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Title Power Calculations for SNP Studies with Censored Outcomes

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Description Conduct asymptotic and empirical power and sample size calculations for Single-Nucleotide Polymorphism (SNP) association studies with right censored time to event outcomes.

Depends R (>= 3.0.0), survival (>= 2.36-9), Rcpp (>= 0.9.10), lattice (>= 0.20-0), foreach (>= 1.3.2), xtable (>= 1.7-0)

SystemRequirements GNU GSL (>= 1.14)

Suggests RColorBrewer, latticeExtra, knitr

LinkingTo Rcpp

License GPL-3

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VignetteBuilder knitr

NeedsCompilation yes

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`survSNP-package` *Power Calculations for SNP Studies with Censored Outcomes*

Description

This package can be used to conduct asymptotic and empirical power and sample size calculations for Single-nucleotide Polymorphism (SNP) association studies with right censored time to event outcomes.

Details

Package:	survSNP
Type:	Package
Version:	0.26
Date:	2023-01-20
License:	GPL-3
LazyLoad:	yes

The functions sim.snp.expsurv.power and survSNP.power.table can be used to conduct power and sample size calculations. The package vignette serves as a tutorial for using this package. The technical details are provided in the reference cited below. It is highly recommended that the vignette along with this are reviewed before using this package. Currently, this package only supports additive risk models.

Author(s)

Kouros Owzar, Zhiguo Li, Nancy Cox, Sin-Ho Jung and Chanhee Yi

References

Kouros Owzar, Zhiguo Li, Nancy Cox and Sin-Ho Jung. Power and Sample Size Calculations for SNP Association Studies with Censored Time-to-Event Outcomes. https://onlinelibrary.wiley.com/doi/full/10.1002/gepi.21645

Examples

```
# See vignette for examples including details on the example
# considered below

results<-sim.snp.expsurv.power(GHR=1.25, B=0, n=500, raf=0.1, erate=0.75, pilm=0.5,
                               lm=1, model="additive", test="additive", alpha=0.05)
results[,c("n","erate","alpha","pow0")]


GHRs<-seq(1.05,1.5,by=0.05)
ns<-c(100,500,700)
rafs<-c(0.1,0.3,0.5)
erates<-c(0.5,0.7,0.9)
res<-survSNP.power.table(GHRs,ns,rafs,erates,pilm=0.5,lm=1,model="additive",
                         test="additive",alpha=0.05)

# Create key for illustration
KEY=paste("q=",levels(factor(res$raf)),sep="")
KEY<-list(lines=list(col=1:length(KEY),lty=1:length(KEY)),
          text=list(labels=paste("q=",levels(factor(res$raf)),sep="")),
          column=3)


# Illustrate Power
print(xyplot(pow0~GHR|factor(erate)*factor(n),group=factor(raf),
             data=res,type="l",lty=KEY$lines$lty,col=KEY$lines$col,
             key=KEY,
             xlab="Genotype Hazard Ratio",ylab="Power"))

# Illustrate Power (restricted to n=100)

print(xyplot(pow0~GHR|factor(erate),group=factor(raf),
             data=subset(res,n==ns[1]),
             type="l",lty=KEY$lines$lty,col=KEY$lines$col,
             key=KEY,
             xlab="Genotype Hazard Ratio",ylab="Power",
             sub=paste("n=",ns[1],", alpha=",round(unique(res$alpha),2))))
```

---

asypow *Calculating the asymptotic power and variance*

Description

This function calculates the asymptotic power and variance assuming that the survival distribution is a mixture of exponentials with rates and the censoring distribution is uniform on the interval (a,b).

Usage

```
asypow(n, theta, a, b, lambda0, q, p, alpha, z,exactvar)
```

Arguments

n	Sample size
theta	Effect size (log genotype hazard ratio (GHR))
a	Censoring distribution parameter (assumed to be uniform on [a,b])
b	Censoring distribution parameter (assumed to be uniform on [a,b])
lambda0	Baseline exponential hazard rate
q	Relative risk allele frequency
p	Relative genotype frequency
alpha	Nominal two-sided type I error rate
z	Genotype scores (right now only additive scores AA=0,AB=1,BB=2 generate correct power)
exactvar	Indicator for using the exact variance formula

Details

This function is called by sim.snp.expsurv.power to calculate the asymptotic variance (exact and approximate) formulas. It is not intended to be called directly by the user. To conduct power calculations, use sim.snp.expsurv.power or the convenience wrapper function survSNP.power.table.

Value

power	Asymptotic power based on exact variance formula
power0	Asymptotic power based on approximate variance formula
v1	First term of asymptotic variance
v2	Second term of asymptotic variance
v12	Third term of the asymptotic variance (covariance)
vapprox	Approximate asymptotic variance formula (=v1)
exact	Exact asymptotic variance formula (=v1+v2+v12)
diff	Difference between variances (=v2+v12)
ratio	Ratio of variances (=v1/(v1+v2+v12))

Author(s)

Kouros Owzar, Zhiguo Li, Nancy Cox, Sin-Ho Jung and Chanhee Yi

References

Kouros Owzar, Zhiguo Li, Nancy Cox and Sin-Ho Jung. Power and Sample Size Calculations for SNP Association Studies with Censored Time-to-Event Outcomes. https://onlinelibrary.wiley.com/doi/full/10.1002/gepi.21645

censbnd *Calculate bound for censoring distribution.*

Description

This function computes the bound

Usage

```
censbnd(lambda, p, crate, rootint = c(0.1, 1000))
```

Arguments

lambda	Baseline exponential hazard rate
p	Relative genotype frequency
crate	Desired censoring rate
rootint	Interval to be searched for the root

Details

The time to event distribution T is assumed to be a mixture of exponentials with parameter $lambda0$, $lambda1$ and $lambda2$ with mixing proportion $p0$,$p1$ and $p2$. Suppose that the censoring distribution is uniform on the interval $[0, b]$. This function calculates b for a desired censoring rate. It is not intended to be called directly by the user. To conduct power calculations, use sim.snp.expsurv.power or the convenience wrapper function survSNP.power.table.

Value

This function returns a list from the uniroot function. The root component of this list in the

Author(s)

Kouros Owzar, Zhiguo Li, Nancy Cox, Sin-Ho Jung and Chanhee Yi

References

Kouros Owzar, Zhiguo Li, Nancy Cox and Sin-Ho Jung. Power and Sample Size Calculations for SNP Association Studies with Censored Time-to-Event Outcomes. https://onlinelibrary.wiley.com/doi/full/10.1002/gepi.21645

Examples

```
censbnd(0.1,hwe(0.1),0.9)$root
```

hwe *Relative genotypic frequencies under HWE*

Description

Compute relative genotypic frequencies for a given relative allelic frequency

Usage

```
hwe(raf)
```

Arguments

raf	Relative minor allele frequency for the B allele.

Details

For a bi-allelic SNP with genotypes *AA*, *AB* and *BB*, with a relative allele frequency q for the *B* allele, this function returns the corresponding relative genotypic frequencies. It is not intended to be called directly by the user. To conduct power calculations, use sim.snp.expsurv.power or the convenience wrapper function survSNP.power.table.

Value

A vector of length three relative genotypic frequencies.

Author(s)

Kouros Owzar, Zhiguo Li, Nancy Cox, Sin-Ho Jung and Chanhee Yi

References

Kouros Owzar, Zhiguo Li, Nancy Cox and Sin-Ho Jung. Power and Sample Size Calculations for SNP Association Studies with Censored Time-to-Event Outcomes. https://onlinelibrary.wiley.com/doi/full/10.1002/gepi.21645

Examples

```
censbnd(0.1,hwe(0.1),0.9)
```

`sim.snp.expsurv.power` *Asymptotic and Empirical Power*

Description

This function calculates asymptotic and empirical power for SNP association studies

Usage

```
sim.snp.expsurv.power(GHR, B, n, raf, erate, pilm, lm, model, test, alpha,
                      exactvar = FALSE, interval = c(0, 10), rootint = c(0.1, 200))
```

Arguments

`GHR`	Genotype Hazard Ratio
`B`	Number of simulation replicates (set to 0 if no empirical calculations are desired)
`n`	Sample size
`raf`	Relative risk allele frequency
`erate`	Event Rate
`pilm`	Probability that the time-to-event is greater than lm
`lm`	Landmark time used for powering the study
`model`	True genetic risk model (choices are "additive", "recessive" or "dominant". For the asymptotic calculations only the "additive" should be used until further notice)
`test`	Hypothesized genetic risk model (choices are "additive", "recessive" or "dominant". For the asymptotic calculations only the "additive" should be used until further notice)
`alpha`	Nominal two-sided type I error rate
`exactvar`	Indicator for using the exact variance formula
`interval`	Interval to search for baseline hazard rate
`rootint`	Interval to search for censoring bound

Details

This function calculates asymptotic and empirical power for SNP association studies

Value

This function returns a `data.frame` with the following columns

`B`	Number of simulation replicates
`raf`	Relative allelic frequency of the B allele
`q0`	Relative genotypic frequency for AA

q1	Relative genotypic frequency for AB
q2	Relative genotypic frequency for BB
lam0	Exponential hazard rate for P(T>t|AA)
lam1	Exponential hazard rate for P(T>t|AB)
lam2	Exponential hazard rate for P(T>t|BB)
GHR	Genotype Hazard Ratio
pilm	Probability that the time to event in the population exceeds the landmark lm: P(T>lm)
lm	Landmark (see pilm above)
model	The true genetic risk model
test	The hypothesized genetic risk model
a	Parameter for the censoring distribution (uniform on [a,b])
b	Parameter for the censoring distribution (uniform on [a,b])
erate	Event rate
n	Sample size
powB	Empirical Power
pow	Asymptotic Power based on the exact variance formula
pow0	Asymptotic Power based on the approximate variance formula
v1	First term of the variance (v1+v2+v12)
v2	Second term of the variance (v1+v2+v12)
v12	Third term (covariance) of the variance (v1+v2+v12)

Author(s)

Kouros Owzar, Zhiguo Li, Nancy Cox, Sin-Ho Jung and Chanhee Yi

References

Kouros Owzar, Zhiguo Li, Nancy Cox and Sin-Ho Jung. Power and Sample Size Calculations for SNP Association Studies with Censored Time-to-Event Outcomes. https://onlinelibrary.wiley.com/doi/full/10.1002/gepi.21645

See Also

survSNP.power.table

Examples

```
# See vignette for examples including details on the example
# considered below

results<-sim.snp.expsurv.power(GHR=1.25, B=0, n=500, raf=0.1, erate=0.75, pilm=0.5,
                               lm=1, model="additive", test="additive", alpha=0.05)
results[,c("n","erate","alpha","pow0")]
```

`sim.snp.expsurv.sctest` *Simulation of Cox Score Statistic*

Description

This function simulates the asymptotic *P*-value for the Cox score statistic under a specified genetic risk model

Usage

```
sim.snp.expsurv.sctest(n, gtprev, lam, a, b, ztest, diag = FALSE)
```

Arguments

`n`	Sample size
`gtprev`	Relative genotypic frequency
`lam`	Exponential hazard rates for conditional time to event survival functions
`a`	Lower bound for the uniform censoring bound
`b`	Upper bound for the uniform censoring bound
`ztest`	Assumed genetic model
`diag`	Set to TRUE if print out of diagnostics is desired

Details

This function simulates the genotypes 0, 1 or 2 from relative genotypic frequencies. Then conditional on genotype, it simulates the time to event from an exponential distribution with parameter $lambdag$. The censoring time is drawn from a uniform law on the interval $[a, b]$. It is not intended to be called directly by the user. To conduct power calculations, use `sim.snp.expsurv.power` or the convenience wrapper function `survSNP.power.table`.

Value

A vector of length 2 containing the observed event rate and the asymptotic *P*-value for the Cox score test

Author(s)

Kouros Owzar, Zhiguo Li, Nancy Cox, Sin-Ho Jung and Chanhee Yi

References

Kouros Owzar, Zhiguo Li, Nancy Cox and Sin-Ho Jung. Power and Sample Size Calculations for SNP Association Studies with Censored Time-to-Event Outcomes. https://onlinelibrary.wiley.com/doi/full/10.1002/gepi.21645

`surv.exp.gt.model` *Exponential Hazard Rates for a Genetic Risk Model*

Description

This function calculates the exponential hazard rates for the conditional survival functions

Usage

```
surv.exp.gt.model(pilm, lm, gtprev, GRR, zmodel, interval)
```

Arguments

`pilm`	Probability that the time-to-event is greater than lm
`lm`	Landmark time used for powering the study
`gtprev`	Relative genotypic frequency
`GRR`	Genotype Hazard Ratio
`zmodel`	Genetic Risk Model (choices are "additive", "recessive" or "dominant")
`interval`	Interval to search for baseline hazard rate

Details

Determines the time to event distributions in the three component mixture model discussed in the reference below. It is not intended to be called directly by the user. To conduct power calculations, use sim.snp.expsurv.power or the convenience wrapper function survSNP.power.table.

Value

A vector of length three containing the exponential hazard rates

Author(s)

Kouros Owzar, Zhiguo Li, Nancy Cox, Sin-Ho Jung and Chanhee Yi

References

Kouros Owzar, Zhiguo Li, Nancy Cox and Sin-Ho Jung. Power and Sample Size Calculations for SNP Association Studies with Censored Time-to-Event Outcomes. https://onlinelibrary.wiley.com/doi/full/10.1002/gepi.21645

`survSNP.power.table` *Table for Asymptotic and Empirical Power*

Description

This function produces a table with the resulting empirical and asymptotic power over a given range of Genotype Hazard Ratios, relative allelic frequencies, sample sizes, and event rates.

Usage

```
survSNP.power.table(GHRs, ns, rafs, erates, pilm, lm, model, test, alpha,
                    exactvar = FALSE, B = 0)
```

Arguments

`GHRs`	A vector of Genotype Hazard Ratios
`ns`	A vector of sample sizes
`rafs`	A vector of relative allelic frequencies (for the risk allele)
`erates`	A vector of event rates
`pilm`	Probability that the time-to-event is greater than lm
`lm`	Landmark time used for powering the study
`model`	True genetic risk model (choices are "additive", "recessive" or "dominant". For the asymptotic calculations only the "additive" should be used until further notice)
`test`	Hypothesized genetic risk model (choices are "additive", "recessive" or "dominant". For the asymptotic calculations only the "additive" should be used until further notice)
`alpha`	Nominal two-sided type I error rate
`exactvar`	Indicator for using the exact variance formula
`B`	Number of simulation replicates (set to 0 if no empirical calculations are desired)

Details

This version only supports additive models.

Value

See output of sim.snp.expsurv.power.

Author(s)

Kouros Owzar, Zhiguo Li, Nancy Cox, Sin-Ho Jung and Chanhee Yi

References

Kouros Owzar, Zhiguo Li, Nancy Cox and Sin-Ho Jung. Power and Sample Size Calculations for SNP Association Studies with Censored Time-to-Event Outcomes. https://onlinelibrary.wiley.com/doi/full/10.1002/gepi.21645

Examples

```
GRRs<-seq(1.5,2,by=0.25)
ns<-c(100,500,1000)
rafs<-c(0.3,0.5,0.7)
erates=c(0.5,0.7,0.9)
res<-survSNP.power.table(GRRs,ns,rafs,erates,pilm=0.5,lm=1,model="additive",
                         test="additive",alpha=0.05)

# Create key for illustration
KEY=paste("q=",levels(factor(res$raf)),sep="")
KEY<-list(lines=list(col=1:length(KEY),lty=1:length(KEY)),
          text=list(labels=paste("q=",levels(factor(res$raf)),sep="")),
          column=3)


# Illustrate Power
print(xyplot(pow0~GHR|factor(erate)*factor(n),group=factor(raf),
             data=res,type="l",lty=KEY$lines$lty,col=KEY$lines$col,
             key=KEY,
             xlab="Genotype Hazard Ratio",ylab="Power"))

# Illustrate Power (restricted to n=100)

print(xyplot(pow0~GHR|factor(erate),group=factor(raf),
             data=subset(res,n==ns[1]),
             type="l",lty=KEY$lines$lty,col=KEY$lines$col,
             key=KEY,
             xlab="Genotype Hazard Ratio",ylab="Power",
             sub=paste("n=",ns[1],", alpha=",round(unique(res$alpha),2))))
```

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