

# Package: kangar00 (via r-universe)

August 23, 2024

**Type** Package

**Title** Kernel Approaches for Nonlinear Genetic Association Regression

**Version** 1.4.1

**Date** 2022-12-05

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**URL** <https://kangar00.manitz.org/>

**BugReports** <https://github.com/jmanitz/kangar00/issues>

**Description** Methods to extract information on pathways, genes and various single-nucleotide polymorphisms (SNPs) from online databases. It provides functions for data preparation and evaluation of genetic influence on a binary outcome using the logistic kernel machine test (LKMT). Three different kernel functions are offered to analyze genotype information in this variance component test: A linear kernel, a size-adjusted kernel and a network-based kernel (Friedrichs et al., 2017, <doi:10.1155/2017/6742763>).

**License** GPL-2

**Encoding** UTF-8

**Collate** 'pathway.r' 'GWASdata.r' 'data.R' 'get\_network\_matrix.r'  
'kernel.r' 'lkmt.r'

**Depends** R (>= 3.5.0)

**Imports** methods, bigmemory, sqldf, biomaRt, KEGGgraph, CompQuadForm,  
data.table, lattice, igraph

**LazyData** true

**Suggests** testthat

**NeedsCompilation** no

**RoxygenNote** 7.2.2

**Repository** <https://jmanitz.r-universe.dev>

**RemoteUrl** <https://github.com/jmanitz/kangar00>

**RemoteRef** HEAD

**RemoteSha** 1055f38042e3e244cb76685a2c991ae0a0c2e019

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kangar00-package	<i>kangar00 package</i>
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## Description

This package includes methods to extract information on pathways, genes and SNPs from online databases and to evaluate these data using the logistic kernel machine test (LKMT) (Liu et al. 2008).

We defined SNP sets representing genes and whole pathways using knowledge on gene membership and interaction from the Kyoto Encyclopedia of Genes and Genomes (KEGG) database (Kanehisa et al. 2014). SNPs are mapped to genes via base pair positions of SNPs and transcript start and end points of genes as documented in the Ensemble database (Cunningham et al. 2015).

In the LKMT, we employed the linear kernel (Wu et al. 2010) as well as two more advanced kernels, adjusting for size bias in the number of SNPs and genes in a pathway (size-adjusted kernels), and incorporating the network structure of genes within the pathway (pathway kernels), respectively (Freytag et al. 2012, 2014). P-values are derived in a variance component test using a moment matching method (Schaid, 2010) or Davies' algorithm (Davies, 1980).

## Details

Package: kangar00  
Version: 1.1  
Date: 2017-08-07  
License: GPL-2

## Author(s)

Juliane Manitz [aut], Stefanie Friedrichs [aut], Patricia Burger [aut], Benjamin Hofner [aut], Ngoc Thuy Ha [aut], Saskia Freytag [ctb], Heike Bickeboeller [ctb]  
Maintainer: Juliane Manitz <r@manitz.de>

## References

- Cunningham F, Ridwan Amode M, Barrell D, et al. Ensembl 2015. Nucleic Acids Research 2015 43 Database issue:D662-D669
- Davies R: Algorithm as 155: the distribution of a linear combination of chi-2 random variables. J R Stat Soc Ser C 1980, 29:323-333.
- Freytag S, Bickeboeller H, Amos CI, Kneib T, Schlather M: A Novel Kernel for Correcting Size Bias in the Logistic Kernel Machine Test with an Application to Rheumatoid Arthritis. Hum Hered. 2012, 74(2):97-108.
- Freytag S, Manitz J, Schlather M, Kneib T, Amos CI, Risch A, Chang-Claude J, Heinrich J, Bickeboeller H: A network-based kernel machine test for the identification of risk pathways in genome-wide association studies. Hum Hered. 2013, 76(2):64-75.
- Friedrichs S, Manitz J, Burger P, Amos CI, Risch A, Chang-Claude JC, Wichmann HE, Kneib T, Bickeboeller H, Hofner B: Pathway-Based Kernel Boosting for the Analysis of Genome-Wide Association Studies. Computational and Mathematical Methods in Medicine. 2017(6742763), 1-17. doi:10.1155/2017/6742763.
- Kanehisa, M., Goto, S., Sato, Y., Kawashima, M., Furumichi, M., and Tanabe, M.; Data, information, knowledge and principle: back to metabolism in KEGG. Nucleic Acids Res. 42, D199-D205 (2014).

- Liu D, Ghosh D, Lin X. Estimation and testing for the effect of a genetic pathway on a disease outcome using logistic kernel machine regression via logistic mixed models. BMC Bioinformatics. 2008 9:292.
- Schaid DJ: Genomic similarity and kernel methods I: advancements by building on mathematical and statistical foundations. Hum Hered 2010, 70:109-131.
- Wu MC, Kraft P, Epstein MP, Taylor DM, Chanock SJ, Hunter DJ, Lin X: Powerful SNP-Set Analysis for Case-Control Genome-Wide Association Studies. Am J Hum Genet 2010, 86:929-42

---

anno

*Example annotation file for three pathways.*

---

### Description

A dataset containing an annotation example for 4056 SNPs in three different pathways.

### Usage

```
data(anno)
```

### Format

A data frame with 4056 rows and 5 variables:

**pathway** includes KEGG identifiers of three example pathways

**gene** names of genes in the pathways

**chr** specifies the chromosome

**snp** includes rs-numbers of example SNPs

**position** gives positions of example SNPs

### Source

simulated data

### Examples

```
data(anno)
head(anno)
# create gwas object
data(pheno)
data(geno)
gwas <- new('GWASdata', pheno=pheno, geno=geno, anno=anno, desc="some study")
```

calc\_kernel

*Calculate the kernel-matrix for a pathway***Description**

Uses individuals' genotypes to create a [kernel](#) object including the calculated kernel matrix for a specific [pathway](#). Each numeric value within this matrix is calculated from two individuals' genotypevectors of the SNPs within the [pathway](#) by a kernel function. It can be interpreted as the genetic similarity of the individuals. Association between the [pathway](#) and a binary phenotype (case-control status) can be evaluated in the logistic kernel machine test, based on the [kernel](#) object. Three kernel functions are available.

**Usage**

```
## S4 method for signature 'GWASdata'
calc_kernel(
  object,
  pathway,
  knots = NULL,
  type = c("lin", "sia", "net"),
  calculation = c("cpu", "gpu"),
  ...
)

## S4 method for signature 'GWASdata'
lin_kernel(object, pathway, knots = NULL, calculation = c("cpu", "gpu"), ...)

## S4 method for signature 'GWASdata'
sia_kernel(object, pathway, knots = NULL, calculation = c("cpu", "gpu"), ...)

## S4 method for signature 'GWASdata'
net_kernel(object, pathway, knots = NULL, calculation = c("cpu", "gpu"), ...)
```

**Arguments**

object	GWASdata object containing the genotypes of the individuals for which a <a href="#">kernel</a> will be calculated.
pathway	object of the class <a href="#">pathway</a> specifying the SNP set for which a <a href="#">kernel</a> will be calculated.
knots	GWASdata object, if specified a <a href="#">kernel</a> will be computed.
type	character indicating the <a href="#">kernel</a> type: Use 'lin' to specify the linear kernel, 'sia' for the size-adjusted or 'net' for the network-based kernel.
calculation	character specifying if the kernel matrix is computed on CPU or GPU.
...	further arguments to be passed to <a href="#">kernel</a> computations.

## Details

Different types of kernels can be constructed:

- type='lin' creates the linear kernel assuming additive SNP effects to be evaluated in the logistic kernel machine test.
- type='sia' calculates the size-adjusted kernel which takes into consideration the numbers of SNPs and genes in a [pathway](#) to correct for size bias.
- type='net' calculates the network-based kernel. Here not only information on gene membership and gene/pathway size in number of SNPs is incorporated, but also the interaction structure of genes in the [pathway](#).

For more details, check the references.

## Value

Returns an object of class [kernel](#), including the similarity matrix of the [pathway](#) for the considered individuals.

If knots are specified low-rank kernel of class a `lowrank_kernel` will be returned, which is not necessarily quadratic and symmetric.

## Methods (by class)

- `lin_kernel(GWASdata)`:
- `sia_kernel(GWASdata)`:
- `net_kernel(GWASdata)`:

## Author(s)

Stefanie Friedrichs, Juliane Manitz

## References

- Wu MC, Kraft P, Epstein MP, Taylor DM, Chanock SJ, Hunter DJ, Lin X Powerful SNP-Set Analysis for Case-Control Genome-Wide Association Studies. *Am J Hum Genet* 2010, 86:929-42
- Freytag S, Bickeboeller H, Amos CI, Kneib T, Schlather M: A Novel Kernel for Correcting Size Bias in the Logistic Kernel Machine Test with an Application to Rheumatoid Arthritis. *Hum Hered.* 2012, 74(2):97-108.
- Freytag S, Manitz J, Schlather M, Kneib T, Amos CI, Risch A, Chang-Claude J, Heinrich J, Bickeboeller H: A network-based kernel machine test for the identification of risk pathways in genome-wide association studies. *Hum Hered.* 2013, 76(2):64-75.

## See Also

[kernel-class,pathway](#)

**Examples**

```
data(gwas)
data(hsa04020)
lin_kernel <- calc_kernel(gwas, hsa04020, knots=NULL, type='lin', calculation='cpu')
summary(lin_kernel)
net_kernel <- calc_kernel(gwas, hsa04020, knots=NULL, type='net', calculation='cpu')
summary(net_kernel)
```

---

geno

*Example genotypes for 50 individuals.*

---

**Description**

A matrix containing example genotypes for 4056 SNPs of 50 individuals. Column names give the rs-numbers of 4056 example SNPs, row names the identifiers of 50 example individuals.

**Usage**

```
data(geno)
```

**Format**

A matrix with 5 rows and 4056 columns:

each entry in the matrix represents a simulated minor allele count for the corresponding SNP and individual.

**Source**

simulated data

**Examples**

```
data(geno)
head(geno)
# create gwas object
data(pheno)
data(anno)
gwas <- new('GWASdata', pheno=pheno, geno=geno, anno=anno, desc="some study")
```

---

`get_anno,snp_info,pathway_info-method`*Annotates SNPs via genes to pathways*

---

## Description

A function to create the annotation for a `GWASdata` object. It combines a `snp_info` and a `pathway_info` object into an annotation `data.frame` used for `pathway` analysis on GWAS. SNPs are assigned to pathways via gene membership.

## Usage

```
## S4 method for signature 'snp_info,pathway_info'  
get_anno(object1, object2, ...)
```

## Arguments

<code>object1</code>	A <code>snp_info</code> object with SNP information as returned by the <code>snp_info</code> function. The included <code>data.frame</code> contains the columns 'chr', 'position' and 'snp'.
<code>object2</code>	A <code>pathway_info</code> object with information on genes contained in pathways. It is created by the <code>pathway_info</code> function and contains a <code>data.frame</code> with columns 'pathway', 'gene_start', 'gene_end', 'chr', 'gene'.
<code>...</code>	further <code>argdata(hsa04020)</code>

## Value

A `data.frame` mapping SNPs to genes and genes to pathways. It includes the columns 'pathway', 'gene', 'chr', 'snp' and 'position'.

## Author(s)

Stefanie Friedrichs, Saskia Freytag, Ngoc-Thuy Ha

## See Also

[snp\\_info](#), [pathway\\_info](#)

## Examples

```
data(hsa04022_info) # pathway_info('hsa04020')  
data(rs10243170_info)# snp_info("rs10243170")  
get_anno(rs10243170_info, hsa04022_info)
```



---

get\_network\_matrix      *Function to calculate the network matrix for a [pathway](#) object*

---

### Description

get\_network\_matrix creates the adjacency matrix representing the gene-gene interaction structure within a particular [pathway](#). Note that a KEGG kgml file is downloaded and saved in the working directory.

### Usage

```
## S4 method for signature 'pathway'
get_network_matrix(object, directed = TRUE, method = "auto")
```

### Arguments

object	A <a href="#">pathway</a> object identifying the pathway for which gene interaction information should be extracted. Here, KEGG IDs of format 'hsa00100' are used and information is downloaded from the KEGG database.
directed	A logical argument, stating whether the network matrix should return directed (TRUE) or undirected (FALSE) links.
method	Download method to be used for downloading files, passed to via <code>KEGGgraph::retrieveKGML</code> to <code>utils::download.file</code> function. Currently supports 'auto' (default), 'internal', 'wininet' (Windows only), 'libcurl', 'wget' and 'curl'.

### Value

get\_network\_matrix returns the modified [pathway](#) object, where the slots `adj` and `sign` are altered according to the downloaded information in the KEGG kgml file.

### Author(s)

Stefanie Friedrichs, Patricia Burger, Juliane Manitz

---

gwas      *Example [GWASdata](#) object.*

---

### Description

An object of type `GWASdata` containing the example files for annotation, phenotypes and genotypes.

### Usage

```
data(gwas)
```

**Format**

An object of class [GWASdata](#):

**geno** contains example genotypes

**anno** example annotation for three pathways

**pheno** exemplary phenotypes for all 'genotyped' individuals

**desc** a description of the GWAS study, here 'example study'

**Source**

simulated data

**Examples**

```
# create gwas object
data(pheno)
data(geno)
data(anno)
gwas <- new('GWASdata', pheno=pheno, geno=geno, anno=anno, desc="some study")
```

---

GWASdata

*S4 class for an object representing a Genome-wide Association Study.*

---

**Description**

S4 class for an object representing a Genome-wide Association Study.

'GWASdata' is a GWASdata object constructor.

show displays basic information on [GWASdata](#) object

summary summarizes the content of a [GWASdata](#) object and gives an overview about the information included in a [GWASdata](#) object. Summary statistics for phenotype and genotype data are calculated.

GeneSNPsize creates a data.frame of [pathway](#) names with numbers of snps and genes in each [pathway](#).

**Usage**

```
GWASdata(object, ...)

## S4 method for signature 'ANY'
GWASdata(geno, anno, pheno = NULL, desc = "")

## S4 method for signature 'GWASdata'
show(object)

## S4 method for signature 'GWASdata'
summary(object)

## S4 method for signature 'GWASdata'
GeneSNPsize(object)
```

**Arguments**

object	A <a href="#">GWASdata</a> object.
...	Further arguments can be added to the function.
geno	An object of any type, including the genotype information.
anno	A <code>data.frame</code> containing the annotation file for the <code>GWASdata</code> object.
pheno	A <code>data.frame</code> specifying individual IDs, phenotypes and covariates to be included in the regression model.
desc	A character giving the GWAS description, e.g. name of study.

**Methods (by generic)**

- `GeneSNPsize(GWASdata)`: creates a `data.frame` of [pathway](#) names with numbers of snps and genes in each pathway.

**Slots**

geno	An object of any type, including genotype information. The format needs to be one line per individual and on column per SNP in minor-allele coding (0,1,2). Other values between 0 and 2, as from impute dosages, are allowed. Missing values must be imputed prior to creation of a <code>GWASdata</code> object.
anno	A <code>data.frame</code> mapping SNPs to genes and genes to pathways. Needs to include the columns 'pathway' (pathway ID, e.g. hsa number from KEGG database), 'gene' (gene name (hgnc_symbol)), 'chr' (chromosome), 'snp' (rsnumber) and 'position' (base pair position of SNP).
pheno	A <code>data.frame</code> specifying individual IDs, phenotypes and covariates to be included in the regression model e.g. ID, pheno, sex, pack.years. Note: IDs have to be in the first column!
desc	A character giving the GWAS description, e.g. name of study.

**Author(s)**

Juliane Manitz, Stefanie Friedrichs

**Examples**

```
# create gwas data object
data(pheno)
data(geno)
data(anno)
gwas <- new('GWASdata', pheno=pheno, geno=geno, anno=anno, desc="some study")
# show and summary methods
gwas
summary(gwas)
# SNPs and genes in pathway
GeneSNPsize(gwas)
```

---

hsa04020

*Example [pathway](#) object for pathway hsa04020.*

---

### Description

An object of class [pathway](#) for the pathway with KEGG identifier hsa04020.

### Usage

```
data(hsa04020)
```

### Format

A [pathway](#) object including 180 genes.

**id** KEGG identifier of the example pathways

**adj** gives the quadratic adjacency matrix for the pathway and with that the network topology.  
Matrix dimensions equal the number of genes in the pathway

**sign** includes a vector of signs to distinguish activations and inhibitions in the adjacency matrix

### Source

simulated data and Ensembl extract

---

hsa04022\_info

*Example [pathway\\_info](#) object for pathway hsa04022.*

---

### Description

An object of class [pathway\\_info](#) for the [pathway](#) with KEGG identifier hsa04020.

### Usage

```
data(hsa04022_info)
```

### Format

A [pathway\\_info](#) object including information on 163 genes.

**info** a data frame including information on genes included in pathway. Has columns 'pathway', 'gene\_start', 'gene\_end', 'chr', and 'gene'

### Source

Ensembl extract

**Examples**

```
## Not run:
pathway_info('hsa04020')

## End(Not run)
```

---

kernel-class	<i>An S4 class representing a kernel matrix calculated for a pathway</i>
--------------	--

---

**Description**

An S4 class representing a kernel matrix calculated for a pathway

show displays the kernel object briefly

summary generates a kernel object summary including the number of individuals and genes for the [pathway](#)

plot creates an image plot of a kernel object

**Usage**

```
## S4 method for signature 'kernel'
show(object)

## S4 method for signature 'kernel'
summary(object)

## S4 method for signature 'kernel,missing'
plot(x, y = NA, hclust = FALSE, ...)
```

**Arguments**

object	An object of class kernel
x	the kernel object to be plotted.
y	missing (placeholder).
hclust	logical, indicating whether a dendrogram should be added.
...	further arguments to be passed to the function.

**Slots**

type A character representing the kernel type: Use 'lin' for linear kernel, 'sia' for the size-adjusted or 'net' for the network-based kernel.

kernel A kernel matrix of dimension equal to the number of individuals

pathway A [pathway](#) object

**Author(s)**

Juliane Manitz

**Examples**

```
data(gwas)
data(hsa04020)
net_kernel <- calc_kernel(gwas, hsa04020, knots=NULL, type='net', calculation='cpu')

show(net_kernel)
summary(net_kernel)
plot(net_kernel, hclust=TRUE)
```

---

lkmt-class

*An S4 class to represent the variance component test.*


---

**Description**

An S4 class to represent the variance component test.

show displays basic information on lkmt object

summary generates a lkmt object summary including the used kernel, pathway and the test result

**Usage**

```
## S4 method for signature 'lkmt'
show(object)
```

```
## S4 method for signature 'lkmt'
summary(object)
```

**Arguments**

object            An object of class lkmt.

**Value**

show Basic information on lkmt object.

summary Summarized information on lkmt object.

**Slots**

formula A formula stating the regression nullmodel that will be used in the variance component test.

kernel An object of class [kernel](#) representing the similarity matrix of the individuals based on which the pathways influence is evaluated.

**GWASdata** An object of class [GWASdata](#) including the data on which the test is conducted.

**statistic** A vector giving the value of the variance component test statistic.

**df** A vector containing the number of degrees of freedom.

**p.value** A vector giving the p-value calculated for the [pathway](#) object considered in the variance component test.

For details on the variance component test see the references.

### Author(s)

Juliane Manitz, Stefanie Friedrichs

### References

- Liu D, Lin X, Ghosh D: Semiparametric regression of multidimensional genetic pathway data: least-squares kernel machines and linear mixed models. *Biometrics* 2007, 63(4):1079-88.
- Wu MC, Kraft P, Epstein MP, Taylor DM, Chanock SJ, Hunter DJ, Lin X: Powerful SNP-Set Analysis for Case-Control Genome-Wide Association Studies. *Am J Hum Genet* 2010, 86:929-42

### Examples

```
data(hsa04020)
data(gwas)
# compute kernel
net_kernel <- calc_kernel(gwas, hsa04020, knots=NULL, type='net', calculation='cpu')
# perform LKMT
res <- lkmt_test(pheno ~ sex + age, net_kernel, gwas, method='satt')
# show and summary methods
show(res)
summary(res)
# summary method
summary(lkmt.net.kernel.hsa04020)
```

---

lkmt.net.kernel.hsa04020

*Example test result for the network-based [kernel](#) for [pathway](#) hsa04020.*

---

### Description

An object of class [lkmt](#) containing exemplary test results for an application of the logistic kernel machine test, derived from the example data.

### Usage

```
data(lkmt.net.kernel.hsa04020)
```

**Format**

An object of class `lkmt` for the network-based `kernel` and the `pathway` `hsa04020`.

**formular** gives a formular defining the nullmodel used in the logistic kernel machine test

**kernel** includes the `kernel` object of the `pathway` to be evaluated

**GWASdata** gives the `GWASdata` object including the study data considered in testing

**statistic** gives the value of the test statistic

**df** specifies the degrees of freedom

**p.value** includes teh p-value resulting from the test

**Source**

simulated data and Ensembl extract

**Examples**

```
data(hsa04020)
data(gwas)
net_kernel <- calc_kernel(gwas, hsa04020, knots=NULL, type='net', calculation='cpu')
lkmt_test(pheno ~ sex + age, net_kernel, gwas, method='satt')
```

---

lkmt\_test

*A function to calculate the p-values for kernel matrices.*

---

**Description**

For parameter 'satt' a pathway's influence on the probability of beeing a case is evaluated in the logistic kernel machine test and p-values are determined using a Satherthwaite approximation as described by Dan Schaid.

For parameter 'davies' a pathways influence on the probability of beeing a case is evaluated using the p-value calculation method described by Davies. Here the function `davies` from package **CompQuadForm** is used.

**Usage**

```
lkmt_test(formula, kernel, GWASdata, method = c("satt", "davies"), ...)
```

```
## S4 method for signature 'matrix'
score_test(x1, x2)
```

```
## S4 method for signature 'matrix'
davies_test(x1, x2)
```



**Arguments**

formula	The formula to be used for the regression nullmodel.
kernel	An object of class <code>kernel</code> including the pathway representing kernel-matrix based on which the test statistic will be calculated.
GWASdata	A <code>GWASdata</code> object stating the data used in analysis.
method	A character specifying which method will be used for p-value calculation. Available are 'satt' for the Satterthwaite approximation and 'davies' for Davies' algorithm. For more details see the references.
...	Further arguments can be given to the function.
x1	A <code>matrix</code> which is the similarity matrix calculated for the pathway to be tested.
x2	An <code>lm</code> or <code>glm</code> object of the nullmodel with fixed effects covariates included, but no genetic random effects.

**Value**

An `lkmt` object including the following test results

- The formula of the regression nullmodel used in the variance component test.
- An object of class `kernel` including the similarity matrix of the individuals based on which the pathways influence is evaluated.
- An object of class `GWASdata` stating the data on which the test was conducted.
- statistic A vector giving the value of the variance component test statistic.
- df A vector giving the number of degrees of freedom.
- p.value A vector giving the p-value calculated for the pathway in the variance component test.

**Author(s)**

Stefanie Friedrichs, Juliane Manitz

**References**

For details on the variance component test

- Wu MC, Kraft P, Epstein MP, Taylor DM, Chanock SJ, Hunter DJ, Lin X: Powerful SNP-Set Analysis for Case-Control Genome-Wide Association Studies. *Am J Hum Genet* 2010, 86:929-42
- Liu D, Lin X, Ghosh D: Semiparametric regression of multidimensional genetic pathway data: least-squares kernel machines and linear mixed models. *Biometrics* 2007, 63(4):1079-88.

For details on the p-value calculation see

- Schaid DJ: Genomic Similarity and Kernel Methods I: Advancements by Building on Mathematical and Statistical Foundations. *Hum Hered* 2010, 70:109-31
- Davies R: Algorithm as 155: the distribution of a linear combination of chi-2 random variables. *J R Stat Soc Ser C* 1980, 29:323-333.

**Examples**

```
data(hsa04020)
data(gwas)
net_kernel <- calc_kernel(gwas, hsa04020, knots=NULL, type='net', calculation='cpu')
lkmt_test(pheno ~ sex + age, net_kernel, gwas, method='satt')
```

---

lowrank\_kernel-class *An S4 class to represent a low-rank kernel for a SNPset at specified knots*

---

**Description**

An S4 class to represent a low-rank kernel for a SNPset at specified knots

**Details**

This kernel is used for predictions. If observations and knots are equal, better construct a full-rank kernel of class [kernel](#).

**Slots**

type character, kernel type: Use 'lin' for the linear kernel, 'sia' for the size-adjusted or 'net' for the network-based kernel.

kernel kernel matrix of dimension equal to individuals

pathway [pathway](#) object

**Author(s)**

Juliane Manitz

**Examples**

```
data(gwas)
data(hsa04020)
square <- calc_kernel(gwas, hsa04020, knots=gwas, type='lin', calculation='cpu')
dim(square@kernel)

gwas2 <- new('GWASdata', pheno=pheno[1:10,], geno=geno[1:10,], anno=anno, desc="study 2")
low_rank <- calc_kernel(gwas, hsa04020, knots = gwas2, type='net', calculation='cpu')
dim(low_rank@kernel)
```

---

`make_psd,matrix-method`*Adjust network matrix to be positive semi-definite*

---

**Description**

Adjust network matrix to be positive semi-definite

**Usage**

```
## S4 method for signature 'matrix'  
make_psd(x, eps = sqrt(.Machine$double.eps))
```

**Arguments**

<code>x</code>	A matrix specifying the network adjacency matrix.
<code>eps</code>	A numeric value, setting the tolerance for smallest eigenvalue adjustment

**Details**

For a matrix  $N$ , the closest positive semi-definite matrix is calculated as  $N^* = \rho * N + (1 + \rho) * I$ , where  $I$  is the identity matrix and  $\rho = 1 / (1 - \lambda)$  with  $\lambda$  the smallest eigenvalue of  $N$ . For more details check the references.

**Value**

The matrix  $x$ , if it is positive definite and the closest positive semi-definite matrix if  $x$  is not positive semi-definite.

**Author(s)**

Juliane Manitz, Saskia Freytag, Stefanie Friedrichs

**References**

- Freytag S, Manitz J, Schlather M, Kneib T, Amos CI, Risch A, Chang-Claude J, Heinrich J, Bickeboeller H: A network-based kernel machine test for the identification of risk pathways in genome-wide association studies. *Hum Hered.* 2013, 76(2):64-75.

**Examples**

```
set.seed(2345)  
m <- matrix(data=sample(size=25, c(0,0,1), replace=TRUE),5,5)  
m <- m + t(m)  
min(eigen(m, only.values = TRUE, symmetric = TRUE)$values)  
round(make_psd(m),2)
```

---

```
net.kernel.hsa04020
```

*Example network-based kernel matrix for pathway hsa04020.*

---

### Description

An example of a kernel object.

### Usage

```
data(net.kernel.hsa04020)
```

### Format

An object of class `kernel` and type 'network' for the pathway hsa04020.

**type** specifies which kernel function was used to calculate the kernel

**kernel** includes the kernel matrix calculated for the pathway

**pathway** includes the `pathway` object of the pathway, for which the kernel matrix was calculated

### Source

simulated data and Ensembl extract

### Examples

```
data(net.kernel.hsa04020)
# derivation
data(gwas)
data(hsa04020)
net_kernel <- calc_kernel(gwas, hsa04020, knots=NULL, type='net', calculation='cpu')
# are the value differences smaller than machine epsilon?
all(abs(net.kernel.hsa04020@kernel - net_kernel@kernel) < sqrt(.Machine$double.eps))
```

---

```
pathway
```

*An S4 class to represent a gene-gene interaction network*

---

### Description

An S4 class to represent a gene-gene interaction network

`pathway` is the `pathway` object constructor.

`show` displays the `pathway` object briefly

`summary` generates a `pathway` object summary including basic network properties.

`pathway2igraph` converts a `pathway` object into an `igraph` object with edge attribute `sign`

analyze [pathway](#) network properties

get\_genes is a helper function that extracts the gene names in a [pathway](#) and returns a vector containing character elements of gene names

plot visualizes the [pathway](#) as [igraph](#) object

sample\_genes randomly selects effect gene in a [pathway](#) according the betweenness centrality and (no -1) neighbors

## Usage

```
pathway(object, ...)  
  
## S4 method for signature 'ANY'  
pathway(id, adj = matrix(0), sign = NULL)  
  
## S4 method for signature 'pathway'  
show(object)  
  
## S4 method for signature 'pathway'  
summary(object)  
  
## S4 method for signature 'pathway'  
pathway2igraph(object)  
  
## S4 method for signature 'pathway'  
analyze(object, ...)  
  
## S4 method for signature 'pathway'  
get_genes(object)  
  
## S4 method for signature 'pathway,missing'  
plot(  
  x,  
  y = NA,  
  highlight.genes = NULL,  
  gene.names = c(NULL, "legend", "nodes"),  
  main = NULL,  
  asp = 0.95,  
  vertex.size = 11,  
  vertex.color = "khaki1",  
  vertex.label.cex = 0.8,  
  edge.width = 2,  
  edge.color = "olivedrab4",  
  ...  
)  
  
## S4 method for signature 'pathway'  
sample_genes(object, no = 3)
```

**Arguments**

<code>object</code>	An object of class <code>pathway-class</code>
<code>...</code>	Further arguments can be added to the function.
<code>id</code>	A character representing the <a href="#">pathway id</a> .
<code>adj</code>	A matrix representing the network adjacency matrix of dimension equaling the number of genes (1 interaction, 0 otherwise)
<code>sign</code>	A numeric vector indicating the interaction type for each link (1 activation, -1 inhibition) in the interaction network for the <a href="#">pathway</a> .
<code>x</code>	<a href="#">pathway</a> object
<code>y</code>	missing (placeholder)
<code>highlight.genes</code>	vector of gene names or node id's, which should be highlighted in a different color, default is NULL so that no genes are highlighted
<code>gene.names</code>	character indicating whether the genes names should appear in a legend ('legend'), as vertex label ('nodes'), or should be omitted (NA)
<code>main</code>	optional overall main title, default is NULL, which uses the <a href="#">pathway id</a>
<code>asp</code>	a numeric constant, which gives the aspect ratio parameter for plot, default is 0.95
<code>vertex.size</code>	a numeric constant specifying the vertex size, default is 11
<code>vertex.color</code>	a character or numeric constant specifying the vertex color, default is 'khaki1'
<code>vertex.label.cex</code>	a numeric constant specifying the the vertex label size, default is 0.8,
<code>edge.width</code>	a numeric constant specifying the edge width, default is 2
<code>edge.color</code>	a character or numeric constant specifying the edge color, default is 'olive-drab4'
<code>no</code>	a numeric constant specifying the number of genes to be sampled, default is 3

**Value**

`pathway2igraph` returns an unweighted [igraph](#) object with edge attribute `sign`

`analyze` returns a `data.frame` consisting of

**id** pathway id,  
**vcount** number of genes,  
**ecount** number of links,  
**inh\_ecount** number of inhibition links,  
**density** network density,  
**av\_deg** average degree,  
**inh\_deg** average degree of inhibition links,  
**diam** network diameter,  
**trans** transitivity, and  
**s\_trans** signed transitivity (Kunegis et al., 2009).

`get_genes` returns a character vector of gene names extracted from adjacency matrix rownames.

`sample_genes` returns a vector of length `no` with vertex id's of sampled genes

**Methods (by generic)**

- `analyze(pathway):`
- `get_genes(pathway):`
- `sample_genes(pathway):`

**Slots**

`id` A character representing the [pathway](#) id, e.g. `hsa00100` as used in the KEGG database.

`adj` A matrix representing the network adjacency matrix of dimension equaling the number of genes (1 interaction, 0 otherwise)

`sign` A numeric vector indicating the interaction type for each link (1 activation, -1 inhibition) in the interaction network for the [pathway](#).

**Author(s)**

Juliane Manitz, Stefanie Friedrichs, Patricia Burger

**References**

Details to the computation and interpretation can be found in:

- Kolaczyk, E. D. (2009). Statistical analysis of network data: methods and models. Springer series in statistics. Springer.
- Kunegis, J., A. Lommatzsch, and C. Bauckhage (2009). The slashdot zoo: Mining a social network with negative edges. In Proceedings of the 18th international conference on World wide web, pp. 741-750. ACM Press.

**Examples**

```
# pathway object constructor
pathway(id="hsa04022")

# convert to igraph object
data(hsa04020)
str(hsa04020)
g <- pathway2igraph(hsa04020)
str(g)

# analyze pathway network properties
data(hsa04020)
summary(hsa04020)
analyze(hsa04020)

# extract gene names from pathway object
get_genes(hsa04020)

# plot pathway as igraph object
plot(hsa04020)
sample3 <- sample_genes(hsa04020, no = 3)
```

```

plot(hsa04020, highlight.genes = sample3)

# sample effect genes
sample3 <- sample_genes(hsa04020, no = 3)
plot(hsa04020, highlight.genes = sample3)
sample5 <- sample_genes(hsa04020, no = 5)
plot(hsa04020, highlight.genes = sample5)

```

---

pathway\_info

*An S4 class for an object assigning genes to pathways*


---

### Description

This function lists all genes forming a particular [pathway](#). Start and end positions of these genes are extracted from the Ensemble database. The database is accessed via the R-package **biomaRt**.

### Usage

```

pathway_info(x)

## S4 method for signature 'character'
pathway_info(x)

## S4 method for signature 'pathway_info'
show(object)

## S4 method for signature 'pathway_info'
summary(object)

```

### Arguments

**x** A character identifying the pathway for which gene information should be extracted. Here KEGG IDs (format: 'hsa00100') are used.

**object** An object of class [pathway\\_info](#).

### Value

A data.frame including as many rows as genes appear in the [pathway](#). For each gene its name, the start and end point and the chromosome it lies on are given.

`show` Basic information on [pathway\\_info](#) object.

`summary` Summarized information on [pathway\\_info](#) object.

### Slots

`info` A data.frame including information on genes contained in pathways with columns 'pathway', 'gene\_start', 'gene\_end', 'chr' and 'gene'.



**Author(s)**

Stefanie Friedrichs, Juliane Manitz

**See Also**

[snp\\_info](#), [get\\_anno](#)

**Examples**

```
data(hsa04022_info) # pathway_info('hsa04020')
show(hsa04022_info)
summary(hsa04022_info)
```

---

pheno

*Example phenotype file for 50 individuals.*

---

**Description**

A dataset containing simulated example phenotypes for 50 individuals row names include the identifiers of 50 example individuals.

**Usage**

```
data(pheno)
```

**Format**

A data frame with 50 rows and 3 variables:

**pheno** includes the case-control status for each individual, coded as 1(case) or 0 (control)

**sex** includes gender information for the 50 individuals, coded as 1 (male) or 0 (female)

**age** numerical value giving the persons age

**Source**

simulated data

**Examples**

```
data(pheno)
head(pheno)
# create gwas object
data(geno)
data(anno)
gwas <- new('GWASdata', pheno=pheno, geno=geno, anno=anno, desc="some study")
```

---

read\_genotype,character-method

*read genotype data from file to one of several available objects, which can be passed to a GWASdata object [GWASdata](#).*

---

## Description

read genotype data from file to one of several available objects, which can be passed to a GWASdata object [GWASdata](#).

## Usage

```
## S4 method for signature 'character'
read_genotype(
  file.path,
  save.path = NULL,
  sep = " ",
  header = TRUE,
  use.fread = TRUE,
  use.big = FALSE,
  row.names = FALSE,
  ...
)
```

## Arguments

file.path	character giving the path to the data file to be read
save.path	character containing the path for the backingfile
sep	character. A field delimiter. See <a href="#">read.big.matrix</a> for details.
header	logical. Does the data set contain column names?
use.fread	logical. Should the dataset be read using the function <a href="#">fread</a> from package <b>data.table</b> ?
use.big	logical. Should the dataset be read using the function <a href="#">read.big.matrix</a> from package <b>bigmemory</b> ?
row.names	logical. Does the dataset include rownames?
...	further arguments to be passed to read_genotype.

## Details

If the data set contains rownames specified, set option has . row . names = TRUE.

**Examples**

```
## Not run:
path <- system.file("extdata", "geno.txt", package = "kangaroo")
geno <- read_geno(path, save.path = getwd(), sep = " ", use.fread = FALSE, row.names = FALSE)

## End(Not run)
```

---

rewire_network	<i>Rewires interactions in a <a href="#">pathway</a>, which go through a gene not represented by any SNPs in the considered <a href="#">GWASdata</a> dataset.</i>
----------------	---

---

**Description**

Rewires interactions in a [pathway](#), which go through a gene not represented by any SNPs in the considered [GWASdata](#) dataset.

**Usage**

```
## S4 method for signature 'pathway'
rewire_network(object, x)
```

**Arguments**

object	<a href="#">pathway</a> object which's network matrix will be rewired
x	A vector of gene names, indicating which genes are not represented by SNPs in the considered <a href="#">GWASdata</a> object and will be removed

**Value**

A [pathway](#) object including the rewired network matrix

**Author(s)**

Juliane Manitz, Stefanie Friedrichs

**Examples**

```
## Not run:
data(hsa04020)
summary(hsa04020)
hsa04020_rewired <- rewire_network(hsa04020, x=c('ADCY3', 'CALML3', 'GNAQ'))
summary(hsa04020_rewired)

## End(Not run)
```

---

rs10243170\_info      *Example [snp\\_info](#) object for SNP rs10243170.*

---

### Description

An object of class [snp\\_info](#) for rs10243170.

### Usage

```
data(rs10243170_info)
```

### Format

A [snp\\_info](#) object including information on the SNP as extracted from the Ensembl database.

**info** a data frame including the extracted information on the SNP. Columns given are 'chr', 'position', and 'rsnumber'

### Source

Ensembl extract

### Examples

```
## Not run:  
snp_info("rs10243170")  
  
## End(Not run)
```

---

snp\_info      *An S4 class for an object assigning SNP positions to rs-numbers (for internal use)*

---

### Description

An S4 class for an object assigning SNP positions to rs-numbers (for internal use)

This function gives for a vector of SNP identifiers the position of each SNP as extracted from the Ensemble database. The database is accessed via the R-package **biomaRt**.

show Shows basic information on [snp\\_info](#) object

summary Summarizes information on [snp\\_info](#) object

**Usage**

```
snp_info(x, ...)  
  
## S4 method for signature 'character'  
snp_info(x)  
  
## S4 method for signature 'snp_info'  
show(object)  
  
## S4 method for signature 'snp_info'  
summary(object)
```

**Arguments**

x	A character vector of SNP rsnumbers for which positions will be extracted.
...	further arguments can be added.
object	An object of class <a href="#">snp_info</a> .

**Value**

A data.frame including the SNP positions with columns 'chromosome', 'position' and 'snp'. SNPs not found in the Ensemble database will not be listed in the returned [snp\\_info](#) object, SNPs with multiple positions will appear several times.

show Basic information on [snp\\_info](#) object.

summary Summarized information on [snp\\_info](#) object.

**Slots**

info A data.frame including information on SNP positions

**Author(s)**

Stefanie Friedrichs

**See Also**

[pathway\\_info](#), [get\\_anno](#)

**Examples**

```
data(rs10243170_info) # snp_info("rs10243170")  
  
rs10243170_info  
summary(rs10243170_info)
```

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