Package 'CopulaREMADA'

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Title Copula Mixed Models for Multivariate Meta-Analysis of Diagnostic Test Accuracy Studies

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Depends R (>= 3.5.0), statmod, matlab, tensor, mc2d

Description The bivariate copula mixed model for meta-analysis of diagnostic test accuracy studies in Nikoloulopoulos (2015) <doi:10.1002/sim.6595> and Nikoloulopoulos (2018) <doi:10.1007/s10182-017-0299-y>. The vine copula mixed model for meta-analysis of diagnostic test accuracy studies accounting for disease prevalence in Nikoloulopoulos (2017) <doi:10.1177/0962280215596769> and also accounting for non-evaluable subjects in Nikoloulopoulos (2020) <doi:10.1515/ijb-2019-0107>. The hybrid vine copula mixed model for meta-analysis of diagnostic test accuracy case-control and cohort studies in Nikoloulopoulos (2018) <doi:10.1177/0962280216682376>. The D-vine copula mixed model for meta-analysis and comparison of two diagnostic tests in Nikoloulopoulos (2019) <doi:10.1177/0962280218796685>. The multinomial quadrivariate D-vine copula mixed model for meta-analysis of diagnostic tests with non-evaluable subjects in Nikoloulopoulos (2020) <doi:10.1177/0962280220913898>. The one-factor copula mixed model for joint meta-analysis of multiple diagnostic tests in Nikoloulopoulos (2022) <doi:10.1111/rssa.12838>. The multinomial six-variate 1-truncated D-vine copula mixed model for meta-analysis of two diagnostic tests accounting for within and between studies dependence in Nikoloulopoulos (2024) <doi:10.1177/09622802241269645>. The 1-truncated D-vine copula mixed models for meta-analysis of diagnostic accuracy studies without a gold standard (Nikoloulopoulos, 2025) <doi:10.1093/biomtc/ujaf037>.

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Contents

CopulaREMADA-package *Copula Mixed Models for Multivariate Meta-Analysis of Diagnostic Test Accuracy Studies*

Description

Fits copula mixed models for multivariate meta-analysis of diagnostic test accuracy studies proposed in Nikoloulopoulos (2015, 2017, 2018a, 2018b, 2019, 2020a, 2020b, 2022, 2024, 2025).

Details

This package contains R functions to implement:

- The copula mixed model for meta-analysis of diagnostic test accuracy studies and produce SROC curves and summary operating points (a pair of average sensitivity and specificity) with a confidence region and a predictive region (Nikoloulopoulos, 2015, 2018a). All the analyses presented in Section 7 of Nikoloulopoulos (2015) are given as code examples in the package;
- The vine copula mixed model for meta-analysis of diagnostic test accuracy studies accounting for disease prevalence and non-evaluable subjects (Nikoloulopoulos, 2017, 2020a);
- The hybrid vine copula mixed model for meta-analysis of diagnostic test accuracy case-control and cohort studies (Nikoloulopoulos, 2018b);
- The D-vine copula mixed model for meta-analysis and comparison of two diagnostic tests (Nikoloulopoulos, 2019).
- The multinomial quadrivariate D-vine copula mixed model for diagnostic studies meta-analysis accounting for non-evaluable subjects (Nikoloulopoulos, 2020b).
- The one-factor copula mixed model for joint meta-analysis of multiple diagnostic tests (Nikoloulopoulos, 2022).
- The multinomial six-variate D-vine copula mixed model for for meta-analysis of two diagnostic tests accounting for within and between studies dependence (Nikoloulopoulos, 2024).
- The 1-truncated D-vine copula mixed model for for meta-analysis of diagnostic test accuracy studies without a gold standard (Nikoloulopoulos, 2025).

Author(s)

Aristidis K. Nikoloulopoulos.

References

Nikoloulopoulos, A.K. (2015) A mixed effect model for bivariate meta-analysis of diagnostic test accuracy studies using a copula representation of the random effects distribution. *Statistics in Medicine*, **34**, 3842–3865. doi:10.1002/sim.6595.

Nikoloulopoulos, A.K. (2017) A vine copula mixed effect model for trivariate meta-analysis of diagnostic test accuracy studies accounting for disease prevalence. *Statistical Methods in Medical Research*, **26**, 2270–2286. doi:10.1177/0962280215596769.

Nikoloulopoulos, A.K. (2018a) On composite likelihood in bivariate meta-analysis of diagnostic test accuracy studies. *AStA Advances in Statistical Analysis*, **102**, 211–227. doi:10.1007/s10182-0170299y.

Nikoloulopoulos, A.K. (2018b) Hybrid copula mixed models for combining case-control and cohort studies in meta-analysis of diagnostic tests. *Statistical Methods in Medical Research*, **27**, 2540–2553. doi:10.1177/0962280216682376.

Nikoloulopoulos, A.K. (2019) A D-vine copula mixed model for joint meta-analysis and comparison of diagnostic tests. *Statistical Methods in Medical Research*, **28**(10-11):3286–3300. doi:10.1177/0962280218796685.

Nikoloulopoulos, A.K. (2020a) An extended trivariate vine copula mixed model for meta-analysis of diagnostic studies in the presence of non-evaluable outcomes. *The International Journal of Biostatistics*, **16**(2). doi:10.1515/ijb20190107.

Nikoloulopoulos, A.K. (2020b) A multinomial quadrivariate D-vine copula mixed model for diagnostic studies meta-analysis in the presence of non-evaluable subjects. *Statistical Methods in Medical Research*, **29**(10), 2988–3005. doi:10.1177/0962280220913898.

Nikoloulopoulos, A.K. (2022) An one-factor copula mixed model for joint meta-analysis of multiple diagnostic tests. *Journal of the Royal Statistical Society: Series A (Statistics in Society)*, **185**(3), 1398–1423. doi:10.1111/rssa.12838.

Nikoloulopoulos, A.K. (2024) Joint meta-analysis of two diagnostic tests accounting for within and between studies dependence. *Statistical Methods in Medical Research*, **33**(10), 1800–1817. doi:10.1177/09622802241269645.

Nikoloulopoulos, A.K. (2025) Vine copula mixed models for meta-analysis of diagnostic accuracy studies without a gold standard. *Biometrics*, **81**(2), ujaf037. doi:10.1093/biomtc/ujaf037.

`arthritis` *The rheumatoid arthritis data*

Description

Data obtained from a meta-analysis that aimed to determine whether anti-cyclic citrullinated peptide (anti-CCP) antibody identifies more accurately patients with rheumatoid arthritis than rheumatoid factor (RF) does. We include $N = 22$ studies that assessed both RF and anti-CCP2 antibody for diagnosing rheumatoid arthritis.

Format

A data frame with 22 observations on the following 8 variables.

TP1 the number of true positives for RF

FN1 the number of false negatives for RF

FP1 the number of false positives for RF

TN1 the number of true negatives for RF

TP2 the number of true positives for anti-CCP2

FN2 the number of false negatives for anti-CCP2

FP2 the number of false positives for anti-CCP2

TN2 the number of true negatives for anti-CCP2

References

Nishimura, K., Sugiyama, D., Kogata, Y., et al. (2007) Meta-analysis: Diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Annals of Internal Medicine*, **146**(11), 797–808.

Dimou, N.L., Adam, M. and Bagos, P.G. (2016) A multivariate method for meta-analysis and comparison of diagnostic tests. *Statistics in Medicine*, **35**(20), 3509–3523.

`betaDG` *The beta-D-Glucan-data*

Description

Data on 8 cohort studies inthemeta-analysis in Karageorgopoulos et al. (2011). The interest there is to assess $beta$-D-Glucan as aserum or plasma marker for the presence of invasive fungal infections.

Usage

```
data(betaDG)
```

Format

A data frame with 8 observations on the following 4 variables.

TP the number of true positives

FN the number of false negatives

FP the number of false positives

TN the number of true negatives

References

Karageorgopoulos, D.E., Vouloumanou, E.K., Ntziora, F., et al. (2011) $beta$-D-Glucan assay for the diagnosis of invasive fungal infections: a meta-analysis. *Clinical Infectious Diseases*, **52**(6), 750–770.

CopulaREMADA *Maximum likelihood estimation for copula mixed models for diagnostic test accurracy studies*

Description

For copula mixed models for diagnostic test accuracy studies numerical evaluation of the MLE is easily done with the following steps:

1. Calculate Gauss-Legendre quadrature points `gl$nodes` and weights `gl$weights`.

2. Convert from independent uniform quadrature points to dependent uniform quadrature points that have distribution 'cop'. The inverse of the conditional distribution `qcondcop` corresponding to the copula 'cop' is used to achieve this.

3. Numerically evaluate the joint probability mass function with the bivariate integral in a double sum.

With Gauss-Legendre quadrature, the same nodes and weights are used for different functions; this helps in yielding smooth numerical derivatives for numerical optimization via quasi-Newton. Our comparisons show that $n_q = 15$ is adequate with good precision to at least at four decimal places.

Usage

```
CopulaREMADA.norm(TP,FN,FP,TN,gl,mgrid,qcond,tau2par)
CopulaREMADA.beta(TP,FN,FP,TN,gl,mgrid,qcond,tau2par)
countermonotonicCopulaREMADA.norm(TP,FN,FP,TN,gl,mgrid)
countermonotonicCopulaREMADA.beta(TP,FN,FP,TN,gl,mgrid)
```

Arguments

`TP`	the number of true positives
`FN`	the number of false negatives
`FP`	the number of false positives
`TN`	the number of true negatives
`gl`	a list containing the components of Gauss-Legendre nodes `gl$nodes` and weights `gl$weights`
`mgrid`	a list containing two matrices with the rows of the output matrix x are copies of the vector `gl$nodes`; columns of the output matrix y are copies of the vector `gl$nodes`
`qcond`	function for the inverse of conditional copula cdf
`tau2par`	function for maping Kendall's tau to copula parameter

Value

A list containing the following components:

`minimum`	the value of the estimated minimum of the negative log-likelihood
`estimate`	the MLE
`gradient`	the gradient at the estimated minimum of of the negative log-likelihood
`hessian`	the hessian at the estimated minimum of the negative log-likelihood
`code`	an integer indicating why the optimization process terminated
`iterations`	the number of iterations performed

For more details see `nlm`

References

Nikoloulopoulos, A.K. (2015) A mixed effect model for bivariate meta-analysis of diagnostic test accuracy studies using a copula representation of the random effects distribution. *Statistics in Medicine*, **34**, 3842–3865. doi:10.1002/sim.6595.

See Also

`rCopulaREMADA`

Examples

```
nq=15
gl=gauss.quad.prob(nq,"uniform")
mgrid<- meshgrid(gl$n,gl$n)

data(LAG)
attach(LAG)
c270est.b=CopulaREMADA.beta(TP,FN,FP,TN,gl,mgrid,qcondcln270,tau2par.cln270)
detach(LAG)

data(MRI)
attach(MRI)
c270est.n=CopulaREMADA.norm(TP,FN,FP,TN,gl,mgrid,qcondcln270,tau2par.cln270)
detach(MRI)

data(CT)
attach(CT)
est.n=countermonotonicCopulaREMADA.norm(TP,FN,FP,TN,gl,mgrid)
est.b=countermonotonicCopulaREMADA.beta(TP,FN,FP,TN,gl,mgrid)
detach(CT)
```

coronary *The coronary CT angiography data*

Description

Data on 26 studies from a systematic review for diagnostic accuracy studies of coronary computed tomography angiography for the detection of coronary artery disease.

Usage

```
data(coronary)
```

Format

A data frame with 26 observations on the following 6 variables.

TP the number of true positives

FN the number of false negatives

FP the number of false positives

TN the number of true negatives

NEP the number of non-evaluable positives

NEN the number of non-evaluable negatives

References

Schuetz, G. M., Schlattmann, P., and Dewey, M. (2012). Use of 3x2 tables with an intention to diagnose approach to assess clinical performance of diagnostic tests: Meta-analytical evaluation of coronary CT angiography studies. *BMJ* (Online), **345**:e6717.

CT *The computing tomography data*

Description

Data on 17 studies of computed tomography (CT) for the diagnosis of lymph node metastasis in women with cervical cancer, one of three imaging techniques in the meta-analysis in Scheidler et al. (1997). Diagnosis of metastatic disease by CT relies on nodal enlargement.

Usage

```
data(CT)
```

Format

A data frame with 17 observations on the following 4 variables.

TP the number of true positives

FN the number of false negatives

FP the number of false positives

TN the number of true negatives

References

Scheidler, J., H. Hricak, K. K. Yu, L. Subak, and M. R. Segal. (1997) Radiological evaluation of lymph node metastases in patients with cervical cancer: A meta-analysis. *Journal of the American Medical Association*, **278**, 1096–1101.

`cvinesim` *Simulation from a trivariate C-vine copula*

Description

Simulation from a trivariate C-vine copula

Usage

```
cvinesim(N,param,qcondcop12,qcondcop13,qcondcop23,
                  tau2par12,tau2par13,tau2par23)
```

Arguments

`N`	sample size
`param`	Kendall's tau values for margins (1,2), (1,3), (23|1)
`qcondcop12`	function for the inverse of conditional copula cdf at the (1,2) bivariate margin
`qcondcop13`	function for the inverse of conditional copula cdf at the (1,3) bivariate margin
`qcondcop23`	function for the inverse of conditional copula cdf at the (2,3|1) bivariate margin
`tau2par12`	function for maping Kendall's tau at the (1,2) bivariate margin to copula parameter
`tau2par13`	function for maping Kendall's tau at the (1,3) bivariate margin to copula parameter
`tau2par23`	function for maping Kendall's tau at the (2,3|1) bivariate margin to the conditional copula parameter

Details

Choices are 'cop' in rcop are bvn, frk, cln, cln90 (rotated by 90 degrees cln), cln180 (rotated by 180 degrees cln), cln270 (rotated by 270 degrees cln).

See help page for dcop for the abbreviations of the copula names.

Value

Nx3 matrix with values in (0,1)

References

Joe H (2011) Dependence comparisons of vine copulae with four or more variables. In: Kurowicka D, Joe H, editors. *Dependence Modeling: Handbook on Vine Copulae*. Singapore: World Scientific; 2011. p. 139–164

Joe H (2014) *Dependence Modeling with Copulas*. Chapman & Hall/CRC.

Joe H (2014) *CopulaModel: Dependence Modeling with Copulas*. Software for book: *Dependence Modeling with Copulas*, Chapman & Hall/CRC, 2014.

See Also

qcondcop dcop rcop

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dcop *Bivariate copula densities*

Description

Bivariate copula densities for parametric families.

Usage

```
dbvn(u,v,cpar)
dfrk(u,v,cpar)
dcln(u,v,cpar)
dcln90(u,v,cpar)
dcln270(u,v,cpar)
```

Arguments

u	value in interval 0,1; could be a vector
v	value in interval 0,1; could be a vector
cpar	copula parameter: scalar.

Details

Choices are 'cop' in dcop are bvn, frk, cln, cln90 (rotated by 90 degrees cln), cln180 (rotated by 180 degrees cln), cln270 (rotated by 270 degrees cln).

The copula names are abbreviations for:

bvn = bivariate normal or Gaussian

frk = Frank

cln = Clayton or Mardia-Takahasi-Cook-Johnson

Value

pdf value(s).

References

Joe H (1997) *Multivariate Models and Dependence Concepts*. Chapman & Hall

Joe H (2014) *Dependence Modeling with Copulas*. Chapman & Hall/CRC.

Joe H (2014) *CopulaModel: Dependence Modeling with Copulas*. Software for book: *Dependence Modeling with Copulas*, Chapman & Hall/CRC, 2014.

See Also

qcondcop rcop

Down *The down syndrome data*

Description

Data on $N = 11$ studies from the systematic review that examined the screening accuracy of shortened humerus and shortened femur of the fetus markers (two out of seven ultrasonographic markers or their combination in detecting Down syndrome in Smith-Bindman et al., 2001).

Format

A data frame with 11 observations on the following 8 variables.

down_n_00 the number of the test results in the diseased where the shortened humerus outcome is negative and the shortened femur outcome is negative

down_n_01 the number of the test results in the diseased where the shortened humerus outcome is negative and the shortened femur outcome is positive

down_n_10 the number of the test results in the diseased where the shortened humerus outcome is positive and the shortened femur outcome is negative

down_n_11 the number of the test results in the diseased where the shortened humerus outcome is positive and the shortened femur outcome is positive

nodown_n_00 the number of the test results in the non-diseased where the shortened humerus outcome is negative and the shortened femur outcome is negative

nodown_n_01 the number of the test results in the non-diseased where the shortened humerus outcome is negative and the shortened femur outcome is positive

nodown_n_10 the number of the test results in the non-diseased where the shortened humerus outcome is positive and the shortened femur outcome is negative

nodown_n_11 the number of the test results in the non-diseased where the shortened humerus outcome is positive and the shortened femur outcome is positive

References

Smith-Bindman R, Hosmer W, Feldstein V et al. Second-trimester ultrasound to detect fetuses with down syndrome: A meta-analysis (2001). *Journal of the American Medical Association*, **285**(8): 1044-1055.

`dvine6dsim` *Simulation from a six-variate 1-truncated D-vine copula*

Description

Simulation from a six-variate 1-truncated D-vine copula.

Usage

```
dvine6dsim(nsim,tau,qcond,tau2par)
```

Arguments

`nsim`	sample size
`tau`	Kendall's tau values
`qcond`	function for the inverse conditional copula cdf
`tau2par`	function for maping Kendall's taus to copula parameters

Details

Choices are 'cop' in rcop are bvn, frk, cln, cln90 (rotated by 90 degrees cln), cln180 (rotated by 180 degrees cln), cln270 (rotated by 270 degrees cln).

See help page for qcondcop for the abbreviations of the copula names.

Value

Nx6 matrix with values in (0,1)

References

Joe H (2011) Dependence comparisons of vine copulae with four or more variables. In: Kurowicka D, Joe H, editors. *Dependence Modeling: Handbook on Vine Copulae*. Singapore: World Scientific; 2011. p. 139–164

Joe H (2014) *Dependence Modeling with Copulas*. Chapman & Hall/CRC.

Joe H (2014) *CopulaModel: Dependence Modeling with Copulas*. Software for book: *Dependence Modeling with Copulas*, Chapman & Hall/CRC, 2014.

Nikoloulopoulos, A.K. (2024) Joint meta-analysis of two diagnostic tests accounting for within and between studies dependence. *Statistical Methods in Medical Research*, **33**(10), 1800–1817. doi:10.1177/09622802241269645.

See Also

qcondcop rcop

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dvinesim *Simulation from a (truncated) quadrivariate D-vine copula*

Description

Simulation from a (truncated) quadrivariate D-vine copula. Lower-order trees (if any) are composed with BVN copulas.

Usage

```
dvinesim(nsim,param,qcond1,pcond1,tau2par1,qcond2,pcond2,tau2par2)
dtrvinesim(nsim,trparam,qcond1,pcond1,tau2par1,qcond2,pcond2,tau2par2)
```

Arguments

nsim	sample size
param	Kendall's tau values for margins (1,2), (2,3), (3,4), (1,3|2), (2,4|3), (1,4|23)
trparam	Kendall's tau values for margins (1,2), (2,3), (3,4)
qcond1	function for the inverse conditional copula cdf at the (1,2) and (3,4) bivariate margins
pcond1	function for the conditional copula cdf at the (1,2) and and (3,4) bivariate margins
tau2par1	function for maping Kendall's tau at the (1,2) and (3,4) bivariate margins to copula parameter
qcond2	function for the inverse conditional copula cdf at the (2,3) bivariate margin
pcond2	function for the conditional copula cdf at the (2,3) bivariate margin
tau2par2	function for maping Kendall's tau at the (2,3) bivariate margin to copula parameter

Details

Choices are 'cop' in rcop are bvn, frk, cln, cln90 (rotated by 90 degrees cln), cln180 (rotated by 180 degrees cln), cln270 (rotated by 270 degrees cln).

See help page for dcop for the abbreviations of the copula names.

Value

Nx4 matrix with values in (0,1)

References

Joe H (2011) Dependence comparisons of vine copulae with four or more variables. In: Kurowicka D, Joe H, editors. *Dependence Modeling: Handbook on Vine Copulae*. Singapore: World Scientific; 2011. p. 139–164

Joe H (2014) *Dependence Modeling with Copulas*. Chapman & Hall/CRC.

Joe H (2014) *CopulaModel: Dependence Modeling with Copulas*. Software for book: *Dependence Modeling with Copulas*, Chapman & Hall/CRC, 2014.

Nikoloulopoulos, A.K. (2018) A D-vine copula mixed model for joint meta-analysis and comparison of diagnostic tests. *Statistical Methods in Medical Research*, in press. doi:10.1177/0962280218796685.

Nikoloulopoulos, A.K. (2018) A multinomial quadrivariate D-vine copula mixed model for diagnostic studies meta-analysis accounting for non-evaluable subjects. *ArXiv e-prints*, arXiv:1812.05915. https://arxiv.org/abs/1812.05915.

See Also

qcondcop dcop rcop

`FactorCopulaREMADA` *Maximum likelihood estimation of 1-factor copula mixed models for joint meta-analysis of T diagnostic tests*

Description

The estimated parameters can be obtained by using a quasi-Newton method applied to the logarithm of the joint likelihood. This numerical method requires only the objective function, i.e., the logarithm of the joint likelihood, while the gradients are computed numerically and the Hessian matrix of the second order derivatives is updated in each iteration. The standard errors (SE) of the ML estimates can be also obtained via the gradients and the Hessian computed numerically during the maximization process.

Usage

```
FactorCopulaREMADA.norm(TP,FN,FP,TN,gl,mgrid,qcond1,tau2par1,qcond2,tau2par2)

FactorCopulaREMADA.beta(TP,FN,FP,TN,gl,mgrid,qcond1,tau2par1,qcond2,tau2par2)
```

Arguments

`TP`	an $n \times T$ matrix where n is the number of studies. Column j has the number of true positives for test j for $j = 1 \dots T$
`FN`	an $n \times T$ matrix where n is the number of studies. Column j has the number of false negatives Column j has the number of true positives for test j for $j = 1 \dots T$
`FP`	an $n \times T$ matrix where n is the number of studies. Column j has the number of false positives Column j has the number of true positives for test j for $j = 1 \dots T$

TN	an $n \times T$ matrix where n is the number of studies. Column j has the number of true negatives Column j has the number of true positives for test j for $j = 1 \ldots T$
gl	a list containing the components of Gauss-Legendre nodes gl$nodes and weights gl$weights
mgrid	a list containing two matrices with the rows of the output matrix x are copies of the vector gl$nodes; columns of the output matrix y are copies of the vector gl$nodes
qcond1	function for the inverse conditional copula cdfs that link the factor with the latent sensitivities
tau2par1	function for maping Kendall's tau to copula parameter at the copulas that link the factor with the latent sensitivities
qcond2	function for the inverse conditional copula cdfs that link the factor with the latent specificities
tau2par2	function for maping Kendall's tau to copula parameter at the copulas that link the factor with the latent specificities

Value

A list containing the following components:

minimum	the value of the estimated minimum of the negative log-likelihood
estimate	the MLE
gradient	the gradient at the estimated minimum of of the negative log-likelihood
hessian	the hessian at the estimated minimum of the negative log-likelihood
code	an integer indicating why the optimization process terminated
iterations	the number of iterations performed

For more details see nlm

References

Nikoloulopoulos, A.K. (2022) An one-factor copula mixed model for joint meta-analysis of multiple diagnostic tests. *Journal of the Royal Statistical Society: Series A (Statistics in Society)*, 185 (3), 1398–1423. doi:10.1111/rssa.12838.

Examples

```
data(arthritis)
attach(arthritis)
TP=cbind(TP1,TP2)
TN=cbind(TN1,TN2)
FP=cbind(FP1,FP2)
FN=cbind(FN1,FN2)


nq=25
```

```
gl=gauss.quad.prob(nq,"uniform")
mgrid=meshgrid(gl$n,gl$n)
qcond1=qcondcln
qcond2=qcondcln270
tau2par1=tau2par.cln
tau2par2=tau2par.cln270

out=FactorCopulaREMADA.norm(TP,FN,FP,TN,gl,mgrid,qcond1,tau2par1,qcond2,tau2par2)
se=sqrt(diag(solve(out$hessian)))

detach(arthritis)
```

`hybridCopulaREMADA` *Maximum likelihood estimation for hybrid copula mixed models for combining case-control and cohort studies in meta-analysis of diagnostic tests*

Description

The estimated parameters can be obtained by using a quasi-Newton method applied to the logarithm of the joint likelihood. This numerical method requires only the objective function, i.e., the logarithm of the joint likelihood, while the gradients are computed numerically and the Hessian matrix of the second order derivatives is updated in each iteration. The standard errors (SE) of the ML estimates can be also obtained via the gradients and the Hessian computed numerically during the maximization process.

Usage

```
hybridCopulaREMADA.norm(TP,FN,FP,TN,type,gl,mgrid1,mgrid2,
               qcondcop12,qcondcop13,
               tau2par12,tau2par13,qcond,tau2par)
hybridCopulaREMADA.beta(TP,FN,FP,TN,type,gl,mgrid1,mgrid2,
               qcondcop12,qcondcop13,
               tau2par12,tau2par13,qcond,tau2par)
```

Arguments

`TP`	the number of true positives
`FN`	the number of false negatives
`FP`	the number of false positives
`TN`	the number of true negatives
`type`	a scalar indicating the study type: 1: Cohort study; 2: Case-control study.
`gl`	a list containing the components of Gauss-Legendre nodes `gl$nodes` and weights `gl$weights`
`mgrid1`	a list containing three-dimensional arrays

mgrid2	a list containing two matrices with the rows of the output matrix x are copies of the vector gl$nodes; columns of the output matrix y are copies of the vector gl$nodes
qcondcop12	function for the inverse of conditional copula cdf at the (1,2) bivariate margin of the vine
qcondcop13	function for the inverse of conditional copula cdf at the (1,3) bivariate margin of the vine
tau2par12	function for maping Kendall's tau at the (1,2) bivariate margin of the vine to copula parameter
tau2par13	function for maping Kendall's tau at the (1,3) bivariate margin of the vine to copula parameter
qcond	function for the inverse of conditional copula cdf
tau2par	function for maping Kendall's tau to the bivariate copula parameter

Value

A list containing the following components:

minimum	the value of the estimated minimum of the negative log-likelihood
estimate	the MLE
gradient	the gradient at the estimated minimum of of the negative log-likelihood
hessian	the hessian at the estimated minimum of the negative log-likelihood
code	an integer indicating why the optimization process terminated
iterations	the number of iterations performed

For more details see nlm

References

Nikoloulopoulos, A.K. (2018) Hybrid copula mixed models for combining case-control and cohort studies in meta-analysis of diagnostic tests. *Statistical Methods in Medical Research*, **27**, 2540–2553. doi:10.1177/0962280216682376.

See Also

VineCopulaREMADA, CopulaREMADA

Examples

```
# simulate the data from N=25 cohort studies
N=25
p=c(0.8,0.7,0.4)
g=c(0.1,0.1,0.05)
taus=c(-0.5,-0.3,-0.0001)
qcondcop12=qcondcop23=qcondcop13=qcondcln90
tau2par12=tau2par23=tau2par13=tau2par.cln90
simdat1=rVineCopulaREMADA.beta(N,p,g,taus,0,0,
```

```
qcondcop12,qcondcop13,qcondcop23,tau2par12,tau2par13,tau2par23)
# simulate data from the N=25 case-control studies
tau=0.5
p=p[-3]
g=g[-3]
simdat2=rCopulaREMADA.beta(N,p,g,tau,rcln,tau2par.cln)
# combine the data
TP=c(simdat1$TP,simdat2$TP)
TN=c(simdat1$TN,simdat2$TN)
FP=c(simdat1$FP,simdat2$FP)
FN=c(simdat1$FN,simdat2$FN)
type=rep(c(1,2),each=N)

# fit the hybrid copula mixed model
nq=21
gl=gauss.quad.prob(nq,"uniform")
mgrid1<- meshgrid(gl$n,gl$n,gl$n,nargout=3)
mgrid2<- meshgrid(gl$n,gl$n)

qcond=qcondcln
tau2par=tau2par.cln
est=hybridCopulaREMADA.beta(TP,FN,FP,TN,type,gl,mgrid1,mgrid2,
qcondcop12,qcondcop13,tau2par12,tau2par13,qcond,tau2par)
```

`imperfect.fivariateVineCopulaREMADA`

Maximum likelihood estimation of 5-variate 1-truncated D-vine copula mixed models for meta-analysis of diagnostic accuracy studies without a gold standard

---

Description

The estimated parameters can be obtained by using a quasi-Newton method applied to the logarithm of the joint likelihood. This numerical method requires only the objective function, i.e., the logarithm of the joint likelihood, while the gradients are computed numerically and the Hessian matrix of the second order derivatives is updated in each iteration. The standard errors (SE) of the ML estimates can be also obtained via the gradients and the Hessian computed numerically during the maximization process.

Usage

```
imperfect.fivevariateVineCopulaREMADA.norm.comprehensive(y11,y10,y01,y00,
                                gl,mgrid,qcond,tau2par,start)

imperfect.fivevariateVineCopulaREMADA.beta.comprehensive(y11,y10,y01,y00,
                                gl,mgrid,qcond,tau2par,start)
```

Arguments

y11	the number of the test results where the index test outcome is positive and the reference test outcome is positive
y10	the number of the test results where the index test outcome is positive and the reference test outcome is negative
y01	the number of the test results where the index test outcome is negative and the reference test outcome is positive
y00	the number of the test results where the index test outcome is negative and the reference test outcome is negative
gl	a list containing the components of Gauss-Legendre nodes gl$nodes and weights gl$weights
mgrid	a list containing five-dimensional arrays. Replicates of the quadrature points that produce a 5-dimensional full grid
qcond	function for the inverse of conditional copula cdf; choices are qconbvn and qcondfrk
tau2par	function for maping Kendall's tau to copula parameter; choices are tau2par.bvn and tau2par.frk
start	starting values for the parameters

Value

A list containing the following components:

LogLikelihood	the maximized log-likelihood
Estimates	the MLE
SE	the standard errors

References

Nikoloulopoulos, A.K. (2025) Vine copula mixed models for meta-analysis of diagnostic accuracy studies without a gold standard. *Biometrics*, **81**(2), ujaf037. doi:10.1093/biomtc/ujaf037.

Examples

```
data(Pap)
attach(Pap)

nq=15
gl=gauss.quad.prob(nq,"uniform")
data(mgrid5d15)
mgrid=mgrid5d15

tau2par=tau2par.bvn
qcond=qcondbvn

start=c(rep(0.6,5),rep(0.5,5),rep(0.01,4))
est.norm=imperfect.fivevariateVineCopulaREMADA.norm.comprehensive(y11,y10,y01,
```

```
y00,gl,mgrid,qcond,tau2par,start)

detach(Pap)
```

`imperfect.quadrivariateVineCopulaREMADA`

Maximum likelihood estimation of quadrivariate 1-truncated D-vine copula mixed models for meta-analysis of diagnostic accuracy studies without a gold standard

---

Description

The estimated parameters can be obtained by using a quasi-Newton method applied to the logarithm of the joint likelihood. This numerical method requires only the objective function, i.e., the logarithm of the joint likelihood, while the gradients are computed numerically and the Hessian matrix of the second order derivatives is updated in each iteration. The standard errors (SE) of the ML estimates can be also obtained via the gradients and the Hessian computed numerically during the maximization process.

Usage

```
imperfect.quadrivariateVineCopulaREMADA.norm.comprehensive(y11,y10,y01,y00,
gl,mgrid,qcond,tau2par,select.random,start)

imperfect.quadrivariateVineCopulaREMADA.beta.comprehensive(y11,y10,y01,y00,
gl,mgrid,qcond,tau2par,select.random,start)
```

Arguments

`y11`	the number of the test results where the index test outcome is positive and the reference test outcome is positive
`y10`	the number of the test results where the index test outcome is positive and the reference test outcome is negative
`y01`	the number of the test results where the index test outcome is negative and the reference test outcome is positive
`y00`	the number of the test results where the index test outcome is negative and the reference test outcome is negative
`gl`	a list containing the components of Gauss-Legendre nodes `gl$nodes` and weights `gl$weights`
`select.random`	vector (t_1, t_2, t_3, t_4), where $1 \leq t_1 < t_2 < t_3 < t_4 \leq 5$, that indicates the random effects
`mgrid`	a list containing four-dimensional arrays. Replicates of the quadrature points that produce a 4-dimensional full grid

qcond	function for the inverse of conditional copula cdf; choices are qconbvn and qcondfrk
tau2par	function for maping Kendall's tau to copula parameter; choices are tau2par.bvn and tau2par.frk
start	starting values for the parameters

Value

A list containing the following components:

LogLikelihood	the maximized log-likelihood
Estimates	the MLE
SE	the standard errors

References

Nikoloulopoulos, A.K. (2025) Vine copula mixed models for meta-analysis of diagnostic accuracy studies without a gold standard. *Biometrics*, **81**(2), ujaf037. doi:10.1093/biomtc/ujaf037.

Examples

```
data(Pap)
attach(Pap)

nq=30
gl=gauss.quad.prob(nq,"uniform")
data(mgrid30)
mgrid=mgrid30

tau2par=tau2par.bvn
qcond=qcondbvn

select.random=1:4
start=c(rep(0.6,5),rep(0.5,4),c(0.1,-0.1,0.1))
est.norm=imperfect.quadrivariateVineCopulaREMADA.norm.comprehensive(y11,y10,y01,
y00,gl,mgrid,qcond,tau2par,select.random,start)

detach(Pap)
```

---

imperfect.trivariateVineCopulaREMADA

Maximum likelihood estimation of trivariate 1-truncated D-vine copula mixed models for meta-analysis of diagnostic accuracy studies without a gold standard

---

Description

The estimated parameters can be obtained by using a quasi-Newton method applied to the logarithm of the joint likelihood. This numerical method requires only the objective function, i.e., the logarithm of the joint likelihood, while the gradients are computed numerically and the Hessian matrix of the second order derivatives is updated in each iteration. The standard errors (SE) of the ML estimates can be also obtained via the gradients and the Hessian computed numerically during the maximization process.

Usage

```
imperfect.trivariateVineCopulaREMADA.norm.comprehensive(y11,
y10,y01,y00,gl,mgrid,qcond,tau2par,select.random,start)

imperfect.trivariateVineCopulaREMADA.norm(y11,
y10,y01,y00,gl,mgrid,qcond1,tau2par1,qcond2,tau2par2,select.random,start)

imperfect.trivariateVineCopulaREMADA.beta.comprehensive(y11,
y10,y01,y00,gl,mgrid,qcond,tau2par,select.random,start)

imperfect.trivariateVineCopulaREMADA.beta(y11,
y10,y01,y00,gl,mgrid,qcond1,tau2par1,qcond2,tau2par2,select.random,start)
```

Arguments

`y11`	the number of the test results where the index test outcome is positive and the reference test outcome is positive
`y10`	the number of the test results where the index test outcome is positive and the reference test outcome is negative
`y01`	the number of the test results where the index test outcome is negative and the reference test outcome is positive
`y00`	the number of the test results where the index test outcome is negative and the reference test outcome is negative
`gl`	a list containing the components of Gauss-Legendre nodes `gl$nodes` and weights `gl$weights`
`mgrid`	a list containing three-dimensional arrays. Replicates of the quadrature points that produce a 3-dimensional full grid
`select.random`	vector (t_1, t_2, t_3), where $1 \leq t_1 < t_2 < t_3 \leq 5$, that indicates the random effects
`qcond`	function for the inverse of conditional copula cdf; choices are `qconbvn` and `qcondfrk`
`tau2par`	function for maping Kendall's tau to copula parameter; choices are `tau2par.bvn` and `tau2par.frk`
`qcond1`	function for the inverse of conditional copula cdf for the (t_1, t_2) bivariate margin; choices are `qcondcln` and `qcondcln180`

tau2par1	function for maping Kendall's tau to copula parameter for the (t_1, t_2) bivariate margin; choices are `tau2par.cln` and `tau2par.cln180`
qcond2	function for the inverse of conditional copula cdf for the (t_2, t_3) bivariate margin; choices are `qcondcln90` and `qcondcln270`
tau2par2	function for maping Kendall's tau to copula parameter for the (t_2, t_3) bivariate margin; choices are `tau2par.cln90` and `tau2par.cln270`
start	starting values for the parameters

Value

A list containing the following components:

LogLikelihood	the maximized log-likelihood
Estimates	the MLE
SE	the standard errors

References

Nikoloulopoulos, A.K. (2025) Vine copula mixed models for meta-analysis of diagnostic accuracy studies without a gold standard. *Biometrics*, **81**(2), ujaf037. doi:10.1093/biomtc/ujaf037.

Examples

```
data(Pap)
attach(Pap)

nq=30
gl=gauss.quad.prob(nq,"uniform")
mgrid<- meshgrid(gl$n,gl$n,gl$n,nargout=3)

tau2par=tau2par.bvn
qcond=qcondbvn

select.random=c(1,2,4)
start=c(rep(0.6,5),rep(0.5,3),c(0.01,-0.01))
est.norm=imperfect.trivariateVineCopulaREMADA.norm.comprehensive(y11,y10,
y01,y00,gl,mgrid,qcond,tau2par,select.random,start)

tau2par1=tau2par.cln180
qcond1=qcondcln180
tau2par2=tau2par.cln270
qcond2=qcondcln270
est.norm.cln=imperfect.trivariateVineCopulaREMADA.norm(y11,y10,y01,
y00,gl,mgrid,qcond1,tau2par1,qcond2,tau2par2,select.random,start)

start=c(rep(0.6,5),rep(0.05,3),c(0.1,-0.1))
est.beta=imperfect.trivariateVineCopulaREMADA.beta.comprehensive(y11,y10,y01,y00,
gl,mgrid,qcond,tau2par,select.random,start)

est.beta.cln=imperfect.trivariateVineCopulaREMADA.beta(y11,y10,y01,y00,
```

```
gl,mgrid,qcond1,tau2par1,qcond2,tau2par2,select.random,start)

detach(Pap)
```

`imperfectCopulaREMADA` *Maximum likelihood estimation of bivariate copula mixed models for meta-analysis of diagnostic accuracy studies without a gold standard*

Description

The estimated parameters can be obtained by using a quasi-Newton method applied to the logarithm of the joint likelihood. This numerical method requires only the objective function, i.e., the logarithm of the joint likelihood, while the gradients are computed numerically and the Hessian matrix of the second order derivatives is updated in each iteration. The standard errors (SE) of the ML estimates can be also obtained via the gradients and the Hessian computed numerically during the maximization process.

Usage

```
imperfectCopulaREMADA.norm(y11,y10,y01,y00,
gl,mgrid,qcond,tau2par,select.random,start)

imperfectCopulaREMADA.beta(y11,y10,y01,y00,
gl,mgrid,qcond,tau2par,select.random,start)
```

Arguments

`y11`	the number of the test results where the index test outcome is positive and the reference test outcome is positive
`y10`	the number of the test results where the index test outcome is positive and the reference test outcome is negative
`y01`	the number of the test results where the index test outcome is negative and the reference test outcome is positive
`y00`	the number of the test results where the index test outcome is negative and the reference test outcome is negative
`gl`	a list containing the components of Gauss-Legendre nodes `gl$nodes` and weights `gl$weights`
`mgrid`	a list containing two matrices with the rows of the output matrix x are copies of the vector `gl$nodes`; columns of the output matrix y are copies of the vector `gl$nodes`
`select.random`	vector (t_1, t_2), where $1 \leq t_1 < t_2 \leq 5$, that indicates the random effects
`qcond`	function for the inverse of conditional copula cdf
`tau2par`	function for maping Kendall's tau to copula parameter
`start`	starting values for the parameters

Value

A list containing the following components:

LogLikelihood	the maximized log-likelihood
Estimates	the MLE
SE	the standard errors

References

Nikoloulopoulos, A.K. (2025) Vine copula mixed models for meta-analysis of diagnostic accuracy studies without a gold standard. *Biometrics*, **81**(2), ujaf037. doi:10.1093/biomtc/ujaf037.

Examples

```
data(Pap)
attach(Pap)

nq=30
gl=gauss.quad.prob(nq,"uniform")
mgrid<- meshgrid(gl$n,gl$n)

tau2par=tau2par.bvn
qcond=qcondbvn

select.random=c(1,2)

start=c(rep(0.6,5),rep(0.5,2),-0.1)
est.norm=imperfectCopulaREMADA.norm(y11,y10,y01,y00,gl,mgrid,
qcond,tau2par,select.random,start)

detach(Pap)
```

---

imperfectREMADA *Maximum likelihood estimation of univariate mixed models for meta-analysis of diagnostic accuracy studies without a gold standard*

Description

The estimated parameters can be obtained by using a quasi-Newton method applied to the logarithm of the joint likelihood. This numerical method requires only the objective function, i.e., the logarithm of the joint likelihood, while the gradients are computed numerically and the Hessian matrix of the second order derivatives is updated in each iteration. The standard errors (SE) of the ML estimates can be also obtained via the gradients and the Hessian computed numerically during the maximization process.

Usage

```
imperfectREMADA.norm(y11,y10,y01,y00,gl,select.random,start)

imperfectREMADA.beta(y11,y10,y01,y00,gl,select.random,start)
```

Arguments

y11	the number of the test results where the index test outcome is positive and the reference test outcome is positive
y10	the number of the test results where the index test outcome is positive and the reference test outcome is negative
y01	the number of the test results where the index test outcome is negative and the reference test outcome is positive
y00	the number of the test results where the index test outcome is negative and the reference test outcome is negative
gl	a list containing the components of Gauss-Legendre nodes gl$nodes and weights gl$weights
select.random	a scalar from 1 to 5 that indicates the random effect
start	starting values for the parameters

Value

A list containing the following components:

LogLikelihood	the maximized log-likelihood
Estimates	the MLE
SE	the standard errors

References

Nikoloulopoulos, A.K. (2025) Vine copula mixed models for meta-analysis of diagnostic accuracy studies without a gold standard. *Biometrics*, **81**(2), ujaf037. doi:10.1093/biomtc/ujaf037.

Examples

```
data(Pap)
attach(Pap)

nq=30
gl=gauss.quad.prob(nq,"uniform")
start=c(rep(0.6,5),0.5)
select.random=1
est.norm=imperfectREMADA.norm(y11,y10,y01,y00,gl,
select.random,start)
start=c(rep(0.6,5),0.1)
est.beta=imperfectREMADA.beta(y11,y10,y01,y00,gl,
select.random,start)

detach(Pap)
```

LAG *The lymphangiography data*

Description

Data on 17 studies of lymphangiography (LAG) for the diagnosis of lymph node metastasis in women with cervical cancer, one of three imaging techniques in the meta-analysis in Scheidler et al. (1997). Diagnosis of metastatic disease by LAG is based on the presence of nodal-filling defects.

Usage

```
data(LAG)
```

Format

A data frame with 17 observations on the following 4 variables.

TP the number of true positives

FN the number of false negatives

FP the number of false positives

TN the number of true negatives

References

Scheidler, J., H. Hricak, K. K. Yu, L. Subak, and M. R. Segal. (1997) Radiological evaluation of lymph node metastases in patients with cervical cancer: A meta-analysis. *Journal of the American Medical Association*, **278**, 1096–1101.

mgrid *A list containing four-dimensional arrays*

Description

A list containing four-dimensional arrays. Replicates of the quadrature points that produce a 4-dimensional full grid.

Examples

```
data(mgrid15)
dim(mgrid15$x)
dim(mgrid15$y)
dim(mgrid15$z)
dim(mgrid15$w)

data(mgrid30)
dim(mgrid30$x)
```

```
dim(mgrid30$y)
dim(mgrid30$z)
dim(mgrid30$w)

data(mgrid50)
dim(mgrid50$x)
dim(mgrid50$y)
dim(mgrid50$z)
dim(mgrid50$w)
```

---

mgrid5d *A list containing five-dimensional arrays*

Description

A list containing five-dimensional arrays. Replicates of the quadrature points that produce a 5-dimensional full grid.

Examples

```
data(mgrid5d15)
dim(mgrid5d15$x1)
dim(mgrid5d15$x2)
dim(mgrid5d15$x3)
dim(mgrid5d15$x4)
dim(mgrid5d15$x5)

data(mgrid5d30)
dim(mgrid5d30$x1)
dim(mgrid5d30$x2)
dim(mgrid5d30$x3)
dim(mgrid5d30$x4)
dim(mgrid5d30$x5)
```

---

mgrid6d *A list containing six-dimensional arrays*

Description

A list containing six-dimensional arrays. Replicates of the quadrature points that produce an 6-dimensional full grid.

Examples

```
data(mgrid6d)
dim(mgrid$x1)
dim(mgrid$x2)
dim(mgrid$x3)
dim(mgrid$x4)
dim(mgrid$x5)
dim(mgrid$x6)
```

MK2016 *The coronary CT angiography data in Menke and Kowalski (2016).*

Description

Data on 30 studies from a systematic review for diagnostic accuracy studies of coronary computed tomography angiography for the detection of coronary artery disease.

Usage

```
data(MK2016)
```

Format

A data frame with 30 observations on the following 6 variables.

TP the number of true positives

FN the number of false negatives

FP the number of false positives

TN the number of true negatives

NEP the number of non-evaluable positives

NEN the number of non-evaluable negatives

References

Menke, J. and Kowalski, J. (2016). Diagnostic accuracy and utility of coronary ct angiography with consideration of unevaluable results: A systematic review and multivariate bayesian random-effects meta-analysis with intention to diagnose. *European Radiology*, **26**(2):451–458.

MRI *The magnetic resonance imaging data*

Description

Data on 10 studies of magnetic resonance imaging (MRI) for the diagnosis of lymph node metastasis in women with cervical cancer, the last imaging technique in the meta-analysis in Scheidler et al. (1997). Diagnosis of metastatic disease by MRI relies on nodal enlargement.

Usage

```
data(MRI)
```

Format

A data frame with 10 observations on the following 4 variables.

TP the number of true positives

FN the number of false negatives

FP the number of false positives

TN the number of true negatives

References

Scheidler, J., H. Hricak, K. K. Yu, L. Subak, and M. R. Segal. (1997) Radiological evaluation of lymph node metastases in patients with cervical cancer: A meta-analysis. *Journal of the American Medical Association*, **278**, 1096–1101.

mutinom6dVineCopulaREMADA

Maximum likelihood estimation for multinomial six-variate 1-truncated D-vine copula mixed models for meta-analysis of two diagnostic tests accounting for within and between studies dependence

Description

The estimated parameters can be obtained by using a quasi-Newton method applied to the logarithm of the joint likelihood. This numerical method requires only the objective function, i.e., the logarithm of the joint likelihood, while the gradients are computed numerically and the Hessian matrix of the second order derivatives is updated in each iteration. The standard errors (SE) of the ML estimates can be also obtained via the gradients and the Hessian computed numerically during the maximization process.

Usage

```
multinom6dVineCopulaREMADA.norm(y001,y011,y101,y111,y000,y010,y100,y110,
          gl,mgrid,qcond1,qcond2,qcond3,qcond4,qcond5,
          tau2par1,tau2par2,tau2par3,tau2par4,tau2par5,
          sel1,sel2,sel3)
multinom6dVineCopulaREMADA.beta(y001,y011,y101,y111,y000,y010,y100,y110,
          gl,mgrid,qcond1,qcond2,qcond3,qcond4,qcond5,
          tau2par1,tau2par2,tau2par3,tau2par4,tau2par5,
          sel1,sel2,sel3)
```

Arguments

y001	the number of the test results in the diseased where the test 1 outcome is negative and the test 2 outcome is negative
y011	the number of the test results in the diseased where the test 1 outcome is negative and the test 2 outcome is positive
y101	the number of the test results in the diseased where the test 1 outcome is positive and the test 2 outcome is negative
y111	the number of the test results in the diseased where the test 1 outcome is positive and the test 2 outcome is positive
y000	the number of the test results in the non-diseased where the test 1 outcome is negative and the test 2 outcome is negative
y010	the number of the test results in the non-diseased where the test 1 outcome is negative and the test 2 outcome is positive
y100	the number of the test results in the non-diseased where the test 1 outcome is positive and the test 2 outcome is negative
y110	the number of the test results in the non-diseased where the test 1 outcome is positive and the test 2 outcome is positive
gl	a list containing the components of Gauss-Legendre nodes `gl$nodes` and weights `gl$weights`
mgrid	a list containing six-dimensional arrays. Replicates of the quadrature points that produce a 6-dimensional full grid
qcond1	function for the inverse conditional copula cdf at the (1,2) bivariate margin
qcond2	function for the inverse conditional copula cdf at the (2,3) bivariate margin
qcond3	function for the inverse conditional copula cdf at the (3,4) bivariate margin
qcond4	function for the inverse conditional copula cdf at the (4,5) bivariate margin
qcond5	function for the inverse conditional copula cdf at the (5,6) bivariate margin
tau2par1	function for maping Kendall's tau at the (1,2) bivariate margin to copula parameter
tau2par2	function for maping Kendall's tau at the (2,3) bivariate margin to copula parameter
tau2par3	function for maping Kendall's tau at the (3,4) bivariate margin to copula parameter

`tau2par4`	function for maping Kendall's tau at the (4,5) bivariate margin to copula parameter
`tau2par5`	function for maping Kendall's tau at the (5,6) bivariate margin to copula parameter
`sel1`	Indicates the position of bivariate copulas with positive dependence only such as the Clayton and the Clayton rotated by 180 degrees
`sel2`	Indicates the position of bivariate copulas with negative dependence only such as the Clayton rotated by 90 degrees and the Clayton rotated by 270 degrees
`sel3`	Indicates the position of bivariate copulas with comprehensive dependence such as the BVN and Frank copulas

Value

A list containing the following components:

`minimum`	the value of the estimated minimum of the negative log-likelihood
`estimate`	the MLE
`gradient`	the gradient at the estimated minimum of of the negative log-likelihood
`hessian`	the hessian at the estimated minimum of the negative log-likelihood
`code`	an integer indicating why the optimization process terminated
`iterations`	the number of iterations performed

For more details see `nlm`

References

Nikoloulopoulos, A.K. (2024) Joint meta-analysis of two diagnostic tests accounting for within and between studies dependence. *Statistical Methods in Medical Research*, **33**(10), 1800–1817. doi:10.1177/09622802241269645.

See Also

`rmultinom6dVineCopulaREMADA`

Examples

```
data(Down)
attach(Down)
y111=down_n_11
y110=nodown_n_11
y101=down_n_10
y100=nodown_n_10
y001=down_n_00
y000=nodown_n_00
y010=nodown_n_01
y011=down_n_01

nq=15
```

```
gl=gauss.quad.prob(nq,"uniform")
data(mgrid6d)

tau2par1=tau2par.cln90
qcond1=qcondcln90
tau2par3=tau2par4=tau2par5=tau2par.cln
qcond3=qcond4=qcond5=qcondcln
tau2par2=tau2par.bvn
qcond2=qcondbvn

sel1=3:5; sel2=1; sel3=2

est=multinom6dVineCopulaREMADA.norm(y001,y011,y101,y111,
y000,y010,y100,y110,gl,mgrid,qcond1,qcond2,qcond3,qcond4,qcond5,
tau2par1,tau2par2,tau2par3,tau2par4,tau2par5,sel1,sel2,sel3)

detach(Down)
```

`mutinomVineCopulaREMADA`

Maximum likelihood estimation for multinomial quadrivariate (truncated) D-vine copula mixed models for diagnostic test accurracy studies accounting for non-evaluable outcomes

---

Description

The estimated parameters can be obtained by using a quasi-Newton method applied to the logarithm of the joint likelihood. This numerical method requires only the objective function, i.e., the logarithm of the joint likelihood, while the gradients are computed numerically and the Hessian matrix of the second order derivatives is updated in each iteration. The standard errors (SE) of the ML estimates can be also obtained via the gradients and the Hessian computed numerically during the maximization process.

Usage

```
multinomVineCopulaREMADA.norm(TP,FN,FP,TN,NEP,NEN,
                                gl,mgrid,qcond1,pcond1,tau2par1,
                                qcond2,pcond2,tau2par2)
multinomVineCopulaREMADA.beta(TP,FN,FP,TN,NEP,NEN,
                                gl,mgrid,qcond1,pcond1,tau2par1,
                                qcond2,pcond2,tau2par2)
tmultinomVineCopulaREMADA.norm(TP,FN,FP,TN,NEP,NEN,
                                gl,mgrid,
                                qcond1,pcond1,tau2par1,
                                qcond2,pcond2,tau2par2)
tmultinomVineCopulaREMADA.beta(TP,FN,FP,TN,NEP,NEN,
                                gl,mgrid,
                                qcond1,pcond1,tau2par1,
                                qcond2,pcond2,tau2par2)
```

Arguments

TP	the number of true positives
FN	the number of false negatives
FP	the number of false positives
TN	the number of true negatives
NEP	the number of non-evaluable positives in the presence of non-evaluable subjects
NEN	the number of non-evaluable negatives in the presence of non-evaluable subjects
gl	a list containing the components of Gauss-Legendre nodes `gl$nodes` and weights `gl$weights`
mgrid	a list containing 4-dimensional arrays.
qcond1	function for the inverse conditional copula cdf at the (1,2) and (3,4) bivariate margin
pcond1	function for the conditional copula cdf at the (1,2) and (3,4) bivariate margin
tau2par1	function for maping Kendall's tau at the (1,2) and (3,4) bivariate margin to copula parameter
qcond2	function for the inverse conditional copula cdf at the (2,3) bivariate margin
pcond2	function for the conditional copula cdf at the (2,3) bivariate margin
tau2par2	function for maping Kendall's tau at the (2,3) bivariate margin to copula parameter

Value

A list containing the following components:

minimum	the value of the estimated minimum of the negative log-likelihood
estimate	the MLE
gradient	the gradient at the estimated minimum of of the negative log-likelihood
hessian	the hessian at the estimated minimum of the negative log-likelihood
code	an integer indicating why the optimization process terminated
iterations	the number of iterations performed

For more details see `nlm`

References

Nikoloulopoulos, A.K. (2020) A multinomial quadrivariate D-vine copula mixed model for diagnostic studies meta-analysis in the presence of non-evaluable subjects. *Statistical Methods in Medical Research*, 29 (10), 2988–3005. doi:10.1177/0962280220913898.

See Also

`rmultinomVineCopulaREMADA`

Examples

```
nq=15
gl=gauss.quad.prob(nq,"uniform")
data(mgrid15)

data(MK2016)
attach(MK2016)

out=tmultinomVineCopulaREMADA.beta(TP,FN,FP,TN,NEP,NEN,
gl,mgrid15,qcondcln180,pcondcln180,tau2par.cln180,
qcondcln90,pcondcln90,tau2par.cln90)

detach(MK2016)
```

OGT *The orale glucose tolerance data*

Description

Data on 10 studies of the oral glucose tolerance test for the diagnosis of diabetes mellitus in patients during acute coronary syndrome hospitalization in Ye et al. (2012).

Usage

```
data(OGT)
```

Format

A data frame with 10 observations on the following 4 variables.

TP the number of true positives

FN the number of false negatives

FP the number of false positives

TN the number of true negatives

References

Ye, Y., Xie, H., Zhao, X., Zhang, S. (2012) The oral glucose tolerance test for the diagnosis of diabetes mellitus in patients during acute coronary syndrome hospitalization: a meta-analysis of diagnostic test accuracy. *Cardiovascular Diabetology*, **11**(5):155.

Pap *The Pap test data*

Description

These data are comprised of $N = 59$ studies that published between January 1984 and March 1992. The diagnostic accuracy of the Pap test (i.e., index test) is evaluated by comparing with the histology test (i.e., reference test), which is not a perfect test (Fahey, et al., 1995).

Format

A data frame with 59 observations on the following 4 variables.

y11 the number of the test results where the Pap test outcome is positive and the histology test outcome is positive

y10 the number of the test results where the Pap test outcome is positive and the histology test outcome is negative

y01 the number of the test results where the Pap test outcome is negative and the histology test outcome is positive

y00 the number of the test results where the Pap test outcome is negative and the histology test outcome is negative

References

Fahey, M. T., Irwig, L., and Macaskill, P. (1995). Meta-analysis of pap test accuracy. *American Journal of Epidemiology*, **142**:680–689.

pcondcop *Bivariate copula conditional distribution functions*

Description

Bivariate copula conditional distribution functions

Usage

```
pcondbvn(v,u,cpar)
pcondfrk(v,u,cpar)
pcondcln(v,u,cpar)
pcondcln90(v,u,cpar)
pcondcln270(v,u,cpar)
```

Arguments

v	conditioning value in interval 0,1; could be a vector
u	value in interval 0,1; could be a vector
cpar	copula parameter: scalar.

Details

Choices appending 'cop' are bvn, frk, cln, cln90 (rotated by 90 degrees cln), cln180 (rotated by 180 degrees cln), cln270 (rotated by 270 degrees cln).

See help page for dcop for the abbreviations of the copula names.

Value

inverse conditional cdf value(s)

References

Joe H (1997) *Multivariate Models and Dependence Concepts*. Chapman & Hall

Joe H (2014) *Dependence Modeling with Copulas*. Chapman & Hall/CRC.

Joe H (2014) *CopulaModel: Dependence Modeling with Copulas*. Software for book: *Dependence Modeling with Copulas*, Chapman & Hall/CRC, 2014.

See Also

dcop rcop

---

qcondcop *Bivariate copula conditional quantile functions*

Description

Bivariate copula conditional quantile functions

Usage

```
qcondbvn(p,u,cpar)
qcondfrk(p,u,cpar)
qcondcln(p,u,cpar)
qcondcln90(p,u,cpar)
qcondcln270(p,u,cpar)
```

Arguments

u	conditioning value in interval 0,1; could be a vector
p	quantile in interval 0,1; could be a vector
cpar	copula parameter: scalar.

Details

Choices appending 'cop' are bvn, frk, cln, cln90 (rotated by 90 degrees cln), cln180 (rotated by 180 degrees cln), cln270 (rotated by 270 degrees cln).

See help page for dcop for the abbreviations of the copula names.

Value

inverse conditional cdf value(s)

References

Joe H (1997) *Multivariate Models and Dependence Concepts*. Chapman & Hall

Joe H (2014) *Dependence Modeling with Copulas*. Chapman & Hall/CRC.

Joe H (2014) *CopulaModel: Dependence Modeling with Copulas*. Software for book: *Dependence Modeling with Copulas*, Chapman & Hall/CRC, 2014.

See Also

dcop rcop

`quadVineCopulaREMADA` *Maximum likelihood estimation of quadrivariate D-vine copula mixed models for joint meta-analysis and comparison of two diagnostic tests*

Description

The estimated parameters can be obtained by using a quasi-Newton method applied to the logarithm of the joint likelihood. This numerical method requires only the objective function, i.e., the logarithm of the joint likelihood, while the gradients are computed numerically and the Hessian matrix of the second order derivatives is updated in each iteration. The standard errors (SE) of the ML estimates can be also obtained via the gradients and the Hessian computed numerically during the maximization process.

Usage

```
quadVineCopulaREMADA.norm(TP1,FN1,FP1,TN1,TP2,FN2,FP2,TN2,
                          gl,mgrid,qcond1,pcond1,tau2par1,
                          qcond2,pcond2,tau2par2)

quadVineCopulaREMADA.beta(TP1,FN1,FP1,TN1,TP2,FN2,FP2,TN2,
                          gl,mgrid,qcond1,pcond1,tau2par1,
                          qcond2,pcond2,tau2par2)
quadVineCopulaREMADA.norm.beta(TP1,FN1,FP1,TN1,TP2,FN2,FP2,TN2,
                          gl,mgrid,qcond1,pcond1,tau2par1,
                          qcond2,pcond2,tau2par2)
```

Arguments

TP1	the number of true positives for test 1
FN1	the number of false negatives for test 1
FP1	the number of false positives for test 1
TN1	the number of true negatives for test 1
TP2	the number of true positives for test 2
FN2	the number of false negatives for test 2
FP2	the number of false positives for test 2
TN2	the number of true negatives for test 2
gl	a list containing the components of Gauss-Legendre nodes `gl$nodes` and weights `gl$weights`
mgrid	a list containing four-dimensional arrays. Replicates of the quadrature points that produce a 4-dimensional full grid
qcond1	function for the inverse conditional copula cdf at the (1,2) bivariate margin
pcond1	function for the conditional copula cdf at the (1,2) bivariate margin
tau2par1	function for maping Kendall's tau at the (1,2) bivariate margin to copula parameter
qcond2	function for the inverse conditional copula cdf at the (3,4) bivariate margin
pcond2	function for the conditional copula cdf at the (3,4) bivariate margin
tau2par2	function for maping Kendall's tau at the (3,4) bivariate margin to copula parameter

Value

A list containing the following components:

minimum	the value of the estimated minimum of the negative log-likelihood
estimate	the MLE
gradient	the gradient at the estimated minimum of of the negative log-likelihood
hessian	the hessian at the estimated minimum of the negative log-likelihood
code	an integer indicating why the optimization process terminated
iterations	the number of iterations performed

For more details see `nlm`

References

Nikoloulopoulos, A.K. (2019) A D-vine copula mixed model for joint meta-analysis and comparison of diagnostic tests. *Statistical Methods in Medical Research*, 28(10-11):3286–3300. doi:10.1177/0962280218796685.

Examples

```
nq=15
gl=gauss.quad.prob(nq,"uniform")
data(mgrid15)

data(arthritis)
attach(arthritis)

qcond1=qcondcln270
pcond1=pcondcln270
tau2par1=tau2par.cln270

qcond2=qcondfrk
pcond2=pcondfrk
tau2par2=tau2par.frk

out<-quadVineCopulaREMADA.norm(TP1,FN1,FP1,TN1,TP2,FN2,FP2,TN2,
gl,mgrid15,qcond1,pcond1,tau2par1,qcond2,pcond2,tau2par2)

detach(arthritis)
```

`rcop` *Simulation from parametric bivariate copula families*

Description

Simulation from parametric bivariate copula families

Usage

```
rbvn(N,cpar)
rfrk(N,cpar)
rcln(N,cpar)
rcln90(N,cpar)
rcln270(N,cpar)
```

Arguments

`N`	sample size
`cpar`	copula parameter: scalar

Details

Choices are 'cop' in rcop are bvn, frk, cln, cln90 (rotated by 90 degrees cln), cln180 (rotated by 180 degrees cln), cln270 (rotated by 270 degrees cln).

See help page for dcop for the abbreviations of the copula names.

Value

nx2 matrix with values in (0,1)

References

Joe H (1997) *Multivariate Models and Dependence Concepts*. Chapman & Hall

Joe H (2014) *Dependence Modeling with Copulas*. Chapman & Hall/CRC.

Joe H (2014) *CopulaModel: Dependence Modeling with Copulas*. Software for book: *Dependence Modeling with Copulas*, Chapman & Hall/CRC, 2014.

See Also

qcondcop dcop

`rCopulaREMADA` *Simulation from copula mixed models for diagnostic test accuaracy studies*

Description

To simulate the data we have used the following steps:

1. Simulate the study size n from a shifted gamma distribution with parameters $\alpha = 1.2, \beta = 0.01, lag = 30$ and round off to the nearest integer.

2. Simulate (u_1, u_2) from a parametric family of copulas 'cop'.

3. Convert to beta realizations or normal realizations.

4. Draw the number of diseased n_1 from a $B(n, 0.43)$ distribution.

5. Set $n_2 = n - n_1, y_j = n_j x_j$ and then round y_j for $j = 1, 2$.

Usage

```
rCopulaREMADA.norm(N,p,si,tau,rcop,tau2par)
rCopulaREMADA.beta(N,p,g,tau,rcop,tau2par)
```

Arguments

`N`	sample size
`p`	Pair (π_1, π_2) of sensitivity/specificity
`si`	Pair (σ_1, σ_2) of variability; normal margins
`g`	Pair (γ_1, γ_2) of variability; beta margins
`tau`	Kendall's tau value
`rcop`	function for copula generation
`tau2par`	function for mapping from Kendall's tau to copula parameter

Value

A list containing the following simulated components:

TP	the number of true positives
FN	the number of false negatives
FP	the number of false positives
TN	the number of true negatives

References

Nikoloulopoulos, A.K. (2015) A mixed effect model for bivariate meta-analysis of diagnostic test accuracy studies using a copula representation of the random effects distribution. *Statistics in Medicine*, **34**, 3842–3865. doi:10.1002/sim.6595.

See Also

CopulaREMADA rcop

Examples

```
nq=15
gl=gauss.quad.prob(nq,"uniform")
mgrid<- meshgrid(gl$n,gl$n)

N=20
tau=-0.5
p=c(0.7,0.9)
g=c(0.2,0.1)
simDat=rCopulaREMADA.beta(N,p,g,tau,rcln270,tau2par.cln270)
TP=simDat$TP
TN=simDat$TN
FP=simDat$FP
FN=simDat$FN
c270est.b=CopulaREMADA.beta(TP,FN,FP,TN,gl,mgrid,qcondcln270,tau2par.cln270)

si=c(2,1)
tau=0.5
simDat=rCopulaREMADA.norm(N,p,si,tau,rcln,tau2par.cln)
TP=simDat$TP
TN=simDat$TN
FP=simDat$FP
FN=simDat$FN
cest.n=CopulaREMADA.norm(TP,FN,FP,TN,gl,mgrid,qcondcln,tau2par.cln)
```

`rFactorCopulaREMADA` *Simulation from 1-factor copula mixed models for joint meta-analysis of T diagnostic tests*

Description

Simulation from 1-factor copula mixed models for joint meta-analysis of T diagnostic tests

Usage

```
rFactorCopulaREMADA.norm(N,p,si,taus,qcond1,tau2par1,qcond2,tau2par2)
rFactorCopulaREMADA.beta(N,p,g,taus,qcond1,tau2par1,qcond2,tau2par2)
```

Arguments

`N`	number of studies
`p`	vector of sensitivities and specificities
`si`	vector of variabilities; normal margins
`g`	vector of variabilities; beta margins
`taus`	Kendall's tau values
`qcond1`	function for the inverse conditional copula cdfs that link the factor with the latent sensitivities
`tau2par1`	function for maping Kendall's tau to copula parameter at the copulas that link the factor with the latent sensitivities
`qcond2`	function for the inverse conditional copula cdfs that link the factor with the latent specificities
`tau2par2`	function for maping Kendall's tau to copula parameter at the copulas that link the factor with the latent specificities

Value

A list with the simulated data in matrices with T columns and N rows.

TP the number of true positives

FN the number of false negatives

FP the number of false positives

TN the number of true negatives

References

Nikoloulopoulos, A.K. (2022) An one-factor copula mixed model for joint meta-analysis of multiple diagnostic tests. *Journal of the Royal Statistical Society: Series A (Statistics in Society)*, 185 (3), 1398–1423. doi:10.1111/rssa.12838.

Examples

```
N=50

qcond1=qcondcln
tau2par1=tau2par.cln
qcond2=qcondcln270
tau2par2=tau2par.cln270

p=c(0.8,0.7,0.8,0.7,0.8,0.7)
mu=log(p/(1-p))
si=rep(1,6)
taus=c(0.6,0.7,0.5,-0.3,-0.4,-0.2)

out=rFactorCopulaREMADA.norm(N,p,si,taus,qcond1,tau2par1,qcond2,tau2par2)

TP=out$TP
FN=out$FN
TN=out$TN
FP=out$FP
```

---

rimperfect.trivariateVineCopulaREMADA

Simulation from trivariate 1-truncated D-vine copula mixed models for meta-analysis of diagnostic accuracy studies without a gold standard

---

Description

Simulation from trivariate 1-truncated D-vine copula mixed models for meta-analysis of diagnostic accuracy studies without a gold standard

Usage

```
rimperfect.trivariateVineCopulaREMADA.norm(N,p,si,taus,select.random,qcond1,
tau2par1,qcond2,tau2par2)
rimperfect.trivariateVineCopulaREMADA.beta(N,p,g,taus,select.random,qcond1,
tau2par1,qcond2,tau2par2)
```

Arguments

N	sample size
p	Vector $(\pi_1, \pi_2, \pi_3, \pi_4, \pi_5)$, where π_1 is the meta-analytic parameter for the prevalence, π_2 and π_3 are the meta-analytic parameters for the sensitivity of the index and the reference test, respectively, and π_4 and π_5 are the meta-analytic parameters for the specificity of the index and the reference test, respectively.
si	Vector $(\sigma_1, \sigma_2, \sigma_3)$, where σ_t, $t = 1, \ldots, 3$ denote the between-study heterogeneities (normal margins)

g	Vector $(\gamma_1, \gamma_2, \gamma_3)$ whereγ_t, $t = 1, \ldots, 3$ denote the between-study heterogeneities (beta margins)
taus	Kendall's tau values
select.random	vector (t_1, t_2, t_3), where $1 \leq t_1 < t_2 < t_3 \leq 5$
qcond1	function for the inverse of conditional copula cdf for the (t_1, t_2) bivariate margin; choices are qcondbvn, qcondfrk, qcondcln, qcondcln90, qcondcln180 and qcondcln270
tau2par1	function for maping Kendall's tau to copula parameter for the (t_1, t_2) bivariate margin; choices are tau2par.bvn, tau2par.frk, tau2par.cln, tau2par.cln90, tau2par.cln180 and tau2par.cln270
qcond2	function for the inverse of conditional copula cdf for the (t_2, t_3) bivariate margin; choices are qcondbvn, qcondfrk, qcondcln, qcondcln90, qcondcln180 and qcondcln270
tau2par2	function for maping Kendall's tau to copula parameter for the (t_2, t_3) bivariate margin; choices are tau2par.bvn, tau2par.frk, tau2par.cln, tau2par.cln90, tau2par.cln180 and tau2par.cln270

Value

Simulated data with 4 columns and N rows.

y11 the number of the test results where the index test outcome is positive and the reference test outcome is positive

y10 the number of the test results where the index test outcome is positive and the reference test outcome is negative

y01 the number of the test results where the index test outcome is negative and the reference test outcome is positive

y00 the number of the test results where the index test outcome is negative and the reference test outcome is negative

References

Nikoloulopoulos, A.K. (2025) Vine copula mixed models for meta-analysis of diagnostic accuracy studies without a gold standard. *Biometrics*, **81**(2), ujaf037. doi:10.1093/biomtc/ujaf037.

Examples

```
N=59
p=c(0.631,0.653,0.902,0.843,0.987)
si=c(1.513,1.341,1.341)
taus=c(0.3,-0.3)
select.random=c(1,2,4)

out=rimperfect.trivariateVineCopulaREMADA.norm(N,p,si,taus,select.random,
qcondcln180,tau2par.cln180,qcondcln270,tau2par.cln270)

g=c(0.290,0.244,0.190)
out=rimperfect.trivariateVineCopulaREMADA.beta(N,p,g,taus,select.random,
qcondcln180,tau2par.cln180,qcondcln270,tau2par.cln270)
```

`rmultinom6dVineCopulaREMADA` *Simulation from multinomial six-variate 1-truncated D-vine copula mixed models for meta-analysis of two diagnostic tests accounting for within and between studies dependence*

Description

Simulation from multinomial six-variate 1-truncated D-vine copula mixed models for meta-analysis of two diagnostic tests accounting for within and between studies dependence

Usage

```
rmultinom6dVineCopulaREMADA.norm(N,p,si,taus,qcond,tau2par)
rmultinom6dVineCopulaREMADA.beta(N,p,g,taus,qcond,tau2par)
```

Arguments

`N`	sample size
`p`	Vector $(\pi_{101}, \pi_{011}, \pi_{111}, \pi_{100}, \pi_{010}, \pi_{110})$ of the meta-analytic parameters of interest for each combination of test results in diseased and non-diseased participants in a 4×2 table
`si`	Vector $(\sigma_{101}, \sigma_{011}, \sigma_{111}, \sigma_{100}, \sigma_{010}, \sigma_{110})$ of variability parameters; normal margins
`g`	Vector $(\gamma_{101}, \gamma_{011}, \gamma_{111}, \gamma_{100}, \gamma_{010}, \gamma_{110})$ of variability parameters; beta margins
`taus`	Kendall's tau values
`qcond`	function for the inverse conditional copula cdf
`tau2par`	function for maping Kendall's taus to copula parameters

Value

Simulated data with 8 columns and N rows.

y001 the number of the test results in the diseased where the test 1 outcome is negative and the test 2 outcome is negative

y011 the number of the test results in the diseased where the test 1 outcome is negative and the test 2 outcome is positive

y101 the number of the test results in the diseased where the test 1 outcome is positive and the test 2 outcome is negative

y111 the number of the test results in the diseased where the test 1 outcome is positive and the test 2 outcome is positive

y000 the number of the test results in the non-diseased where the test 1 outcome is negative and the test 2 outcome is negative

y010 the number of the test results in the non-diseased where the test 1 outcome is negative and the test 2 outcome is positive

y100 the number of the test results in the non-diseased where the test 1 outcome is positive and the test 2 outcome is negative

y110 the number of the test results in the non-diseased where the test 1 outcome is positive and the test 2 outcome is positive

References

Nikoloulopoulos, A.K. (2024) Joint meta-analysis of two diagnostic tests accounting for within and between studies dependence. *Statistical Methods in Medical Research*, **33**(10), 1800–1817. doi:10.1177/09622802241269645.

See Also

dvine6dsim

Examples

```
N=11
p=c(0.03667409,  0.09299767,  0.29450436,  0.01733081,  0.04923809,  0.02984361)
si=c(1.69868880, 0.54292079,  0.58489574,  0.92918177,  0.48998484,  0.57004098)
taus=c(-0.52475006,  0.55768873, 0.18454559,  0.02233204,  0.57570506)


tau2par=tau2par.bvn
qcond=qcondbvn

out=rmultinom6dVineCopulaREMADA.norm(N,p,si,taus,qcond,tau2par)


y101=out[,1]
y011=out[,2]
y111=out[,3]
y001=out[,4]
y100=out[,5]
y010=out[,6]
y110=out[,7]
y000=out[,8]
```

`rmultinomVineCopulaREMADA` *Simulation from multinomial quadrivariate (truncated) D-vine copula mixed models for diagnostic test accurracy studies accounting for non-evaluable outcomes*

Description

Simulation from multinomial quadrivariate (truncated) D-vine copula mixed models for diagnostic test accurracy studies accounting for non-evaluable outcomes

Usage

```
rmultinomVineCopulaREMADA.norm(N,p,si,taus,qcond1,
                                    pcond1,tau2par1,qcond2,
                                    pcond2,tau2par2)
rmultinomVineCopulaREMADA.beta(N,p,g,taus,qcond1,
                                    pcond1,tau2par1,qcond2,
                                    pcond2,tau2par2)
```

Arguments

N	sample size
p	Vector (π_1, π_2, π_3) of sensitivity/specificity/prevalence
si	Vector $(\sigma_1, \sigma_2, \sigma_3)$ of variability; normal margins
g	Vector $(\gamma_1, \gamma_2, \gamma_3)$ of variability; beta margins
taus	Kendall's tau values
qcond1	function for the inverse conditional copula cdf at the (1,2) and (3,4) bivariate margin
pcond1	function for the conditional copula cdf at the (1,2) and (3,4) bivariate margin
tau2par1	function for maping Kendall's tau at the (1,2) and (3,4) bivariate margin to copula parameter
qcond2	function for the inverse conditional copula cdf at the (2,3) bivariate margin
pcond2	function for the conditional copula cdf at the (2,3) bivariate margin
tau2par2	function for maping Kendall's tau at the (2,3) bivariate margin to copula parameter

Value

Simulated data with 6 columns and N rows.

TP the number of true positives

FN the number of false negatives

FP the number of false positives

TN the number of true negatives

NEP the number of non-evaluable positives

NEN the number of non-evaluable negatives

References

Nikoloulopoulos, A.K. (2020) A multinomial quadrivariate D-vine copula mixed model for diagnostic studies meta-analysis in the presence of non-evaluable subjects. *Statistical Methods in Medical Research*, 29 (10), 2988–3005. doi:10.1177/0962280220913898.

See Also

dvinesim

Examples

```
N=30
p=c(0.898745016,0.766105342,0.059168715,0.109217888)
g=c(0.090270947,0.079469009,0.367463579,0.154976269)
taus=c( 0.82050793,-0.51867629,0.26457961)

qcond1=qcondcln180
pcond1=pcondcln180
tau2par1=tau2par.cln180

qcond2=qcondcln90
pcond2=pcondcln90
tau2par2=tau2par.cln90

out=rmultinomVineCopulaREMADA.beta(N,p,g,taus,qcond1,pcond1,tau2par1,qcond2,pcond2,tau2par2)

TP=out[,1]
NEP=out[,2]
FN=out[,3]
TN=out[,4]
NEN=out[,5]
FP=out[,6]
```

`rVineCopulaREMADA` *Simulation from trivariate vine copula mixed models for diagnostic test accuaracy studies accounting for disease prevalence and non-evaluable results*

Description

Simulation from trivariate vine copula mixed models for diagnostic test accuaracy studies accounting for disease prevalence and non-evaluable results

Usage

```
rVineCopulaREMADA.beta(N,p,g,taus,omega1,omega0,qcondcop12,qcondcop13,
qcondcop23,tau2par12,tau2par13,tau2par23)
rVineCopulaREMADA.norm(N,p,si,taus,omega1,omega0,qcondcop12,qcondcop13,
qcondcop23,tau2par12,tau2par13,tau2par23)
```

Arguments

`N`	sample size
`p`	Vector (π_1, π_2, π_3) of sensitivity/specificity/prevalence
`si`	Vector $(\sigma_1, \sigma_2, \sigma_3)$ of variability; normal margins
`g`	Vector $(\gamma_1, \gamma_2, \gamma_3)$ of variability; beta margins
`taus`	Kendall's tau values

omega1	the probability for non-evaluable positives
omega0	the probability for non-evaluable negatives
qcondcop12	function for the inverse of conditional copula cdf at the (1,2) bivariate margin
qcondcop13	function for the inverse of conditional copula cdf at the (1,3) bivariate margin
qcondcop23	function for the inverse of conditional copula cdf at the (2,3|1) bivariate margin
tau2par12	function for maping Kendall's tau at the (1,2) bivariate margin to copula parameter
tau2par13	function for maping Kendall's tau at the (1,3) bivariate margin to copula parameter
tau2par23	function for maping Kendall's tau at the (2,3|1) bivariate margin to the conditional copula parameter

Value

Simuated data with 6 columns and N rows.

TP the number of true positives

FN the number of false negatives

FP the number of false positives

TN the number of true negatives

NEP the number of non-evaluable positives

NEN the number of non-evaluable negatives

References

Nikoloulopoulos, A.K. (2017) A vine copula mixed effect model for trivariate meta-analysis of diagnostic test accuracy studies accounting for disease prevalence. *Statistical Methods in Medical Research*, **26**, 2270–2286. doi:10.1177/0962280215596769.

Nikoloulopoulos, A.K. (2018) A vine copula mixed model for trivariate meta-analysis of diagnostic studies accounting for disease prevalence and non-evaluable subjects. *ArXiv e-prints*, arXiv:1812.03685. https://arxiv.org/abs/1812.03685.

See Also

rCopulaREMADA rcop cvinesim

Examples

```
p=c(0.8,0.7,0.4)
g=c(0.1,0.1,0.05)
taus=c(-0.5,-0.3,-0.0001)
qcondcop12=qcondcop23=qcondcop13=qcondcln90
tau2par12=tau2par23=tau2par13=tau2par.cln90
# in the absence of non-evaluable results
omega1=0
omega0=0
```

```
rVineCopulaREMADA.beta(50,p,g,taus,omega1,omega0,
qcondcop12,qcondcop13,qcondcop23,tau2par12,
tau2par13,tau2par23)
# in the presence of non-evaluable results
omega1=0.1
omega0=0.2
rVineCopulaREMADA.beta(50,p,g,taus,omega1,omega0,
qcondcop12,qcondcop13,qcondcop23,tau2par12,
tau2par13,tau2par23)
```

SROC *Summary receiver operating characteristic curves for copula mixed effect models for bivariate meta-analysis of diagnostic test accuracy studies*

Description

Summary receiver operating characteristic (SROC) curves are demonstrated for the proposed models through quantile regression techniques and different characterizations of the estimated bivariate random effects distribution

Usage

```
SROC.norm(param,dcop,qcondcop,tau2par,TP,FN,FP,TN,
          points=TRUE,curves=TRUE,
          NEP=rep(0,length(TP)),NEN=rep(0,length(TP)))
SROC.beta(param,dcop,qcondcop,tau2par,TP,FN,FP,TN,
          points=TRUE,curves=TRUE,
          NEP=rep(0,length(TP)),NEN=rep(0,length(TP)))
SROC(param.beta,param.normal,TP,FN,FP,TN,
          NEP=rep(0,length(TP)),NEN=rep(0,length(TP)))
```

Arguments

param	A vector with the sensitivities, specifities, variabilities and Kendall's tau value (the latter only for SROC.norm and SROC.beta)
param.beta	A vector with the sensitivity, specifity and variabilities of the countermonotonic CopulaREMADA with beta margins
param.normal	A vector with the sensitivity, specifity and variabilities of the countermonotonic CopulaREMADA with normal margins
dcop	function for copula density
qcondcop	function for the inverse of conditional copula cdf
tau2par	function for maping Kendall's tau to copula parameter
TP	the number of true positives
FN	the number of false negatives

FP	the number of false positives
TN	the number of true negatives
points	logical: print individual studies
curves	logical: print quantile regression curves
NEP	the number of non-evaluable positives in the presence of non-evaluable subjects
NEN	the number of non-evaluable negatives in the presence of non-evaluable subjects

Value

Summary receiver operating characteristic curves

References

Nikoloulopoulos, A.K. (2015) A mixed effect model for bivariate meta-analysis of diagnostic test accuracy studies using a copula representation of the random effects distribution. *Statistics in Medicine*, **34**, 3842–3865. doi:10.1002/sim.6595.

See Also

CopulaREMADA rCopulaREMADA

Examples

```
nq=15
gl=gauss.quad.prob(nq,"uniform")
mgrid<- meshgrid(gl$n,gl$n)

data(telomerase)
attach(telomerase)
est.n=countermonotonicCopulaREMADA.norm(TP,FN,FP,TN,gl,mgrid)
est.b=countermonotonicCopulaREMADA.beta(TP,FN,FP,TN,gl,mgrid)
SROC(est.b$e,est.n$e,TP,FN,FP,TN)
detach(telomerase)

data(LAG)
attach(LAG)
c180est.b=CopulaREMADA.beta(TP,FN,FP,TN,gl,mgrid,qcondcln180,tau2par.cln180)
SROC.beta(c180est.b$e,dcln180,qcondcln180,tau2par.cln180,TP,FN,FP,TN)
detach(LAG)

data(MRI)
attach(MRI)
c270est.n=CopulaREMADA.norm(TP,FN,FP,TN,gl,mgrid,qcondcln270,tau2par.cln270)
SROC.norm(c270est.n$e,dcln270,qcondcln270,tau2par.cln270,TP,FN,FP,TN)
detach(MRI)

data(MK2016)
attach(MK2016)
p=c(0.898745016,0.766105342,0.059168715,0.109217888)
g=c(0.090270947,0.079469009,0.367463579,0.154976269)
```

```
taus=c(0.82050793,-0.51867629,0.26457961)
SROC.beta(c(p[1:2],g[1:2],taus[1]),
          dcln180,qcondcln180,tau2par.cln180,
          TP,FN,FP,TN,points=TRUE,curves=TRUE,NEP,NEN)
detach(MK2016)
```

---

tau2par *Mapping of Kendall's tau and copula parameter*

Description

Bivariate copulas: mapping of Kendall's tau and copula parameter.

Usage

```
tau2par.bvn(tau)
tau2par.frk(tau)
tau2par.cln(tau)
tau2par.cln90(tau)
tau2par.cln180(tau)
tau2par.cln270(tau)
```

Arguments

tau	Kendall's tau for the copula

Details

For abbreviations of names of copula families (after the dot in function names), see dcop help page.

Value

copula parameter

References

Joe H (1997) *Multivariate Models and Dependence Concepts*. Chapman & Hall

Joe H (2014) *Dependence Modeling with Copulas*. Chapman & Hall/CRC.

Joe H (2014) *CopulaModel: Dependence Modeling with Copulas*. Software for book: *Dependence Modeling with Copulas*, Chapman & Hall/CRC, 2014.

See Also

dcop

telomerase *The telomerase data*

Description

In Glas et al. (2003) the telomerase marker for the diagnosis of bladder cancer is evaluated using 10 studies. The interest was to define if this non-invasive and cheap marker could replace the standard of cystoscopy or histopathology.

Usage

```
data(telomerase)
```

Format

A data frame with 10 observations on the following 4 variables.

TP the number of true positives

FN the number of false negatives

FP the number of false positives

TN the number of true negatives

References

Glas A.S., Roos D., Deutekom M., Zwinderman A.H., Bossuyt P.M., Kurth K.H. (2003) Tumor markers in the diagnosis of primary bladder cancer. A systematic review. *Journal of Urology*, **169**(6), 1975–82.

vine.vuong *Vuong's test for the comparison of non-nested vine copula mixed models for diagnostic test accuaracy studies*

Description

Vuong (1989)'s test for the comparison of non-nested vine copula mixed models for diagnostic test accuaracy studies. It shows if a vine copula mixed model provides better fit than the standard GLMM. We compute the Vuong's test with Model 1 being the vine copula mixed model with BVN copula and normal margins, i.e., the standard GLMM.

Usage

```
vine.vuong.beta(qcondcop12,qcondcop13,qcondcop23,
tau2par12,tau2par13,tau2par23,param1,param2,TP,FN,FP,TN,gl,mgrid,NEP,NEN)
vine.vuong.norm(qcondcop12,qcondcop13,qcondcop23,
tau2par12,tau2par13,tau2par23,param1,param2,TP,FN,FP,TN,gl,mgrid,NEP,NEN)
tvine.vuong.beta(qcondcop12,qcondcop13,
tau2par12,tau2par13,param1,param2,TP,FN,FP,TN,gl,mgrid,NEP,NEN)
tvine.vuong.norm(qcondcop12,qcondcop13,
tau2par12,tau2par13,param1,param2,TP,FN,FP,TN,gl,mgrid,NEP,NEN)
tvine2.vuong.beta(qcondcop12,qcondcop13,
tau2par12,tau2par13,param1,param2,TP,FN,FP,TN,gl,mgrid,NEP,NEN)
tvine2.vuong.norm(qcondcop12,qcondcop13,
tau2par12,tau2par13,param1,param2,TP,FN,FP,TN,gl,mgrid,NEP,NEN)
```

Arguments

qcondcop12	function for the inverse of conditional copula cdf at the (1,2) bivariate margin for Model 2
qcondcop13	function for the inverse of conditional copula cdf at the (1,3) bivariate margin for Model 2
qcondcop23	function for the inverse of conditional copula cdf at the (2,3|1) bivariate margin for Model 2
tau2par12	function for maping Kendall's tau at the (1,2) bivariate margin to copula parameter for Model 2
tau2par13	function for maping Kendall's tau at the (1,3) bivariate margin to copula parameter for Model 2
tau2par23	function for maping Kendall's tau at the (2,3|1) bivariate margin to the conditional copula parameter for Model 2
param1	parameters for the Model 1. i.e., the GLMM
param2	parameters for the Model 2
TP	the number of true positives
FN	the number of false negatives
FP	the number of false positives
TN	the number of true negatives
gl	a list containing the components of Gauss-Legendre nodes `gl$nodes` and weights `gl$weights`
mgrid	a list containing three-dimensional arrays
NEP	the number of non-evaluable positives in the presence of non-evaluable subjects
NEN	the number of non-evaluable negatives in the presence of non-evaluable subjects

Value

A list containing the following components:

z	the test statistic
p-value	the p-value

References

Nikoloulopoulos, A.K. (2017) A vine copula mixed effect model for trivariate meta-analysis of diagnostic test accuracy studies accounting for disease prevalence. *Statistical Methods in Medical Research*, **26**, 2270–2286. doi:10.1177/0962280215596769.

Nikoloulopoulos, A.K. (2020) An extended trivariate vine copula mixed model for meta-analysis of diagnostic studies in the presence of non-evaluable outcomes. *The International Journal of Biostatistics*, 16(2). doi:10.1515/ijb20190107.

Vuong Q.H. (1989) Likelihood ratio tests for model selection and non-nested hypotheses. *Econometrica*, **57**, 307–333.

See Also

CopulaREMADA

Examples

```
nq=15
gl=gauss.quad.prob(nq,"uniform")
mgrid=meshgrid(gl$n,gl$n,gl$n,nargout=3)

data(betaDG)
attach(betaDG)
#nest.n2=VineCopulaREMADA.norm(TP,FN,FP,TN,gl,mgrid,
#qcondbvn,qcondbvn,qcondbvn,
#tau2par.bvn,tau2par.bvn,tau2par.bvn)
nest.n2.est= #nest.n2$e
c(0.87186926,  0.13696066,  0.70614956,  0.69152133,
0.51780203,  0.70883558, -0.41354870,0.07701287, -0.12111253)
#c090est.b2=VineCopulaREMADA.beta(TP,FN,FP,TN,gl,mgrid,
#qcondcln90,qcondcln,qcondcln90,tau2par.cln90,tau2par.cln,tau2par.cln90)
c090est.b2.est= #c090est.b2$e
c(0.85528463,  0.14667571,  0.68321231,  0.04897466,
0.02776290,  0.08561436, -0.34639172, 0.04621924, -0.21627977)
c090vuong.b2=vine.vuong.beta(qcondcln90,qcondcln,qcondcln90,
tau2par.cln90,tau2par.cln,tau2par.cln90,
nest.n2.est,c090est.b2.est,TP,FN,FP,TN,gl,mgrid)
c090vuong.b2
detach(betaDG)
```

`VineCopulaREMADA` *Maximum likelihood estimation for (truncated) vine copula mixed models for diagnostic test accurracy studies accounting for disease prevalence and non-evaluable outcomes*

Description

The estimated parameters can be obtained by using a quasi-Newton method applied to the logarithm of the joint likelihood. This numerical method requires only the objective function, i.e., the logarithm of the joint likelihood, while the gradients are computed numerically and the Hessian matrix of the second order derivatives is updated in each iteration. The standard errors (SE) of the ML estimates can be also obtained via the gradients and the Hessian computed numerically during the maximization process.

Usage

```
VineCopulaREMADA.norm(TP,FN,FP,TN,gl,mgrid,
                              qcondcop12,qcondcop13,qcondcop23,
                              tau2par12,tau2par13,tau2par23,
                              NEP,NEN)
VineCopulaREMADA.beta(TP,FN,FP,TN,gl,mgrid,
                              qcondcop12,qcondcop13,qcondcop23,
                              tau2par12,tau2par13,tau2par23,
                              NEP,NEN)
tVineCopulaREMADA.norm(TP,FN,FP,TN,gl,mgrid,
                              qcondcop12,qcondcop13,
                              tau2par12,tau2par13,
                              NEP,NEN)
tVineCopulaREMADA.beta(TP,FN,FP,TN,gl,mgrid,
                              qcondcop12,qcondcop13,
                              tau2par12,tau2par13,
                              NEP,NEN)
```

Arguments

TP	the number of true positives
FN	the number of false negatives
FP	the number of false positives
TN	the number of true negatives
gl	a list containing the components of Gauss-Legendre nodes gl$nodes and weights gl$weights
mgrid	a list containing three-dimensional arrays. Replicates of the quadrature points that produce a 3-dimensional full grid
qcondcop12	function for the inverse of conditional copula cdf at the (1,2) bivariate margin
qcondcop13	function for the inverse of conditional copula cdf at the (1,3) bivariate margin
qcondcop23	function for the inverse of conditional copula cdf at the (2,3|1) bivariate margin
tau2par12	function for maping Kendall's tau at the (1,2) bivariate margin to copula parameter
tau2par13	function for maping Kendall's tau at the (1,3) bivariate margin to copula parameter

tau2par23	function for maping Kendall's tau at the (2,3|1) bivariate margin to the conditional copula parameter
NEP	the number of non-evaluable positives in the presence of non-evaluable subjects
NEN	the number of non-evaluable negatives in the presence of non-evaluable subjects

Value

A list containing the following components:

minimum	the value of the estimated minimum of the negative log-likelihood
estimate	the MLE
gradient	the gradient at the estimated minimum of of the negative log-likelihood
hessian	the hessian at the estimated minimum of the negative log-likelihood
code	an integer indicating why the optimization process terminated
iterations	the number of iterations performed

For more details see nlm

References

Nikoloulopoulos, A.K. (2017) A vine copula mixed effect model for trivariate meta-analysis of diagnostic test accuracy studies accounting for disease prevalence. *Statistical Methods in Medical Research*, **26**, 2270–2286. doi:10.1177/0962280215596769.

Nikoloulopoulos, A.K. (2020) An extended trivariate vine copula mixed model for meta-analysis of diagnostic studies in the presence of non-evaluable outcomes. *The International Journal of Biostatistics*, 16(2). doi:10.1515/ijb20190107.

See Also

rVineCopulaREMADA

Examples

```
nq=15
gl=gauss.quad.prob(nq,"uniform")
mgrid=meshgrid(gl$n,gl$n,gl$n,nargout=3)

data(OGT)
attach(OGT)
out=tVineCopulaREMADA.norm(TP,FN,FP,TN,gl,mgrid,
qcondbvn,qcondbvn,tau2par.bvn,tau2par.bvn)
detach(OGT)
##########################################
# In the precence of non-evaluable results #
data(coronary)
attach(coronary)
out=tVineCopulaREMADA.norm(TP,FN,FP,TN,gl,mgrid,
qcondbvn,qcondbvn,tau2par.bvn,tau2par.bvn,NEP,NEN)
detach(coronary)
```

vuong *Vuong's test for the comparison of non-nested copula mixed models for diagnostic test accuaracy studies*

Description

Vuong (1989)'s test for the comparison of non-nested copula mixed models for diagnostic test accuaracy studies. It shows if a copula mixed model provides better fit than the standard GLMM. We compute the Vuong's test with Model 1 being the copula mixed model with BVN copula and normal margins, i.e., the standard GLMM.

Usage

```
vuong.norm(qcond,tau2par,param1,param2,TP,FN,FP,TN,gl,mgrid)
vuong.beta(qcond,tau2par,param1,param2,TP,FN,FP,TN,gl,mgrid)
countermonotonicity.vuong(param1,param2,TP,FN,FP,TN,gl,mgrid)
```

Arguments

qcond	function for conditional copula cdf for Model 2
tau2par	function for maping Kendall's tau to copula parameter for Model 2
param1	parameters for the Model 1. i.e., the GLMM
param2	parameters for the Model 2
TP	the number of true positives
FN	the number of false negatives
FP	the number of false positives
TN	the number of true negatives
gl	a list containing the components of Gauss-Legendre nodes `gl$nodes` and weights `gl$weights`
mgrid	a list containing two matrices with the rows of the output matrix X are copies of the vector `gl$nodes`; columns of the output matrix Y are copies of the vector `gl$nodes`

Value

A list containing the following components:

z	the test statistic
p-value	the p-value

References

Nikoloulopoulos, A.K. (2015) A mixed effect model for bivariate meta-analysis of diagnostic test accuracy studies using a copula representation of the random effects distribution. *Statistics in Medicine*, **34**, 3842–3865. doi:10.1002/sim.6595.

Vuong Q.H. (1989) Likelihood ratio tests for model selection and non-nested hypotheses. *Econometrica*, **57**:307–333.

See Also

CopulaREMADA

Examples

```
nq=15
gl=gauss.quad.prob(nq,"uniform")
mgrid<- meshgrid(gl$n,gl$n)

data(MRI)
attach(MRI)
c270est.b=CopulaREMADA.beta(TP,FN,FP,TN,gl,mgrid,qcondcln270,tau2par.cln270)
nest.n=CopulaREMADA.norm(TP,FN,FP,TN,gl,mgrid,qcondbvn,tau2par.bvn)
c90est.n=CopulaREMADA.norm(TP,FN,FP,TN,gl,mgrid,qcondcln90,tau2par.cln90)
vuong.beta(qcondcln270,tau2par.cln270,nest.n$e,c270est.b$e,TP,FN,FP,TN,gl,mgrid)
vuong.norm(qcondcln90,tau2par.cln90,nest.n$e,c90est.n$e,TP,FN,FP,TN,gl,mgrid)
detach(MRI)

data(CT)
attach(CT)
est.n=countermonotonicCopulaREMADA.norm(TP,FN,FP,TN,gl,mgrid)
est.b=countermonotonicCopulaREMADA.beta(TP,FN,FP,TN,gl,mgrid)
countermonotonicity.vuong(est.n$e,est.b$e,TP,FN,FP,TN,gl,mgrid)
detach(CT)
```

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