Package: phenopath (via r-universe)

November 25, 2026

Type Package

Title Genomic trajectories with heterogeneous genetic and environmental backgrounds

Version 1.38.0

Date 2017-10-24

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Description PhenoPath infers genomic trajectories (pseudotimes) in the presence of heterogeneous genetic and environmental backgrounds and tests for interactions between them.

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Imports Rcpp (>= 0.12.8), SummarizedExperiment, methods, stats, dplyr, tibble, ggplot2, tidyr

Suggests knitr, rmarkdown, forcats, testthat, BiocStyle, SingleCellExperiment

biocViews ImmunoOncology, RNASeq, GeneExpression, Bayesian, SingleCell, PrincipalComponent

LinkingTo Rcpp

RoxygenNote 6.0.1

VignetteBuilder knitr

Config/pak/sysreqs libicu-dev zlib1g-dev

Repository Bioconductor 3.24

Date/Publication 2026-11-23 22:39:14 UTC

RemoteUrl https://github.com/bioc/phenopath

RemoteRef RELEASE_3_24

RemoteSha 52cfdc710f11e6411c0ed6442ace7e4b2f11f4f3

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`clvm` *Fit a CLVM Model*

Description

Fit a covariate latent variable model using coordinate ascent variational inference.

Usage

```
clvm(y, x, maxiter = 10000, elbo_tol = 1e-05, thin = 1, verbose = TRUE,
  z_init = 1, tau_q = 1, tau_mu = 1, tau_c = 1, a = 2, b = 2,
  tau_alpha = 1, a_beta = 10, b_beta = 1, q = rep(0, nrow(y)),
  model_mu = FALSE, scale_y = TRUE)
```

Arguments

`y`	A N-by-G (dynamic) input matrix
`x`	A N-by-P (static) input matrix
`maxiter`	Maximum number of CAVI iterations
`elbo_tol`	The (percent) change in the ELBO below which it is considered converged
`thin`	The number of iterations to wait each time before re-calculating the elbo
`verbose`	Print convergence messages
`z_init`	The initialisation of the latent trajectory. Should be one of 1. A positive integer describing which principal component of the data should be used for initialisation (default 1), *or* 2. A numeric vector of length number of samples to be used directly for initialisation, *or* 3. The text character `"random"`, for random initialisation from a standard normal distribution.
`tau_q`	Hyperparameter tau_q

tau_mu	Hyperparameter tau_mu
tau_c	Hyperparameter tau_c
a	Hyperparameter a
b	Hyperparameter b
tau_alpha	Hyperparameter tau_alpha
a_beta	Hyperparameter a_beta
b_beta	Hyperparameter b_beta
q	Priors on the latent variables
model_mu	Logical - should a gene-specific intercept term be modelled?
scale_y	Logical - should the expression matrix be centre scaled?

Value

A list whose entries correspond to the converged values of the variational parameters along with the ELBO.

Examples

```
sim <- simulate_phenopath()
fit <- clvm(sim$y, matrix(sim$x))
```

---

interaction_effects *Get the interaction effect sizes*

Description

Get the interaction effect sizes

Usage

```
interaction_effects(phenopath_fit)
```

Arguments

phenopath_fit	An object of class phenopath_fit

Value

TODO

Examples

```
sim <- simulate_phenopath()
fit <- phenopath(sim$y, sim$x, elbo_tol = 1e-2)
beta <- interaction_effects(fit)
```

interaction_sds *Get the interaction standard deviations*

Description

Get the interaction standard deviations

Usage

```
interaction_sds(phenopath_fit)
```

Arguments

phenopath_fit	An object of class phenopath_fit

Value

TODO

Examples

```
sim <- simulate_phenopath()
fit <- phenopath(sim$y, sim$x, elbo_tol = 1e-2)
beta_sd <- interaction_sds(fit)
```

interactions *Tidy summary of interactions*

Description

Computes a tidy data frame of the interaction effects, pathway scores, and significance for each gene and covariate interaction.

Usage

```
interactions(phenopath_fit, n = 3)
```

Arguments

phenopath_fit	An object returned by a call to phenopath
n	The number of standard deviations away from 0 the posterior of the interaction effect sizes should be to be designated as significant

Value

A data frame with the following columns:

- `feature` The feature (usually gene)
- `covariate` The covariate, specified from the order originally supplied to the call to `phenopath`
- `interaction_effect_size` The effect size of the interaction ($beta$ from the statistical model)
- `significant` Boolean for whether the interaction effect is significantly different from 0
- `chi` The precision of the ARD prior on $beta$
- `pathway_loading` The pathway loading $lambda$, showing the overall effect for each gene marginalised over the covariate

Examples

```
sim <- simulate_phenopath()
fit <- phenopath(sim$y, sim$x, elbo_tol = 1e-2)
interactions(fit)
```

`phenopath` *PhenoPath - genomic trajectories with heterogeneous backgrounds*

Description

PhenoPath learns genomic trajectories in the presence of heterogenous environmental and genetic backgrounds. It takes input gene expression measurements that are modelled by a single unobserved factor (the "trajectory"). The regulation of genes along the trajectory is perturbed by an additional set of covariates (such as genetic or environmental status) allowing for the identification of covariate-trajectory interactions. The model is fitted using mean-field co-ordinate ascent variational inference.

Usage

```
phenopath(exprs_obj, x, sce_assay = "exprs", elbo_tol = 1e-05, z_init = 1,
  ...)
```

Arguments

`exprs_obj`	Input gene expression, either 1. An SummarizedExperiment object, *or* 2. A cell-by-gene matrix of normalised expression values in log form.
`x`	The covariate vector, either 1. The name of a column of `colData(exprs_obj)` if `exprs_obj` is an `SummarizedExperiment`, *or* 2. A numeric of factor vector of length equal to the number of cells, *or* 3. A formula from which to build a model matrix from `colData(exprs_obj)`, if `exprs_obj` is a SummarizedExperiment

sce_assay	The assay from exprs_obj to use as expression if exprs_object is a SummarizedExperiment
elbo_tol	The relative pct change in the ELBO below which is considered converged. See convergence section in details below.
z_init	The initialisation of the latent trajectory. Should be one of 1. A positive integer describing which principal component of the data should be used for initialisation (default 1), *or* 2. A numeric vector of length number of samples to be used directly for initialisation, *or* 3. The text character "random", for random initialisation from a standard normal distribution.
...	Additional arguments to be passed to clvm. See description below for more details or call ?clvm.

Details

Input expression

If an SummarizedExperiment is provided, assay(exprs_obj, sce_assay) is used. This is assumed to be in a form that is suitably normalised and approximately normal, such as the log of TPM values (plus a suitable offset) or similar.

Encoding covariates

See the vignette.

Convergence of variational inference

It is strongly recommended to call plot_elbo(phenopath_fit) after the fitting procedure to ensure the ELBO has approximately converged (though convergence metrics are printed during the fitting process). For a good introduction to variational inference see Blei, D.M., Kucukelbir, A. & McAuliffe, J.D., 2017. Variational Inference: A Review for Statisticians. Journal of the American Statistical Association.

Additional arguments

Addition arguments to clvm are passed via .... For full documentation, call ?clvm. Some notable options:

- thin - The ELBO is expensive to compute for larger datasets. The model will compute the ELBO and compare convergence every thin iterations.
- q and tau_q - Priors (such as capture times) for the latent space. Note that model_mu should be true if q is non-zero.
- scale_y By default the input expression is centre-scaled for each gene. If scale_y is FALSE this does not happen - but note that model_mu should be TRUE in such a case.

Value

An S3 structure with the following entries:

- m_z The converged mean estimates of the trajectory
- s_z The converged standard deviation estimates of z
- m_beta A P-by-G matrix of interaction coefficients
- s_beta A P-by-G matrix of interaction standard deviations

See Also

clvm for the underlying CAVI function, trajectory to extract the latent trajectory, interaction_effects for the interaction effect sizes, significant_interactions for the results of Bayesian significance testing.

Examples

```
sim <- simulate_phenopath() # returns a list with gene expression in y and covariates in x
fit <- phenopath(sim$y, sim$x, elbo_tol = 1e-2)

# Extract the trajectory
z <- trajectory(fit)
```

---

plot_elbo *Plots the ELBO*

Description

Plots the evidence lower bound (ELBO) as a function of iterations

Usage

```
plot_elbo(fit)
```

Arguments

fit	An object returned by a call to phenopath

Value

A ggplot2 object of the ELBO against the number of iterations

Examples

```
sim <- simulate_phenopath()
fit <- phenopath(sim$y, sim$x)
plot_elbo(fit)
```

print.phenopath_fit *Print a PhenoPath fit*

Description

Print a PhenoPath fit

Usage

```
## S3 method for class 'phenopath_fit'
print(x, ...)
```

Arguments

x	A phenopath_fit returned by a call to phenopath
...	Additional arguments

Value

A string representation of a phenopath_fit object.

Examples

```
sim <- simulate_phenopath()
fit <- phenopath(sim$y, sim$x, elbo_tol = 1e-2)
print(fit)
```

significant_interactions *Significance testing for interaction features*

Description

Given the results of clvm, decide which features show significant iteractions between the latent trajectory and covariates. Significant features are designated as those where the variational mean of the interaction coefficient falls outside the $n\sigma$ interval of 0.

Usage

```
significant_interactions(phenopath_fit, n = 3)
```

Arguments

phenopath_fit	The results of a call to clvm
n	The number of standard deviations away from 0 the posterior estimate of beta should be to be designated significant.

Value

A logical vector describing whether each feature passes the significance test.

Examples

```
sim <- simulate_phenopath()
fit <- phenopath(sim$y, sim$x, elbo_tol = 1e-2)
signints <- significant_interactions(fit)
```

`simulate_phenopath` *Simulate from phenopath model*

Description

Simulate synthetic data from the phenopath model, where each gene is sampled from one of four types (see details).

Usage

```
simulate_phenopath(N = 100, G = 40, G_de = NULL, G_pst = NULL,
  G_pst_beta = NULL, G_de_pst_beta = NULL)
```

Arguments

`N`	Number of samples to simulate
`G`	Number of genes to simulate. Should be divisible by 4
`G_de`	Number of genes to simulate from the *differential expression* regime
`G_pst`	Number of genes to simulate from the *pseudotime* regime
`G_pst_beta`	Number of genes to simulate from the *pseudotime + beta interactions* regime
`G_de_pst_beta`	Number of genes to simulate from the *differential expression + pseudotime + interactions* regime

Details

Will simulate data for a number of genes corresponding to one of four regimes:

1. `de` ('differential expression'), where the gene has no association to the latent trajectory and exhibits differential expression only
2. `pst` ('pseudotime'), the gene shows pseudotemporal regulation but no differential regulation
3. `pst_beta` ('pseudotime + beta interactions'), the gene shows pseudotemporal regulation that is modulated by covariate interactions
4. `de_pst_beta` ('differential expression + pseudotime + interactions), all of the above

Value

A list with four entries:

- `parameters` A `tibble` with an entry for each gene and a column for each parameter value and simulation regime (see details).
- `y` The N-by-G simulated gene expression matrix.
- `x` The N-length vector of covariates.
- `z` The N-length vector of pseudotimes.

Examples

```
sim <- simulate_phenopath()
```

`trajectory` *Get the latent PhenoPath trajectory*

Description

Get the latent PhenoPath trajectory

Usage

```
trajectory(phenopath_fit)
```

Arguments

`phenopath_fit`	An object of class `phenopath_fit`

Value

A vector of latent trajectory (pseudotime) values

Examples

```
sim <- simulate_phenopath()
fit <- phenopath(sim$y, sim$x, elbo_tol = 1e-2)
z <- trajectory(fit)
```

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