Package 'etma'

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Author Chin Lin

Maintainer Chin Lin <xup6fup@gmail.com>

Description Traditional meta-regression based method has been developed for using meta-analysis data, but it faced the challenge of inconsistent estimates. This package purpose a new statistical method to detect epistasis using incomplete information summary, and have proven it not only successfully let consistency of evidence, but also increase the power compared with traditional method (Detailed tutorial is shown in website).

License GPL (>= 3)

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etma-package *Epistasis Test in Meta-Analysis*

Description

Traditional meta-regression based method has been developed for using meta-analysis data, but it faced the challenge of inconsistent estimates. This package purpose a new statistical method to detect epistasis using incomplete information summary, and have proven it not only successfully let consistency of evidence, but also increase the power compared with traditional method (Detailed tutorial is shown in website).

Author(s)

Chin Lin

Maintainer: Chin Lin <xup6fup@gmail.com>

References

Lin C, Chu CM, Su SL (2016) Epistasis Test in Meta-Analysis: A Multi-Parameter Markov Chain Monte Carlo Model for Consistency of Evidence. PLoS ONE 11(4): e0152891. doi:10.1371/journal.pone.0152891

See Also

ETMA, data.GST, data.PAH, data.RAS

Examples

```
#Detailed tutorial is shown in website <http://rpubs.com/chinlin/ETMA>
#The simple toy example (just test this algorithm)
#Note: the computing time in this example is about 3-5 secs

data(data.RAS)
ggint.toy=ETMA(case.ACE.0,case.ACE.1,ctrl.ACE.0,ctrl.ACE.1,
                  case.AGT.0,case.AGT.1,ctrl.AGT.0,ctrl.AGT.1,
                  data=data.RAS,iterations.step1=100,iterations.step2=300,
                  start.seed=1,show.detailed.plot=FALSE,show.final.plot=FALSE)
print(ggint.toy)
summary(ggint.toy)

#The fastest complete example (Note: the computing time in this example is about 15 mins)
#Other examples can refer the help(ETMA)
#Note: the complete example need about 20,000/200,000 learning time in step 1/2, respectively.
#
#data(data.PAH)
#ggint2=ETMA(case.CYP1A1.0,case.CYP1A1.1,ctrl.CYP1A1.0,ctrl.CYP1A1.1,
#                  case.GSTM1.0,case.GSTM1.1,ctrl.GSTM1.0,ctrl.GSTM1.1,
#                 data=data.PAH,start.seed=1,show.detailed.plot=TRUE,show.p.matrix=TRUE)
#
#print(ggint2)
```

```
#
#Epistasis Test in Meta-Analysis (ETMA)
#A MCMC algorithm for detecting gene-gene interaction in meta-analysis.
#
#This analysis include 13 studies. (df = 10)
#
#                      b      se    OR 95%ci.l 95%ci.u t value p value
#SNP1(mutation) -0.19967 0.14580 0.819   0.592   1.133 -1.3695  0.2008
#SNP2(mutation) -0.01963 0.14025 0.981   0.717   1.340 -0.1400  0.8915
#Interaction     0.79747 0.28886 2.220   1.166   4.225  2.7608  0.0201
#
#summary(ggint2)
#
#Epistasis Test in Meta-Analysis (ETMA)
#A MCMC algorithm for detecting gene-gene interaction in meta-analysis.
#
#This analysis include 13 studies. (df = 10)
#
#                      b      se    OR 95%ci.l 95%ci.u t value p value
#SNP1(mutation) -0.19967 0.14580 0.819   0.592   1.133 -1.3695  0.2008
#SNP2(mutation) -0.01963 0.14025 0.981   0.717   1.340 -0.1400  0.8915
#Interaction     0.79747 0.28886 2.220   1.166   4.225  2.7608  0.0201
#
#                                    OR 95%ci.l 95%ci.u t value p value
#SNP1(wild type) & SNP2(mutation) 0.981   0.717   1.340 -0.1400  0.8915
#SNP1(mutation) & SNP2(wild type) 0.819   0.592   1.133 -1.3695  0.2008
#SNP1(mutation) & SNP2(mutation)  1.783   1.506   2.110  7.6478 <0.0001
```

`data.GST` *The data of GSTs family interaction on cancer.*

Description

This data used the data from a meta-analysis included about 500 studies investigating the associations between GSTM1/GSTT1 and cancer, and saved the studies both reported the genotype of GSTM1 and GSTT1. Finally, there are 360 studies (375 populations) included in this data.

Usage

```
data("data.GST")
```

Format

A data frame with 375 observations on the following 12 variables.

`Study` the first author and published year in included studies.

`Ethnicity` the ethnicity of each population.

`Country` the location of study.

`Cancer` the subtype of cancer in each study.

`case.GSTM1.0` the number of GSTM1 functional type in cases.

`ctrl.GSTM1.0` the number of GSTM1 null type in cases (risk type).

`case.GSTM1.1` the number of GSTM1 functional type in controls.

`ctrl.GSTM1.1` the number of GSTM1 null type in controls (risk type).

`case.GSTT1.0` the number of GSTT1 functional type in cases.

`ctrl.GSTT1.0` the number of GSTT1 null type in cases (risk type).

`case.GSTT1.1` the number of GSTT1 functional type in controls.

`ctrl.GSTT1.1` the number of GSTT1 null type in controls (risk type).

References

Fang J, Wang S, Zhang S, Su S, Song Z, Deng Y, et al. (2013) Association of the Glutathione S-Transferase M1, T1 Polymorphisms with Cancer: Evidence from a Meta-Analysis. PLoS ONE 8(11): e78707. doi:10.1371/journal.pone.0078707

See Also

ETMA

Examples

```
data(data.GST)
head(data.GST)
```

---

data.PAH *The data of metabolic pathway of PAH interaction on oral cancer.*

Description

This data used the data from a meta-analysis included about 50 studies investigating the associations between CYP1A1/GSTM1 and oral cancer, and saved the studies both reported the genotype of GSTM1 and CYP1A1 rs4646903. Finally, there are 13 studies included in this data.

Usage

```
data("data.PAH")
```

Format

A data frame with 13 observations on the following 11 variables.

`Athour` the first author in included studies.

`Year` the published year in included studies.

`Country` the location of study.

`case.CYP1A1.0` the number of AA genotype (rs4646903) in cases.

`case.CYP1A1.1` the number of AC/CC genotype (rs4646903) in cases (risk type).

`ctrl.CYP1A1.0` the number of AA genotype (rs4646903) in controls.

`ctrl.CYP1A1.1` the number of AC/CC genotype (rs4646903) in controls (risk type).

`case.GSTM1.0` the number of GSTM1 functional type in cases.

`case.GSTM1.1` the number of GSTM1 null type in cases (risk type).

`ctrl.GSTM1.0` the number of GSTM1 functional type in controls.

`ctrl.GSTM1.1` the number of GSTM1 null type in controls (risk type).

References

Liu H, Jia J, Mao X, Lin Z. (2015) Association of CYP1A1 and GSTM1 Polymorphisms With Oral Cancer Susceptibility: A Meta-Analysis. Medicine 94(27): e895. doi: 10.1097/MD.0000000000000895

See Also

ETMA

Examples

```
data(data.PAH)
head(data.PAH)
```

---

data.RAS *The data of RAS interaction on chronic kidney disease.*

Description

This used the data from a meta-analysis included about 100 studies investigating the associations between ACE insertion/deletion (I/D) and chronic kidney disease, and re-collected the studies included AGT M235T information. Finally, there are 34 studies included in this data.

Usage

```
data("data.RAS")
```

Format

A data frame with 34 observations on the following 12 variables.

`Author` the first author in included studies.

`Year` the published year in included studies.

`Race` the race of each population.

`Tyep` the subtype of chronic kidney disease in each study.

`case.ACE.0` the number of I allele (rs4340) in cases.

`case.ACE.1` the number of D allele (rs4340) in cases (risk allele).

`ctrl.ACE.0` the number of I allele (rs4340) in controls.

`ctrl.ACE.1` the number of D allele (rs4340) in controls (risk allele).

`case.AGT.0` the number of M allele (rs699) in cases.

`case.AGT.1` the number of T allele (rs699) in cases (risk allele).

`ctrl.AGT.0` the number of M allele (rs699) in controls.

`ctrl.AGT.1` the number of T allele (rs699) in controls (risk allele).

References

Lin C, Yang HY, Wu CC, Lee HS, Lin YF, Lu KC, et al. (2014) Angiotensin-Converting Enzyme Insertion/Deletion Polymorphism Contributes High Risk for Chronic Kidney Disease in Asian Male with Hypertension: A Meta-Regression Analysis of 98 Observational Studies. PLoS ONE 9(1): e87604. doi:10.1371/journal.pone.0087604

See Also

ETMA

Examples

```
data(data.RAS)
head(data.RAS)
```

ETMA *Epistasis Test in Meta-Analysis (ETMA)*

Description

This function is a Markov chain Monte Carlo (MCMC) based method, called "Epistasis Test in Meta-Analysis (ETMA)", using the genotype summary data for estimating a consistent estimate of epistasis in meta-analysis.

Usage

```
ETMA(case.x1.0, case.x1.1, ctrl.x1.0, ctrl.x1.1,
case.x2.0, case.x2.1, ctrl.x2.0, ctrl.x2.1,
data = NULL, sig.level = 0.05, max.step.EM = 20,
iterations.step1 = 20000, iterations.step2 = 200000, start.seed = NULL,
show.detailed.plot = TRUE, show.final.plot = TRUE,
show.p.matrix = FALSE, progress.bar = TRUE)
```

Arguments

case.x1.0	the number of wild type of SNP1 in case group.
case.x1.1	the number of mutation type of SNP1 in case group.
ctrl.x1.0	the number of wild type of SNP1 in control group.
ctrl.x1.1	the number of mutation type of SNP1 in control group.
case.x2.0	the number of wild type of SNP2 in case group.
case.x2.1	the number of mutation type of SNP2 in case group.
ctrl.x2.0	the number of wild type of SNP2 in control group.
ctrl.x2.1	the number of mutation type of SNP1 in control group.
data	an optional data frame, list or environment (or object coercible by as.data.frame to a data frame) containing the variables in the model. If not found in data, the variables are taken from environment(formula), typically the environment from which lm is called.
sig.level	the significance level used to calculate confidence intervals.
max.step.EM	the maximum number of iterations if convergence is too slow.
iterations.step1	the length of chain to obtain the study-level parameters [p(disease|base),p(SNP1=1),p(SNP2=1)] in step 1.
iterations.step2	the length of chain to obtain the global-level parameters [OR(SNP1),OR(SNP2),OR(interaction)] in step 2.
start.seed	the start seed of this algorithm (if you want your results can be reproduced). A NULL value means a random seed in this algorithm.
show.detailed.plot	a logical indicating whether showing the MCMC plot in each step.
show.final.plot	a logical indicating whether showing the MCMC plot in the last step.
show.p.matrix	a logical indicating whether a p.matrix should be printed.
progress.bar	a logical indicating whether a progress bar should be presented.

Value

b	the beta values of each SNP and interaction term (Sequence is SNP1, SNP2, and interaction).

vcov	the variance covariance matrix of beta value.
LKK	the log of likelihood value in the last step.
se	the stardard errors of each SNP and interaction term (Sequence is SNP1, SNP2, and interaction).
df	the degree of freedom in this analysis.
OR	the odds ratios of each SNP and interaction term (Sequence is SNP1, SNP2, and interaction).
ci.l	the lower bounds of confidence interval based on a specific significance level (please see the sig.level).
ci.u	the upper bounds of confidence interval based on a specific significance level (please see the sig.level).
t	the t value of each each SNP and interaction term (Sequence is SNP1, SNP2, and interaction).
pval	the p value of each each SNP and interaction term (Sequence is SNP1, SNP2, and interaction).
sig.level	the significance level for calculating the confidence interval.
p.matrix	the p matrix in iterations process.

Author(s)

Chin Lin <xup6fup@gmail.com>

References

Lin C, Chu CM, Su SL (2016) Epistasis Test in Meta-Analysis: A Multi-Parameter Markov Chain Monte Carlo Model for Consistency of Evidence. PLoS ONE 11(4): e0152891. doi:10.1371/journal.pone.0152891

See Also

data.GST, data.PAH, data.RAS

Examples

```
#Detailed tutorial is shown in website <http://rpubs.com/chinlin/ETMA>
#The simple toy example (just test this algorithm)
#Note: the computing time in this example is about 3-5 secs

data(data.RAS)
ggint.toy=ETMA(case.ACE.0,case.ACE.1,ctrl.ACE.0,ctrl.ACE.1,
                 case.AGT.0,case.AGT.1,ctrl.AGT.0,ctrl.AGT.1,
                 data=data.RAS,iterations.step1=100,iterations.step2=300,
                 start.seed=1,show.detailed.plot=FALSE,show.final.plot=FALSE)
print(ggint.toy)
summary(ggint.toy)

#Following examples are complete examples.
#They need 20,000/200,000 learning time in step 1/step 2, respectively (default).
```

```
#Please note they need more than 15 mins, and one of example need about 3 hrs.
#The complete learning time is necessary in real data analysis.
#Please use default setting as following to analysis your data.
#
#Example 1 (Note: the computing time in this example is about 3 hrs)
#
#data(data.GST)
#ggint1=ETMA(case.GSTM1.0,case.GSTM1.1,ctrl.GSTM1.0,ctrl.GSTM1.1,
#                  case.GSTT1.0,case.GSTT1.1,ctrl.GSTT1.0,ctrl.GSTT1.1,
#                 data=data.GST,start.seed=1,show.detailed.plot=TRUE,show.p.matrix=TRUE)
#print(ggint1)
#summary(ggint1)
#
#Example 2 (Note: the computing time in this example is about 15 mins)
#
#data(data.PAH)
#ggint2=ETMA(case.CYP1A1.0,case.CYP1A1.1,ctrl.CYP1A1.0,ctrl.CYP1A1.1,
#                  case.GSTM1.0,case.GSTM1.1,ctrl.GSTM1.0,ctrl.GSTM1.1,
#                 data=data.PAH,start.seed=1,show.detailed.plot=TRUE,show.p.matrix=TRUE)
#
#print(ggint2)
#summary(ggint2)
#
#Example 3 (Note: the computing time in this example is about 15 mins)
#
#data(data.RAS)
#ggint3=ETMA(case.ACE.0,case.ACE.1,ctrl.ACE.0,ctrl.ACE.1,
#                  case.AGT.0,case.AGT.1,ctrl.AGT.0,ctrl.AGT.1,
#                 data=data.RAS,start.seed=1,show.detailed.plot=TRUE,show.p.matrix=TRUE)
#print(ggint3)
#summary(ggint3)
```

`print.ggint` *Print Method for 'ggint' Objects*

Description

Print method for objects of class "ggint".

Usage

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

Arguments

`x`	an object of class "ggint".
`...`	other arguments.

See Also

etma

Examples

```
#Following examples are complete examples.
#They need 20,000/200,000 learning time in step 1/step 2, respectively (default).
#Please note they need more than 15 mins, and one of example need about 3 hrs.
#The complete learning time is necessary in real data analysis.
#Please use default setting as following to analysis your data.
#
#Example 1 (Note: the computing time in this example is about 3 hrs)
#
#data(data.GST)
#ggint1=ETMA(case.GSTM1.0,case.GSTM1.1,ctrl.GSTM1.0,ctrl.GSTM1.1,
#                  case.GSTT1.0,case.GSTT1.1,ctrl.GSTT1.0,ctrl.GSTT1.1,
#                 data=data.GST,start.seed=1,show.detailed.plot=TRUE,show.p.matrix=TRUE)
#print(ggint1)
#
#Example 2 (Note: the computing time in this example is about 15 mins)
#
#data(data.PAH)
#ggint2=ETMA(case.CYP1A1.0,case.CYP1A1.1,ctrl.CYP1A1.0,ctrl.CYP1A1.1,
#                  case.GSTM1.0,case.GSTM1.1,ctrl.GSTM1.0,ctrl.GSTM1.1,
#                 data=data.PAH,start.seed=1,show.detailed.plot=TRUE,show.p.matrix=TRUE)
#
#print(ggint2)
#
#Example 3 (Note: the computing time in this example is about 15 mins)
#
#data(data.RAS)
#ggint3=ETMA(case.ACE.0,case.ACE.1,ctrl.ACE.0,ctrl.ACE.1,
#                  case.AGT.0,case.AGT.1,ctrl.AGT.0,ctrl.AGT.1,
#                 data=data.RAS,start.seed=1,show.detailed.plot=TRUE,show.p.matrix=TRUE)
#print(ggint3)
```

`summary.ggint` *Summary Method for 'ggint' Objects*

Description

Summary method for objects of class "ggint".

Usage

```
## S3 method for class 'ggint'
summary(object, ...)
```

Arguments

object	an object of class "ggint".
...	other arguments.

See Also

etma

Examples

```
#Following examples are complete examples.
#They need 20,000/200,000 learning time in step 1/step 2, respectively (default).
#Please note they need more than 15 mins, and one of example need about 3 hrs.
#The complete learning time is necessary in real data analysis.
#Please use default setting as following to analysis your data.
#
#Example 1 (Note: the computing time in this example is about 3 hrs)
#
#data(data.GST)
#ggint1=ETMA(case.GSTM1.0,case.GSTM1.1,ctrl.GSTM1.0,ctrl.GSTM1.1,
#                  case.GSTT1.0,case.GSTT1.1,ctrl.GSTT1.0,ctrl.GSTT1.1,
#                 data=data.GST,start.seed=1,show.detailed.plot=TRUE,show.p.matrix=TRUE)
#print(ggint1)
#summary(ggint1)
#
#Example 2 (Note: the computing time in this example is about 15 mins)
#
#data(data.PAH)
#ggint2=ETMA(case.CYP1A1.0,case.CYP1A1.1,ctrl.CYP1A1.0,ctrl.CYP1A1.1,
#                  case.GSTM1.0,case.GSTM1.1,ctrl.GSTM1.0,ctrl.GSTM1.1,
#                 data=data.PAH,start.seed=1,show.detailed.plot=TRUE,show.p.matrix=TRUE)
#
#print(ggint2)
#summary(ggint2)
#
#Example 3 (Note: the computing time in this example is about 15 mins)
#
#data(data.RAS)
#ggint3=ETMA(case.ACE.0,case.ACE.1,ctrl.ACE.0,ctrl.ACE.1,
#                  case.AGT.0,case.AGT.1,ctrl.AGT.0,ctrl.AGT.1,
#                 data=data.RAS,start.seed=1,show.detailed.plot=TRUE,show.p.matrix=TRUE)
#print(ggint3)
#summary(ggint3)
```

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