

Package ‘iCARH’

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Title Integrative Conditional Autoregressive Horseshoe Model

Description Implements the integrative conditional autoregressive horseshoe model

discussed in Jendoubi, T., Ebbels, T.M. Integrative analysis of time course metabolic data and biomarker discovery.

BMC Bioinformatics 21, 11 (2020) <[doi:10.1186/s12859-019-3333-0](https://doi.org/10.1186/s12859-019-3333-0)>.

The model consists in three levels: Metabolic pathways level modeling interdependencies between variables via a conditional auto-regressive (CAR) component, integrative analysis level to identify potential associations between heterogeneous omic variables via a Horseshoe prior and experimental

design level to capture experimental design conditions through a mixed-effects model.

The package also provides functions to simulate data from the model, construct pathway matrices, post process and plot model parameters.

Depends rstan, MASS, stats, ggplot2, glue

Imports RCurl, KEGGgraph, igraph, reshape2, mc2d, abind, Matrix

Suggests knitr, rmarkdown

VignetteBuilder knitr

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Contents

iCARH.getBeta	2
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iCARH.getPathwaysMat	3
iCARH.model	4
iCARH.params	5
iCARH.plotBeta	6
iCARH.simulate	8
Index	10

iCARH.getBeta	<i>Return model parameters</i>
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Description

Group of functions to return model parameters of interest

Usage

```
iCARH.getBeta(fit)

iCARH.getARCoeff(fit)

iCARH.getTreatmentEffect(fit)

iCARH.getPathwaysCoeff(fit, path.names = NULL)

iCARH.getDataImputation(fit)
```

Arguments

fit	Object returned by iCARH.model
path.names	pathway names

Value

the iCARH.get[*] functions return a an array with corresponding model parameters MCMC draws.

Functions

- iCARH.getBeta: Get beta parameter draws from all chains combined
- iCARH.getARCoeff: return theta coefficients
- iCARH.getTreatmentEffect: return alpha coefficients
- iCARH.getPathwaysCoeff: return phi coefficients
- iCARH.getDataImputation: return complete data (including imputed data)

Examples

```

data.sim = iCARH.simulate(4, 10, 14, 8, 2, path.probs=0.3, Zgroupeff=c(0,4),
beta.val=c(1,-1,0.5, -0.5))
XX = data.sim$XX
Y = data.sim$Y
Z = data.sim$Z
pathways = data.sim$pathways

rstan_options(auto_write = TRUE)
options(mc.cores = 2)
fit = iCARH.model(XX, Y, Z, groups=rep(c(0,1), each=5), pathways,
control = list(adapt_delta = 0.99, max_treedepth=10), iter = 2, chains = 2)
if(!is.null(fit$icarh))
iCARH.getBeta(fit)

```

iCARH.getPathwaysMat	<i>Builds pathways adjacency matrices</i>
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Description

Builds pathways adjacency matrices from specified KEGG identifiers. Returns a list of pathway adjacency matrices based on shortest paths.

Usage

```
iCARH.getPathwaysMat(keggid, org)
```

Arguments

keggid	KEGG identifiers as specified in KEGG. keggid is list that might contain multiple identifiers per metabolite.
org	organism

Value

list of pathway matrices based on shortest paths between two metabolites

Examples

```

keggid = list("C08363")
iCARH.getPathwaysMat(keggid, "rno")
gc()
keggid = list("Unk1", "C00350", c("C08363", "C01245"))
iCARH.getPathwaysMat(keggid, "rno")
gc()

```

iCARH.model

*Runs the integrative CAR Horseshoe model***Description**

Infers treatment effects, association with heterogeneous omic variables, pathway perturbation among other parameters (e.g. time dependence). Regression coefficients (beta parameter) are initialized using a univariate regression ignoring time and metabolite dependence.

Usage

```
iCARH.model(
  X,
  Y = NULL,
  drug,
  groups = NULL,
  pathways,
  tau = 1.2,
  NA_value = -99999,
  init = T,
  ...
)
```

Arguments

X	the metabolomics time-course data with dimensions timepoints x observations x variables
Y	the additional omic time-course data with dimensions timepoints x observations x variables
drug	treatment effect. Could be either continuous (an administered drug or other external factor) or binary (cases vs controls). In the binary case the groups argument can be safely removed. NA values not allowed in drug. Dimensions are timepoints x observations
groups	grouping vector (binary). Use when drug is continuous.
pathways	pathway adjacency matrices as returned by iCARH.getPathwaysMat
tau	global sparsity parameter τ as in Jendoubi, T., & Ebbels, T. (2018)
NA_value	NA values are incompatible with stan. This is a wrapper to encode missing values in X and Y. NAs will be replaced by NA_value and will be inferred (only for X and Y data).
init	If TRUE use iCARH provided initialization function. Passed to Stan otherwise. Please see Stan manual on init possible values.
...	additional stan parameters

Value

stan object

Examples

```

data.sim = iCARH.simulate(4, 8, 10, 2, 2, path.probs=0.3, Zgroupeff=c(0,4),
beta.val=c(1,-1,0.5, -0.5))
XX = data.sim$XX
Y = data.sim$Y
Z = data.sim$Z
pathways = data.sim$pathways

rstan_options(auto_write = TRUE)
options(mc.cores = 2)
fit = iCARH.model(XX, Y, Z,groups=rep(c(0,1), each=4), pathways,
  control = list(adapt_delta = 0.99, max_treedepth=10), iter = 2, chains = 2)

```

iCARH.params

*Summarize and return model parameters***Description**

Group of functions to summarize and return model parameters of interest

Usage

```

iCARH.params(
  fit,
  pars = c("theta", "alpha", "beta", "phi"),
  path.names = NULL,
  prob = 0.95,
  use_cache = TRUE,
  digits = 2,
  ...
)

```

Arguments

<code>fit</code>	Object returned by iCARH.model
<code>pars</code>	Parameters of interest ("theta","alpha","beta","phi"). All parameters by default.
<code>path.names</code>	Specify pathway names.
<code>prob</code>	Confidence level. Defaults to 0.95.
<code>use_cache</code>	passed to stan summary method.
<code>digits</code>	The number of significant digits for printing out the summary; defaults to 2. The effective sample size is always rounded to integers.
<code>...</code>	not used currently

Value

contain summaries for all chains. Included in the summaries are means, standard deviations (Est.Error), effective sample sizes (Eff.Sample), and split Rhats. Monte Carlo standard errors (MC.Error) are also reported.

Functions

- iCARH.params: Summary of model parameters

Examples

```
data.sim = iCARH.simulate(4, 10, 14, 8, 2, path.probs=0.3, Zgroupeff=c(0,4),
  beta.val=c(1,-1,0.5, -0.5))
XX = data.sim$XX
Y = data.sim$Y
Z = data.sim$Z
pathways = data.sim$pathways

rstan_options(auto_write = TRUE)
options(mc.cores = 2)
fit = iCARH.model(XX, Y, Z, groups=rep(c(0,1), each=5), pathways,
  control = list(adapt_delta = 0.99, max_treedepth=10), iter = 2, chains = 2)
if(!is.null(fit$icarh))
  iCARH.params(fit)
```

iCARH.plotBeta

Postprocess and plot model parameters

Description

Group of functions to postprocess and plot model parameters of interest, compute WAIC (Watanabe-Akaike Information Criterion) and MADs (Mean Absolute Deviation) for posterior predictive checks and check normality assumptions.

Usage

```
iCARH.plotBeta(fit, indx = TRUE, indy = TRUE)

iCARH.plotARCoeff(fit, indx = TRUE)

iCARH.plotTreatmentEffect(fit, indx = TRUE)

iCARH.plotPathwayPerturbation(fit, path.names, indpath = TRUE)

iCARH.plotDataImputation(fit, indx = T, indy = T, plotx = T, ploty = T, ...)
```

```

iCARH.checkRhats(fit)

iCARH.checkNormality(fit)

iCARH.waic(fit)

iCARH.mad(fit)

```

Arguments

<code>fit</code>	object returned by <code>iCARH.model</code>
<code>indx</code>	vector to specify X variables to plot. Selects all variables of X by default.
<code>indy</code>	vector to specify Y variables to plot. Selects all variables of Y by default.
<code>path.names</code>	pathway names
<code>indpath</code>	vector to specify pathways to plot. Selects all pathways by default.
<code>plotx</code>	plot X data imputation?
<code>ploty</code>	plot Y data imputation?
<code>...</code>	passed to <code>ggplot2::geom_violin</code>

Value

the `iCARH.plot[*]` functions return a `ggplot` graph object. `iCARH.checkNormality` returns the normalized data. `iCARH.waic` and `iCARH.mad` return corresponding `waic` (scalar) and `mad` (vector of $J * (J + 1) / 2$) values. `iCARH.checkRhats` checks model convergence.

Functions

- `iCARH.plotBeta`: Plot boxplots of posterior densities of β coefficients.
- `iCARH.plotARCoeff`: Plot boxplots of posterior densities of theta (time effect) coefficients.
- `iCARH.plotTreatmentEffect`: Plot boxplots of posterior densities of treatment effect coefficients.
- `iCARH.plotPathwayPerturbation`: Plot posterior densities of pathway perturbation parameters
- `iCARH.plotDataImputation`: Plot imputed values
- `iCARH.checkRhats`: check model convergence and return Rhat coefficients
- `iCARH.checkNormality`: Check normality assumptions. Returns normalized data and performs quantile-quantile plot
- `iCARH.waic`: Compute Watanabe-Akaike Information Criterion (WAIC)
- `iCARH.mad`: Compute MADs (Mean Absolute Deviation) between true covariance matrix and inferred covariance matrix for posterior predictive checks

Examples

```
data.sim = iCARH.simulate(4, 10, 14, 8, 2, path.probs=0.3, Zgroupeff=c(0,4),
beta.val=c(1,-1,0.5, -0.5))
XX = data.sim$XX
Y = data.sim$Y
Z = data.sim$Z
pathways = data.sim$pathways

rstan_options(auto_write = TRUE)
options(mc.cores = 2)
fit = iCARH.model(XX, Y, Z, groups=rep(c(0,1), each=5), pathways,
control = list(adapt_delta = 0.99, max_treedepth=10), iter = 2, chains = 2)
if(!is.null(fit$icarh))
gplot = iCARH.plotBeta(fit, indx=1:3, indy=1:2)
```

iCARH.simulate

Simulates longitudinal data based on the iCARH model.

Description

Simulates longitudinal data based on the iCARH model. Returns two types of datasets with relevant parameters (see below).

Usage

```
iCARH.simulate(
  Tp,
  N,
  J,
  P,
  K,
  path.names = NULL,
  path.probs = FALSE,
  pathway.perturb.ratio = 0.5,
  Ygroupeff = NULL,
  Zgroupeff = NULL,
  fe = 0,
  num.corr.y = 0,
  beta.val = NULL,
  sigma2 = 1,
  arz = 0.7,
  sdx = 0.01
)
```

Arguments

Tp	number of time points
N	number of samples (by default first N/2 controls and last N/2 cases)
J	number of metabolites
P	number of pathways (will probably change)
K	number of bacteria profiles (Y variables)
path.names	pathways to sample from as specified in KEGG. If not specified, path.probs will be considered.
path.probs	if TRUE, KEGG like density of pathways per metabolite is used to sample from. If scalar, path.probs is the expected ratio of metabolites in each pathway. Needs to be specified if path.names is not.
pathway.perturb.ratio	expected ratio of perturbed pathways
Ygroupeff	vector of 2xK variables (treatment effect on Y variables)
Zgroupeff	vector of 2 variables for treatment effect
fe	fixed effect
num.corr.y	number of correlated Y variables. The last num.corr.y will be highly correlated to the first num.corr.y variables
beta.val	beta values (regression coefficients) to sample from. Values will be randomly sampled if not specified.
sigma2	individual variance of metabolites
arz	autoregressive coefficient for treatment simulation
sdz	noise for autoregressive process, recommended value is 0.01

Value

list with the following objects :

XX	metabolomics data, X data
Y	additional omic data, Y data
Z	treatment
beta	effects of Y variables on X variables, column K+1 represents effect of treatment on X variables
pathways	pathway adjacency matrices
path.perturb	which pathways are perturbed?
phi	"spatial" dependence parameter, indicative of pathway perturbation
arx	autoregressive coefficients for X data
ary	autoregressive coefficients for Y data

Examples

```
data.sim = iCARH.simulate(4, 8, 10, 2, 2, path.probs=0.3, Zgroupeff=c(0,4),
beta.val=c(1,-1,0.5, -0.5))
```

Index

`iCARH.checkNormality (iCARH.plotBeta)`, 6
`iCARH.checkRhats (iCARH.plotBeta)`, 6
`iCARH.getARCoeff (iCARH.getBeta)`, 2
`iCARH.getBeta`, 2
`iCARH.getDataImputation`
 (`iCARH.getBeta`), 2
`iCARH.getPathwaysCoeff (iCARH.getBeta)`,
 2
`iCARH.getPathwaysMat`, 3
`iCARH.getTreatmentEffect`
 (`iCARH.getBeta`), 2
`iCARH.mad (iCARH.plotBeta)`, 6
`iCARH.model`, 4
`iCARH.params`, 5
`iCARH.plotARCoeff (iCARH.plotBeta)`, 6
`iCARH.plotBeta`, 6
`iCARH.plotDataImputation`
 (`iCARH.plotBeta`), 6
`iCARH.plotPathwayPerturbation`
 (`iCARH.plotBeta`), 6
`iCARH.plotTreatmentEffect`
 (`iCARH.plotBeta`), 6
`iCARH.simulate`, 8
`iCARH.waic (iCARH.plotBeta)`, 6