via stochastic transcriptional profiles" by Sameer S Bajikar*, Christiane Fuchs*, Andreas Roller, Fabian J Theis^ and Kevin A Janes^: PNAS 2014, 111(5), E626-635 (* joint first authors, ^ joint last authors)

**Examples**

```r
data(toycluster.EXPLN)
par(mfrow=c(3,4))
for (i in 1:ncol(toycluster.EXPLN)) {
  hist(toycluster.EXPLN[,i],xlab="synthetic data from EXP-LN model",
       main=colnames(toycluster.EXPLN)[i],col="grey")
}
par(mfrow=c(1,1))
```

**toycluster.LNLN**

*Synthetic data from the LN-LN model*

**Description**

A matrix containing synthetic measurements from the stochastic profiling LN-LN model. There is data for 12 genes (columns) and 16 tissue samples (rows). Each measurement is the sum of 10 i.i.d. random variables from a mixture of lognormal distributions.

**Usage**

```r
data(toycluster.LNLN)
```

**Format**

The format is: num [1:16, 1:12] 0.789 4.698 4.643 8.734 12.458 ... - attr(*, "dimnames")=List of 2 ..$ : chr [1:16] "V1" "V2" "V3" "V4" ... ..$ : chr [1:12] "gene 1" "gene 2" "gene 3" "gene 4" ...

**Details**

The true underlying parameters are:

- TY = 2, i.e. there are two types of cells
- p = (0.225, 0.775), that is the probability for cell type I and II, respectively
- \( \mu_1 = (1.8853, 2.2758, 0.4748, 0.2658, 1.5745, 2.3938, 1.7389, 2.2148, 0.2104, 2.1032, 0.0638, 1.8109) \), that is the log-mean for cell type I for genes 1 to 12
\[
\mu_2 = (-2.6637, -0.6590, -1.6308, -2.0753, -3.4486, -3.4865, -2.1848, -1.3868, -2.8238),
\]
that is the log-mean for cell type II for genes 1 to 12

\[
\sigma = 0.225,
\]
that is the log-standard deviation for both cell types

**Source**

"Parameterizing cell-to-cell regulatory heterogeneities via stochastic transcriptional profiles" by Sameer S Bajikar*, Christiane Fuchs*, Andreas Roller, Fabian J Theis^ and Kevin A Janes^: PNAS 2014, 111(5), E626-635 (* joint first authors, ^ joint last authors)

**References**

"Parameterizing cell-to-cell regulatory heterogeneities via stochastic transcriptional profiles" by Sameer S Bajikar*, Christiane Fuchs*, Andreas Roller, Fabian J Theis^ and Kevin A Janes^: PNAS 2014, 111(5), E626-635 (* joint first authors, ^ joint last authors)

**Examples**

```r
data(toycluster.rLNLN)
par(mfrow=c(3,4))
for (i in 1:ncol(toycluster.rLNLN)) {
  hist(toycluster.rLNLN[,i],xlab="synthetic data from LN-LN model",
       main=colnames(toycluster.rLNLN)[i],col="grey")
}
par(mfrow=c(1,1))
```

---

**toycluster.rLNLN** | *Synthetic data from the rLN-LN model*

---

**Description**

A matrix containing synthetic measurements from the stochastic profiling rLN-LN model. There is data for 12 genes (columns) and 16 tissue samples (rows). Each measurement is the sum of 10 i.i.d. random variables from a mixture of lognormal distributions.

**Usage**

```r
data(toycluster.rLNLN)
```

**Format**

The format is: num [1:16, 1:12] 3.46 2.34 3.98 3.42 3.43 ... - attr(*, "dimnames")=List of 2 ..$ : chr [1:16] "V1" "V2" "V3" "V4" ... ..$ : chr [1:12] "gene 1" "gene 2" "gene 3" "gene 4" ...
Details

The true underlying parameters are:

TY = 2, i.e. there are two types of cells

p = (0.225, 0.775), that is the probability for cell type I and II, respectively

mu1 = (0.1287, 1.6249, 1.0075, 0.5521, 0.1200, 1.1661, 1.4261, 1.8238, 2.4261, 1.2568, 0.9342, 1.8876), that is the log-mean for cell type I for genes 1 to 12

mu2 = (-2.2181, -1.6432, -0.9966, -3.1968, -1.9852, -1.0545, -2.3596, -3.0939, -1.3195, -3.2041, -1.2185, -1.3895), that is the log-mean for cell type II for genes 1 to 12

sigma = (0.225, 0.625), that are the log-standard deviations for the two cell types

Source

"Parameterizing cell-to-cell regulatory heterogeneities via stochastic transcriptional profiles" by Sameer S Bajikar*, Christiane Fuchs*, Andreas Roller, Fabian J Theis^ and Kevin A Janes^: PNAS 2014, 111(5), E626-635 (* joint first authors, ^ joint last authors)

References

"Parameterizing cell-to-cell regulatory heterogeneities via stochastic transcriptional profiles" by Sameer S Bajikar*, Christiane Fuchs*, Andreas Roller, Fabian J Theis^ and Kevin A Janes^: PNAS 2014, 111(5), E626-635 (* joint first authors, ^ joint last authors)

Examples

data(toycluster.rLNLN)
par(mfrow=c(3,4))
for (i in 1:ncol(toycluster.rLNLN)) {
    hist(toycluster.rLNLN[,i],xlab="synthetic data from rLN-LN model",
         main=colnames(toycluster.rLNLN)[i],col="grey")
}
par(mfrow=c(1,1))
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