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Title Design and Monitoring of Clinical Trials with Negative Binomial Endpoint

Description Calculates various functions needed for design and monitoring clinical trials with negative binomial endpoint
with variable follow-up.

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NBDesign-package *Design and Monitoring of Clinical Trials with Negative Binomial Endpoint*

Description

Calculates various functions needed for design and monitoring clinical trials with negative binomial endpoint with variable follow-up.

Details

The DESCRIPTION file:

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LazyData:	true
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Index of help topics:

```
NBDesign-package        Design and Monitoring of Clinical Trials with
                        Negative Binomial Endpoint
negint2                 A utility functon to calculate the mean
                        exposure under different scenarios
ynegbinompower          Two-sample sample size calculation for negative
                        binomial distribution with variable follow-up
ynegbinompowersim       Two-sample sample size calculation for negative
                        binomial distribution with variable follow-up
ynegbinomsize           Two-sample sample size calculation for negative
                        binomial distribution with variable follow-up
```

Author(s)

NA

Maintainer: NA

`negint2` *A utility functon to calculate the mean exposure under different scenarios*

Description

This will calculate the mean exposure under different scenarios: 2: fixed follow-up with drop-out, 3: variable follow-up with a maximum (maxfu), 4: variable follow-up with a maximum and drop-out

Usage

```
negint2(ux=0.5,fixedfu=1,type=2,u=c(0.5,0.5,1),ut=c(0.5,1.0,1.5),
  tfix=ut[length(ut)]+0.5,maxfu=10.0,tchange=c(0,0.5,1),
  ratec=c(0.15,0.15,0.15),eps=1.0e-03)
```

Arguments

`ux`	the parameter a in (a*t)/(1+a*t)
`fixedfu`	the minimum follow-up time
`type`	follow-up type, type=2: fixed fu with fu time `fixedfu` but subject to censoring; type=3: depending on entry time, minimum fu is `fixedfu` and maximum fu is `maxfu`; type=4: same as 3 but subject to censoring
`u`	recruitment rate
`ut`	recruitment interval, must have the same length as `u`
`tfix`	fixed study duration, often equals to recruitment time plus minimum follow-up
`maxfu`	maximum follow-up time, should not be greater than `tfix`
`tchange`	a strictly increasing sequence of time points starting from zero at which the drop-out rate changes. The first element of tchange must be zero. The above rates and `tchange` must have the same length.
`ratec`	piecewise constant drop-out rate
`eps`	error tolerance for the numerical intergration

Details

Let τ_{min} and τ_{max} correspond to the minimum follow-up time `taumin` and the maximum follow-up time `taumax`. Let T_f, C, E and R be the follow-up time, the drop-out time, the study entry time and the total recruitment period(R is the last element of `ut`). For type 2 follow-up $T_f = min(C, \tau_{min})$. For type 3 follow-up, $T_f = min(R + \tau_{min} - E, \tau_{max})$. For type 4 follow-up, $T_f = min(R + \tau_{min} - E, \tau_{max}, C)$. Let f be the density of T_f. We calculate

$$\int_0^\infty tf(t)dt$$

and

$$\int_0^\infty \frac{at}{1+at} f(t)dt$$

where a is the `ux`.

Value

mt	mean of (a*t)/(1+a*t)
tt	mean of t
vt	variance of t

Author(s)

Xiaodong Luo

Examples

```
##calculating the exposure for type 4 follow-up
exp4=negint2(ux=0.5,fixedfu=1,type=2,u=c(0.5,0.5,1),ut=c(0.5,1.0,1.5),
  tfix=2.0,maxfu=1.0,tchange=c(0,0.5,1),
  ratec=c(0.15,0.15,0.15),eps=1.0e-03)
#mean exposure
meanexp=exp4$tt
#var exposure
varexp=exp4$vt
c(meanexp,sqrt(varexp))
#mean of (ux*t)/(1+ux*t)
meanuxt=exp4$mt
```

---

ynegbinompower — *Two-sample sample size calculation for negative binomial distribution with variable follow-up*

Description

This will calculate the power for the negative binomial distribution for the 2-sample case under different follow-up scenarios: 1: fixed follow-up, 2: fixed follow-up with drop-out, 3: variable follow-up with a minimum fu and a maximum fu, 4: variable follow-up with a minimum fu and a maximum fu and drop-out.

Usage

```
ynegbinompower(nsize=200,r0=1.0,r1=0.5,shape0=1,shape1=shape0,pi1=0.5,
     alpha=0.05,twosided=1,fixedfu=1,type=1,u=c(0.5,0.5,1),ut=c(0.5,1.0,1.5),
     tfix=ut[length(ut)]+0.5,maxfu=10.0,tchange=c(0,0.5,1),
     ratec1=c(0.15,0.15,0.15),ratec0=ratec1,eps=1.0e-03)
```

Arguments

nsize	total number of subjects in two groups
r0	event rate for the control
r1	event rate for the treatment

`shape0`	dispersion parameter for the control
`shape1`	dispersion parameter for the treatment
`pi1`	allocation prob for the treatment
`alpha`	type-1 error
`twosided`	1: two-side, others: one-sided
`fixedfu`	fixed follow-up time for each patient
`type`	follow-up time type, type=1: fixed fu with fu time `fixedfu`; type=2: same as 1 but subject to censoring; type=3: depending on entry time, minimum fu is `fixedfu` and maximum fu is `maxfu`; type=4: same as 3 but subject to censoring
`u`	recruitment rate
`ut`	recruitment interval, must have the same length as `u`
`tfix`	fixed study duration, often equals to recruitment time plus minimum follow-up
`maxfu`	maximum follow-up time, should not be greater than `tfix`
`tchange`	a strictly increasing sequence of time points starting from zero at which the drop-out rate changes. The first element of tchange must be zero. The above rates and `tchange` must have the same length.
`ratec1`	piecewise constant drop-out rate for the treatment
`ratec0`	piecewise constant drop-out rate for the control
`eps`	error tolerance for the numerical intergration

Details

Let τ_{min} and τ_{max} correspond to the minimum follow-up time `fixedfu` and the maximum follow-up time `maxfu`. Let T_f, C, E and R be the follow-up time, the drop-out time, the study entry time and the total recruitment period(R is the last element of `ut`). For type 1 follow-up, $T_f = \tau_{min}$. For type 2 follow-up $T_f = min(C, \tau_{min})$. For type 3 follow-up, $T_f = min(R + \tau_{min} - E, \tau_{max})$. For type 4 follow-up, $T_f = min(R + \tau_{min} - E, \tau_{max}, C)$. Let f be the density of T_f. Suppose that Y_i is the number of event obsevred in follow-up time t_i for patient i with treatment assignment Z_i, $i = 1, \ldots, n$. Suppose that Y_i follows a negative binomial distribution such that

$$P(Y_i = y \mid Z_i = j) = \frac{\Gamma(y + 1/k_j)}{\Gamma(y+1)\Gamma(1/k_j)} \left(\frac{k_j u_i}{1 + k_j u_i}\right)^y \left(\frac{1}{1 + k_j u_i}\right)^{1/k_j},$$

where

$$\log(u_i) = \log(t_i) + \beta_0 + \beta_1 Z_i.$$

Let $\hat{\beta}_0$ and $\hat{\beta}_1$ be the MLE of β_0 and β_1. The varaince of $\hat{\beta}_1$ is

$$\text{var}(\hat{\beta}_1) = 1/\tilde{a}_0(r_0) + 1/\tilde{a}_1(r_1)$$

where

$$\tilde{a}_j(r) = \sum_{i=1}^{n} I(Z_i = j) k_j r t_i / (1 + k_j r t_i), \qquad j = 0, 1,$$

and $k_j, j = 0, 1$ are the dispersion parameters for control $j = 0$ and treatment $j = 1$. Note that Zhu and Lakkis (2014) use

$$a_j(r) = \sum_{i=1}^{n} I(Z_i = j)k_j rE(t_i)/\{1 + k_j rE(t_i)\},$$

to replace $\tilde{a}_j(r), j = 0, 1$. Using Jensen's inequality, we can show $a_j(r) \geq \tilde{a}_j(r)$, which means Zhu and Lakkis's method will underestimate variance of $\hat{\beta}_1$, which leads to either smaller than required sample size or inflated power. For comparison, I provide sample sizes under both $\tilde{a}_j(r)$ and $a_j(r)$.

Zhu and Lakkis (2014) discuss three types of the variance under the null. The first way is to set $\tilde{r}_0 = \tilde{r}_1 = r_0$, using event rate from the control group. The second way is to set $\tilde{r}_0 = r_0, \tilde{r}_1 = r_1$, using true event rates. The third way is to set $\tilde{r}_0 = \tilde{r}_1 = \tilde{r}$, where $\tilde{r} = \pi_1 r_1 + \pi_0 r_0$, using maximum likelihood estimation.

Therefore, for each type of follow-up, there are 3 sample sizes calculated (because there are 3 varainces under the null) for with and without approximation of Zhu and Lakkis (2014).

Note that PASS14.0 provides 3 ways of null varaince with the default being the MLE. PASS does not allow different dispersion parameters between treatmetn and control. EAST only provides the second way of null varaince but allows for different dispersion parameters. Both of these softwares base on the approximatin method of Zhu and Lakkis (2014), which underestimate the required sample sizes.

Value

`tildeXPWR` powers (in percentage) not based on current approach, i.e. not based on the Zhu and Lakkis's approximation

`XPWR` powers (in percentage) based on on the Zhu and Lakkis's approximation

`tildemineffsize` minimum detectable effect sizes not based on approximation

`mineffsize` minimum detectable effect sizes based on approximation

`Exposure` mean exposure under different follow-up types with element 1 for control, element 2 for treatment and element 3 for overall.

`SDExp` Sd of the exposure under different follow-up types with element 1 for control, element 2 for treatment and column 3 for overall.

Author(s)

Xiaodong Luo

References

Zhu~H and Lakkis~H. Sample size calculation for comparing two negative binomial rates. Statistics in Medicine 2014, 33: 376-387.

Examples

```
##calculating the sample sizes
abc=ynegbinompower(nsize=200,r0=1.0,r1=0.5,shape0=1,
        pi1=0.5,alpha=0.05,twosided=1,fixedfu=1,
        type=4,u=c(0.5,0.5,1),ut=c(0.5,1.0,1.5),
        tchange=c(0,0.5,1),
        ratec1=c(0.15,0.15,0.15),eps=1.0e-03)
###Zhu and Lakkis's powers (i.e. with approximation)
abc$XPWR
###Our powers (i.e. without approximation)
abc$tildeXPWR
```

---

ynegbinompowersim — *Two-sample sample size calculation for negative binomial distribution with variable follow-up*

Description

This will calculate the power for the negative binomial distribution for the 2-sample case under different follow-up scenarios: 1: fixed follow-up, 2: fixed follow-up with drop-out, 3: variable follow-up with a minimum fu and a maximum fu, 4: variable follow-up with a minimum fu and a maximum fu and drop-out.

Usage

```
ynegbinompowersim(nsize=200,r0=1.0,r1=0.5,shape0=1,shape1=shape0,pi1=0.5,
   alpha=0.05,twosided=1,fixedfu=1,type=1,u=c(0.5,0.5,1),ut=c(0.5,1.0,1.5),
   tfix=ut[length(ut)]+0.5,maxfu=10.0,tchange=c(0,0.5,1),
   ratec1=c(0.15,0.15,0.15),ratec0=ratec1,rn=10000)
```

Arguments

`nsize`	total number of subjects in two groups
`r0`	event rate for the control
`r1`	event rate for the treatment
`shape0`	dispersion parameter for the control
`shape1`	dispersion parameter for the treatment
`pi1`	allocation prob for the treatment
`alpha`	type-1 error
`twosided`	1: two-side, others: one-sided
`fixedfu`	fixed follow-up time for each patient
`type`	follow-up time type, type=1: fixed fu with fu time `fixedfu`; type=2: same as 1 but subject to censoring; type=3: depending on entry time, minimum fu is `fixedfu` and maximum fu is `maxfu`; type=4: same as 3 but subject to censoring

u	recruitment rate
ut	recruitment interval, must have the same length as u
tfix	fixed study duration, often equals to recruitment time plus minimum follow-up
maxfu	maximum follow-up time, should not be greater than tfix
tchange	a strictly increasing sequence of time points starting from zero at which the drop-out rate changes. The first element of tchange must be zero. The above rates and tchange must have the same length.
ratec1	piecewise constant drop-out rate for the treatment
ratec0	piecewise constant drop-out rate for the control
rn	Number of repetitions

Details

Let τ_{min} and τ_{max} correspond to the minimum follow-up time fixedfu and the maximum follow-up time maxfu. Let T_f, C, E and R be the follow-up time, the drop-out time, the study entry time and the total recruitment period(R is the last element of ut). For type 1 follow-up, $T_f = \tau_{min}$. For type 2 follow-up $T_f = min(C, \tau_{min})$. For type 3 follow-up, $T_f = min(R + \tau_{min} - E, \tau_{max})$. For type 4 follow-up, $T_f = min(R + \tau_{min} - E, \tau_{max}, C)$. Let f be the density of T_f. Suppose that Y_i is the number of event obsevred in follow-up time t_i for patient i with treatment assignment Z_i, $i = 1, \ldots, n$. Suppose that Y_i follows a negative binomial distribution such that

$$P(Y_i = y \mid Z_i = j) = \frac{\Gamma(y + 1/k_j)}{\Gamma(y + 1)\Gamma(1/k_j)} \left(\frac{k_j u_i}{1 + k_j u_i}\right)^y \left(\frac{1}{1 + k_j u_i}\right)^{1/k_j},$$

where $k_j, j = 0, 1$ are the dispersion parameters for control $j = 0$ and treatment $j = 1$ and

$$\log(u_i) = \log(t_i) + \beta_0 + \beta_1 Z_i.$$

The data will be gnerated according to the above model. Note that the piecewise exponential distribution and the piecewise uniform distribution are genrated using R package PWEALL functions "rpwe" and "rpwu", respectively.

The parameters in the model are estimated by MLE using the R package MASS function "glm.nb".

Value

power	simulation power (in percentage)

Author(s)

Xiaodong Luo

Examples

```
##calculating the sample sizes
abc=ynegbinompowersim(nsize=200,r0=1.0,r1=0.5,shape0=1,
        pi1=0.5,alpha=0.05,twosided=1,fixedfu=1,
        type=4,u=c(0.5,0.5,1),ut=c(0.5,1.0,1.5),
        tchange=c(0,0.5,1),
```

```
        ratec1=c(0.15,0.15,0.15),rn=10)
###Power
abc$power
```

---

ynegbinomsize *Two-sample sample size calculation for negative binomial distribution with variable follow-up*

Description

This will calculate the sample size for the negative binomial distribution for the 2-sample case under different follow-up scenarios: 1: fixed follow-up, 2: fixed follow-up with drop-out, 3: variable follow-up with a minimum fu and a maximum fu, 4: variable follow-up with a minimum fu and a maximum fu and drop-out.

Usage

```
ynegbinomsize(r0=1.0,r1=0.5,shape0=1,shape1=shape0,pi1=0.5,
      alpha=0.05,twosided=1,beta=0.2,fixedfu=1,
     type=1,u=c(0.5,0.5,1),ut=c(0.5,1.0,1.5),tfix=ut[length(ut)]+0.5,maxfu=10.0,
      tchange=c(0,0.5,1),ratec1=c(0.15,0.15,0.15),ratec0=ratec1,eps=1.0e-03)
```

Arguments

r0	event rate for the control
r1	event rate for the treatment
shape0	dispersion parameter for the control
shape1	dispersion parameter for the treatment
pi1	allocation prob for the treatment
alpha	type-1 error
twosided	1: two-side, others: one-sided
beta	tyep-2 error
fixedfu	fixed follow-up time for each patient
type	follow-up time type, type=1: fixed fu with fu time `fixedfu`; type=2: same as 1 but subject to censoring; type=3: depending on entry time, minimum fu is `fixedfu` and maximum fu is `maxfu`; type=4: same as 3 but subject to censoring
u	recruitment rate
ut	recruitment interval, must have the same length as `u`
tfix	fixed study duration, often equals to recruitment time plus minimum follow-up `fixedfu`
maxfu	maximum follow-up time, should not be greater than `tfix`
tchange	a strictly increasing sequence of time points starting from zero at which the drop-out rate changes. The first element of tchange must be zero.

`ratec1`	piecewise constant drop-out rate for the treatment. The rate and `tchange` must have the same length.
`ratec0`	piecewise constant drop-out rate for the control. The rate and `tchange` must have the same length.
`eps`	error tolerance for the numerical intergration

Details

Let τ_{min} and τ_{max} correspond to the minimum follow-up time `fixedfu` and the maximum follow-up time `maxfu`. Let T_f, C, E and R be the follow-up time, the drop-out time, the study entry time and the total recruitment period(R is the last element of `ut`). For type 1 follow-up, $T_f = \tau_{min}$. For type 2 follow-up $T_f = min(C, \tau_{min})$. For type 3 follow-up, $T_f = min(R + \tau_{min} - E, \tau_{max})$. For type 4 follow-up, $T_f = min(R + \tau_{min} - E, \tau_{max}, C)$. Let f be the density of T_f. Suppose that Y_i is the number of event obsevred in follow-up time t_i for patient i with treatment assignment Z_i, $i = 1, \dots, n$. Suppose that Y_i follows a negative binomial distribution such that

$$P(Y_i = y \mid Z_i = j) = \frac{\Gamma(y + 1/k_j)}{\Gamma(y + 1)\Gamma(1/k_j)} \left(\frac{k_j u_i}{1 + k_j u_i} \right)^y \left(\frac{1}{1 + k_j u_i} \right)^{1/k_j},$$

where

$$\log(u_i) = \log(t_i) + \beta_0 + \beta_1 Z_i.$$

Let $\hat\beta_0$ and $\hat\beta_1$ be the MLE of β_0 and β_1. The varaince of $\hat\beta_1$ is

$$\text{var}(\hat\beta_1) = 1/\tilde a_0(r_0) + 1/\tilde a_1(r_1)$$

where

$$\tilde a_j(r) = \sum_{i=1}^n I(Z_i = j) k_j r t_i / (1 + k_j r t_i), \qquad j = 0, 1,$$

and $k_j, j = 0, 1$ are the dispersion parameters for control $j = 0$ and treatment $j = 1$. Note that Zhu and Lakkis (2014) use

$$a_j(r) = \sum_{i=1}^n I(Z_i = j) k_j r E(t_i) / \{1 + k_j r E(t_i)\},$$

to replace $\tilde a_j(r), j = 0, 1$. Using Jensen's inequality, we can show $a_j(r) \geq \tilde a_j(r)$, which means Zhu and Lakkis's method will underestimate variance of $\hat\beta_1$, which leads to either smaller than required sample size or inflated power. For comparison, I provide sample sizes under both $\tilde a_j(r)$ and $a_j(r)$.

Zhu and Lakkis (2014) discuss three types of the variance under the null. The first way is to set $\tilde r_0 = \tilde r_1 = r_0$, using event rate from the control group. The second way is to set $\tilde r_0 = r_0, \tilde r_1 = r_1$, using true event rates. The third way is to set $\tilde r_0 = \tilde r_1 = \tilde r$, where $\tilde r = \pi_1 r_1 + \pi_0 r_0$, using maximum likelihood estimation.

Therefore, for each type of follow-up, there are 3 sample sizes calculated (because there are 3 varainces under the null) for with and without approximation of Zhu and Lakkis (2014).

Note that PASS14.0 provides 3 ways of null varaince with the default being the MLE. PASS does not allow different dispersion parameters between treatmetn and control. EAST only provides the second way of null varaince but allows for different dispersion parameters. Both of these softwares base on the approximatin method of Zhu and Lakkis (2014), which underestimate the required sample sizes.

Value

`tildeXN`	sample sizes based on current approach, i.e. not based on the Zhu and Lakkis's approximation
`XN`	sample sizes based on the Zhu and Lakkis's approximation
`Exposure`	mean exposure under different follow-up types with element 1 for control, element 2 for treatment and element 3 for overall.
`SDExp`	Sd of the exposure under different follow-up types with element 1 for control, element 2 for treatment and column 3 for overall.

Author(s)

Xiaodong Luo

References

Zhu~H and Lakkis~H. Sample size calculation for comparing two negative binomial rates. Statistics in Medicine 2014, 33: 376-387.

Examples

```
##calculating the sample sizes
abc=ynegbinomsize(r0=1.0,r1=0.5,shape0=1,pi1=0.5,alpha=0.05,twosided=1,
    beta=0.2,fixedfu=1,type=4,u=c(0.5,0.5,1),ut=c(0.5,1.0,1.5),
    tfix=1.5,maxfu=1,tchange=c(0,0.5,1),ratec1=c(0.15,0.15,0.15),
    eps=1.0e-03)
###Zhu and Lakkis's sample sizes (i.e. with approximation)
abc$XN
###Our sample sizes (i.e. without approximation)
abc$tildeXN
```

Index