Package: twoCoprimary (via r-universe)

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Type Package

Title Sample Size and Power Calculation for Two Co-Primary Endpoints

Version 1.1.1

Description Comprehensive functions to calculate sample size and power for clinical trials with two co-primary endpoints. The package supports five endpoint combinations: two continuous endpoints (Sozu et al. 2011 <doi:10.1080/10543406.2011.551329>), two binary endpoints using asymptotic methods (Sozu et al. 2010 <doi:10.1002/sim.3972>) and exact methods (Homma and Yoshida 2025 <doi:10.1177/09622802251368697>), mixed continuous and binary endpoints (Sozu et al. 2012 <doi:10.1002/bimj.201100221>), and mixed count and continuous endpoints (Homma and Yoshida 2024 <doi:10.1002/pst.2337>). All methods appropriately account for correlation between endpoints and provide both sample size and power calculation capabilities.

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`corrbound2Binary` *Calculate Correlation Bounds Between Two Binary Outcomes*

Description

Computes the lower and upper bounds of the correlation coefficient between two binary outcomes based on their marginal probabilities, as described in Prentice (1988).

Usage

```
corrbound2Binary(p1, p2)
```

Arguments

`p1`	True probability of responders for the first outcome (0 < p1 < 1)
`p2`	True probability of responders for the second outcome (0 < p2 < 1)

Details

For two binary outcomes with marginal probabilities p1 and p2, the correlation coefficient rho is bounded by:

$$\rho \in [L(p_1, p_2), U(p_1, p_2)]$$

where

$$L(p_1, p_2) = \max\left\{-\sqrt{\frac{p_1 p_2}{(1-p_1)(1-p_2)}}, -\sqrt{\frac{(1-p_1)(1-p_2)}{p_1 p_2}}\right\}$$

$$U(p_1, p_2) = \min\left\{\sqrt{\frac{p_1(1-p_2)}{p_2(1-p_1)}}, \sqrt{\frac{p_2(1-p_1)}{p_1(1-p_2)}}\right\}$$

Value

A named numeric vector with two elements:

`L_bound`	Lower bound of the correlation
`U_bound`	Upper bound of the correlation

References

Prentice, R. L. (1988). Correlated binary regression with covariates specific to each binary observation. *Biometrics*, 44(4), 1033-1048.

Examples

```
# Calculate correlation bounds for two binary outcomes
corrbound2Binary(p1 = 0.3, p2 = 0.5)

# When probabilities are equal, upper bound is 1
corrbound2Binary(p1 = 0.4, p2 = 0.4)

# When p1 + p2 = 1, lower bound is -1
corrbound2Binary(p1 = 0.3, p2 = 0.7)
```

---

corrbound2MixedCountContinuous

Calculate Correlation Bounds Between Count and Continuous Outcomes

---

Description

Computes the lower and upper bounds of the correlation coefficient between an overdispersed count outcome (negative binomial) and a continuous outcome (normal), as described in Homma and Yoshida (2024).

Usage

```
corrbound2MixedCountContinuous(lambda, nu, mu, sd)
```

Arguments

lambda	Mean parameter for the negative binomial distribution (lambda > 0)
nu	Dispersion parameter for the negative binomial distribution (nu > 0)
mu	Mean for the continuous outcome
sd	Standard deviation for the continuous outcome (sd > 0)

Details

The correlation bounds are calculated using the Frechet-Hoeffding bounds for copulas, as described in Trivedi and Zimmer (2007). The negative binomial distribution has mean lambda and variance:

$$Var(Y_1) = \lambda + \frac{\lambda^2}{\nu}$$

The variance of the negative binomial distribution is: Var(Y1) = lambda + lambda^2/nu

Value

A named numeric vector with two elements:

L_bound	Lower bound of the correlation
U_bound	Upper bound of the correlation

References

Homma, G., & Yoshida, T. (2024). Sample size calculation in clinical trials with two co-primary endpoints including overdispersed count and continuous outcomes. *Pharmaceutical Statistics*, 23(1), 46-59.

Trivedi, P. K., & Zimmer, D. M. (2007). Copula modeling: an introduction for practitioners. *Foundations and Trends in Econometrics*, 1(1), 1-111.

Examples

```
# Calculate correlation bounds for NB(1.25, 0.8) and N(0, 250)
corrbound2MixedCountContinuous(lambda = 1.25, nu = 0.8, mu = 0, sd = 250)

# Higher dispersion parameter
corrbound2MixedCountContinuous(lambda = 2.0, nu = 2.0, mu = 50, sd = 200)

# Different follow-up time
corrbound2MixedCountContinuous(lambda = 1.0 * 2, nu = 1.0, mu = 0, sd = 300)
```

---

dbibinom *Probability Mass Function of Bivariate Binomial Distribution*

Description

Calculates the probability mass function of the bivariate binomial distribution for given parameters, as described in Homma and Yoshida (2025).

Usage

```
dbibinom(N, y1, y2, p1, p2, rho)
```

Arguments

N	Sample size (number of trials)
y1	Observed value(s) of the first random variable (0 to N)
y2	Observed value(s) of the second random variable (0 to N)
p1	True probability of responders for the first outcome ($0 < p1 < 1$)
p2	True probability of responders for the second outcome ($0 < p2 < 1$)
rho	Correlation coefficient between the two binary outcomes

Details

The bivariate binomial distribution BiBin(N, p1, p2, gamma) has probability mass function given by equation (3) in Homma and Yoshida (2025):

$$P(Y_1 = y_1, Y_2 = y_2) = f(y_1|N, p_1) \times g(y_2|y_1, N, p_1, p_2, \gamma)$$

where

$$g(y_2|y_1, N, p_1, p_2, \gamma) = \frac{1}{(1+\gamma)^N} \sum_{m \in \mathcal{M}} \binom{y_1}{m} \binom{N-y_1}{y_2-m} (\xi+\gamma)^m (1-\xi)^{y_1-m} \xi^{y_2-m} (1-\xi+\gamma)^{N-y_1-(y_2-m)}$$

with $\xi = p_2 + \gamma(p_2 - p_1)$ and $\mathcal{M} = \{m : m = \max(0, y_2 - (N - y_1)), \ldots, \min(y_1, y_2)\}$.

Value

Probability mass function value(s) for the bivariate binomial distribution. If y1 and y2 are vectors, returns a vector of probabilities.

References

Homma, G., & Yoshida, T. (2025). Exact power and sample size in clinical trials with two co-primary binary endpoints. *Statistical Methods in Medical Research*, 34(11), 2183-2201.

Examples

```
# Calculate single probability mass
dbibinom(N = 100, y1 = 30, y2 = 50, p1 = 0.3, p2 = 0.5, rho = 0.5)

# Verify that probabilities sum to 1
N <- 20
p1 <- 0.3
p2 <- 0.5
rho <- 0.5
sum(outer(0:N, 0:N, function(x, y) dbibinom(N, x, y, p1, p2, rho)))
```

`design_table` *Create Design Comparison Table for Two Co-Primary Endpoints*

Description

Generates a comprehensive table comparing sample sizes or power across different parameter combinations and correlation values. This function is useful for sensitivity analyses and exploring how design parameters affect statistical properties.

Usage

```
design_table(
  param_grid,
  rho_values = c(0, 0.3, 0.5, 0.8),
  r = 1,
  alpha = 0.025,
  beta = 0.2,
 endpoint_type = c("continuous", "binary", "mixed_cont_binary", "mixed_count_cont"),
  Test = "AN",
  known_var = TRUE,
  nMC = 1000,
  output_var = NULL,
  n_grid = 100
)
```

Arguments

param_grid	A data.frame containing parameter combinations. Required columns depend on endpoint_type and calculation_mode: • For continuous endpoints (sample size): delta1, delta2, sd1, sd2 • For continuous endpoints (power): n1, n2, delta1, delta2, sd1, sd2 • For binary endpoints (sample size): p11, p12, p21, p22 • For binary endpoints (power): n1, n2, p11, p12, p21, p22 • For mixed continuous-binary (sample size): delta, sd, p1, p2 • For mixed continuous-binary (power): n1, n2, delta, sd, p1, p2 • For mixed count-continuous (sample size): r1, r2, nu, t, mu1, mu2, sd • For mixed count-continuous (power): n1, n2, r1, r2, nu, t, mu1, mu2, sd
rho_values	Numeric vector of correlation values to evaluate. Default is c(0, 0.3, 0.5, 0.8).
r	Allocation ratio (n1/n2). Required for sample size calculation. Default is 1.
alpha	One-sided significance level. Default is 0.025.
beta	Type II error rate (1 - power). Required for sample size calculation. Default is 0.2 (power = 0.8).
endpoint_type	Character string specifying endpoint type: "continuous", "binary", "mixed_cont_binary", or "mixed_count_cont".
Test	Test method. For endpoint_type = "binary" the four asymptotic methods "AN" (asymptotic normal), "ANc" (with continuity correction), "AS" (arcsine) and "ASc" (arcsine with continuity correction) route to the approximate functions, while "Chisq", "Fisher", "Fisher-midP", "Z-pool" and "Boschloo" route to the exact functions and are substantially more expensive. For endpoint_type = "mixed_cont_binary" the four asymptotic methods and "Fisher" are available. Default is "AN". Not used for the continuous and mixed count-continuous endpoint types.
known_var	Logical indicating whether variance is known for continuous endpoints. Default is TRUE.

nMC	Number of Monte Carlo simulations for certain calculations. Default is 1000.
output_var	Character string specifying which variable to output in the result columns: "N" (total sample size, default for sample size calculation) or "powerCoprimary" (co-primary power, default for power calculation).
n_grid	Number of grid points used to maximize the null tail probability over the nuisance parameter in the two exact unconditional tests, that is "Z-pool" and "Boschloo" (default is 100). The other three tests read their p-values off a distribution and ignore this argument. A finer grid locates the maximum more accurately at a proportionally higher computational cost, and the default reproduces the results of earlier versions of the package.

Details

This function performs systematic calculations across all combinations of parameters specified in param_grid and correlation values in rho_values.

The calculation mode (sample size vs power) is automatically determined:

- If param_grid contains n1 and n2: calculates power
- Otherwise: calculates sample size (requires r, alpha, beta)

For binary endpoints with two correlations (rho1, rho2), both are set to the same value from rho_values for each calculation.

The output format follows the style of Sozu et al. (2011), with parameters displayed in the leftmost columns and results for each correlation in subsequent columns.

Value

A data.frame of class "twoCoprimary_table" with:

- Parameter columns (from param_grid)
- Result columns for each correlation value (rho_0.0, rho_0.3, etc.)

References

Sozu, T., Sugimoto, T., & Hamasaki, T. (2011). Sample size determination in superiority clinical trials with multiple co-primary correlated endpoints. *Journal of Biopharmaceutical Statistics*, 21(4), 650-668.

Examples

```
# Sample size calculation for continuous endpoints
param_grid <- expand.grid(
  delta1 = c(0.3, 0.5),
  delta2 = c(0.1, 0.2, 0.3),
  sd1 = c(1.0, 1.5),
  sd2 = c(1.0, 1.5)
)

result <- design_table(
```

```
  param_grid = param_grid,
  rho_values = c(0, 0.3, 0.5, 0.8),
  r = 1,
  alpha = 0.025,
  beta = 0.2,
  endpoint_type = "continuous"
)
print(result)

# Power calculation for continuous endpoints
param_grid_power <- expand.grid(
  n1 = c(50, 100),
  n2 = c(50, 100),
  delta1 = 0.5,
  delta2 = 0.5,
  sd1 = 1.0,
  sd2 = 1.0
)

result_power <- design_table(
  param_grid = param_grid_power,
  rho_values = c(0, 0.3, 0.5, 0.8),
  alpha = 0.025,
  endpoint_type = "continuous"
)
print(result_power)

# Binary endpoints
param_grid_binary <- expand.grid(
  p11 = c(0.6, 0.7),
  p12 = c(0.4, 0.5),
  p21 = c(0.4, 0.5),
  p22 = c(0.2, 0.3)
)

result_binary <- design_table(
  param_grid = param_grid_binary,
  rho_values = c(0.3, 0.5, 0.7),
  r = 1,
  alpha = 0.025,
  beta = 0.2,
  endpoint_type = "binary",
  Test = "AN"
)
print(result_binary)
```

`plot.twoCoprimary` *Plot Method for twoCoprimary Objects*

Description

Visualizes power or sample size relationships for two co-primary endpoints designs. The function automatically determines the appropriate plot based on the input object.

Usage

```
## S3 method for class 'twoCoprimary'
plot(
  x,
  type = NULL,
  n_points = 50,
  n_range = NULL,
  rho_range = NULL,
  col = "steelblue",
  lwd = 2,
  main = NULL,
  xlab = NULL,
  ylab = NULL,
  show_reference = TRUE,
  ...
)
```

Arguments

x	An object of class "twoCoprimary" from power or sample size calculation functions
type	Type of plot to generate: **"power_curve"** Power as a function of sample size (default for power calculation results) **"sample_size_rho"** Sample size as a function of correlation (default for sample size calculation results) **"effect_contour"** Contour plot showing combinations of standardized effect sizes achieving target power. The two axes, and the two columns of the returned data, are δ_k/σ_k
n_points	Number of points to compute for the curve. Default is 50. Each point runs a full calculation, so a smaller value is advisable for objects produced with an exact binary test or with Monte Carlo integration.
n_range	Sample size range for power_curve plot. If NULL, automatically determined from the object.
rho_range	Correlation range for sample_size_rho plot. If NULL, the range is seq(0, 0.9, length.out = n_points) for continuous and mixed continuous-binary endpoints, and is derived from the Frechet-Hoeffding bounds of the supplied marginal parameters for binary and mixed count-continuous endpoints.
col	Line color. Default is "steelblue".
lwd	Line width. Default is 2.
main	Plot title. If NULL, automatically generated.

xlab	X-axis label. If NULL, automatically generated.
ylab	Y-axis label. If NULL, automatically generated.
show_reference	Logical. If TRUE, shows reference lines (e.g., target power, current values). Default is TRUE.
...	Additional graphical parameters passed to plot()

Details

The function creates publication-quality plots to visualize the relationship between design parameters and statistical properties. The plot type is automatically selected based on the input object, but can be overridden using the type argument.

For power calculation results (when n1 and n2 are specified), the default is to show how power changes with sample size.

For sample size calculation results (when power is specified), the default is to show how required sample size changes with correlation.

The function works with all endpoint types (continuous, binary, mixed) by automatically detecting the appropriate parameters from the input object.

Value

Invisibly returns the data used to create the plot as a data frame.

Examples

```
# Power calculation result
result_power <- power2Continuous(
  n1 = 100, n2 = 100,
  delta1 = 0.5, delta2 = 0.5,
  sd1 = 1, sd2 = 1,
  rho = 0.5, alpha = 0.025,
  known_var = TRUE
)
plot(result_power)  # Shows power curve

# Sample size calculation result
result_ss <- ss2Continuous(
  delta1 = 0.5, delta2 = 0.5,
  sd1 = 1, sd2 = 1,
  rho = 0.5, r = 1,
  alpha = 0.025, beta = 0.2,
  known_var = TRUE
)
plot(result_ss)  # Shows sample size vs correlation

# Custom plot with specified type
plot(result_power, type = "power_curve", n_range = c(50, 200))
```

`power2BinaryApprox` *Power Calculation for Two Co-Primary Binary Endpoints (Approximate)*

Description

Calculates the power for a two-arm superiority trial with two co-primary binary endpoints using various asymptotic normal approximation methods, as described in Sozu et al. (2010).

Usage

```
power2BinaryApprox(n1, n2, p11, p12, p21, p22, rho1, rho2, alpha, Test)
```

Arguments

`n1`	Sample size for group 1 (test group)
`n2`	Sample size for group 2 (control group)
`p11`	True probability of responders in group 1 for the first outcome ($0 < p11 < 1$)
`p12`	True probability of responders in group 1 for the second outcome ($0 < p12 < 1$)
`p21`	True probability of responders in group 2 for the first outcome ($0 < p21 < 1$)
`p22`	True probability of responders in group 2 for the second outcome ($0 < p22 < 1$)
`rho1`	Correlation between the two outcomes for group 1
`rho2`	Correlation between the two outcomes for group 2
`alpha`	One-sided significance level (typically 0.025 or 0.05)
`Test`	Statistical testing method. One of: • `"AN"`: Asymptotic normal method without continuity correction • `"ANc"`: Asymptotic normal method with continuity correction • `"AS"`: Arcsine method without continuity correction • `"ASc"`: Arcsine method with continuity correction

Details

This function implements four approximate power calculation methods:

Asymptotic Normal (AN): Uses the standard normal approximation without continuity correction (equations 3-4 in Sozu et al. 2010).

Asymptotic Normal with Continuity Correction (ANc): Includes Yates's continuity correction (equation 5 in Sozu et al. 2010).

Arcsine (AS): Uses arcsine transformation without continuity correction (equation 6 in Sozu et al. 2010).

Arcsine with Continuity Correction (ASc): Arcsine method with continuity correction (equation 7 in Sozu et al. 2010).

The correlation between test statistics for the two endpoints depends on the method:

For AN and ANc methods:

$$\rho_{nml} = \frac{\sum_{j=1}^{2} \rho_j \sqrt{\nu_{j1}\nu_{j2}}/n_j}{se_1 \times se_2}$$

where $\nu_{jk} = p_{jk}(1 - p_{jk})$.

For AS method:

$$\rho_{arc} = \frac{n_2\rho_1 + n_1\rho_2}{n_1 + n_2}$$

This is the weighted average of the correlations from both groups.

For ASc method:

$$\rho_{arc,c} = \frac{1}{se_1 \times se_2}\left(\frac{\rho_1\sqrt{\nu_{11}\nu_{12}}}{4n_1\sqrt{\nu_{11,c}\nu_{12,c}}} + \frac{\rho_2\sqrt{\nu_{21}\nu_{22}}}{4n_2\sqrt{\nu_{21,c}\nu_{22,c}}}\right)$$

where $\nu_{jk,c} = (p_{jk} + c_j)(1 - p_{jk} - c_j)$, $c_1 = -1/(2n_1)$, and $c_2 = 1/(2n_2)$.

The correlation bounds are automatically checked using `corrbound2Binary`.

Value

A data frame with the following columns:

`n1`	Sample size for group 1
`n2`	Sample size for group 2
`p11`, `p12`, `p21`, `p22`	Response probabilities
`rho1`, `rho2`	Correlations
`alpha`	One-sided significance level
`Test`	Testing method used
`power1`	Power for the first endpoint alone
`power2`	Power for the second endpoint alone
`powerCoprimary`	Power for both co-primary endpoints

References

Sozu, T., Sugimoto, T., & Hamasaki, T. (2010). Sample size determination in clinical trials with multiple co-primary binary endpoints. *Statistics in Medicine*, 29(21), 2169-2179.

Examples

```
# Power calculation using asymptotic normal method
power2BinaryApprox(
  n1 = 200,
  n2 = 100,
  p11 = 0.5,
  p12 = 0.4,
  p21 = 0.3,
  p22 = 0.2,
  rho1 = 0.7,
```

```
  rho2 = 0.7,
  alpha = 0.025,
  Test = 'AN'
)

# Power calculation with continuity correction
power2BinaryApprox(
  n1 = 200,
  n2 = 100,
  p11 = 0.5,
  p12 = 0.4,
  p21 = 0.3,
  p22 = 0.2,
  rho1 = 0.7,
  rho2 = 0.7,
  alpha = 0.025,
  Test = 'ANc'
)

# Power calculation using arcsine method
power2BinaryApprox(
  n1 = 150,
  n2 = 150,
  p11 = 0.6,
  p12 = 0.5,
  p21 = 0.4,
  p22 = 0.3,
  rho1 = 0.5,
  rho2 = 0.5,
  alpha = 0.025,
  Test = 'AS'
)
```

`power2BinaryExact` *Exact Power Calculation for Two Co-Primary Binary Endpoints*

Description

Calculates the exact power for a two-arm superiority trial with two co-primary binary endpoints using the bivariate binomial distribution, as described in Homma and Yoshida (2025).

Usage

```
power2BinaryExact(
  n1,
  n2,
  p11,
  p12,
  p21,
```

```
  p22,
  rho1,
  rho2,
  alpha,
  Test,
  n_grid = 100
)
```

Arguments

n1	Sample size for group 1 (test group)
n2	Sample size for group 2 (control group)
p11	True probability of responders in group 1 for the first outcome (0 < p11 < 1)
p12	True probability of responders in group 1 for the second outcome (0 < p12 < 1)
p21	True probability of responders in group 2 for the first outcome (0 < p21 < 1)
p22	True probability of responders in group 2 for the second outcome (0 < p22 < 1)
rho1	Correlation between the two outcomes for group 1
rho2	Correlation between the two outcomes for group 2
alpha	One-sided significance level (typically 0.025 or 0.05)
Test	Statistical testing method. One of: • "Chisq": One-sided Pearson chi-squared test • "Fisher": Fisher exact test • "Fisher-midP": Fisher mid-p test • "Z-pool": Z-pooled exact unconditional test • "Boschloo": Boschloo exact unconditional test
n_grid	Number of grid points used to maximize the null tail probability over the nuisance parameter in the two exact unconditional tests, that is "Z-pool" and "Boschloo" (default is 100). The other three tests read their p-values off a distribution and ignore this argument. A finer grid locates the maximum more accurately at a proportionally higher computational cost, and the default reproduces the results of earlier versions of the package.

Details

This function calculates exact power using equation (9) in Homma and Yoshida (2025):

$$power_A(\theta) = \sum_{(a_{1,1},a_{2,1})\in\mathcal{A}_1} \sum_{(a_{1,2},a_{2,2})\in\mathcal{A}_2} f(a_{1,1}|N_1,p_{1,1})\times f(a_{2,1}|N_2,p_{2,1})\times g(a_{1,2}|a_{1,1},N_1,p_{1,1},p_{1,2},\gamma_1)\times g(a_{2,2}|a_{2,1},N$$

where $\mathcal{A}_k$ is the rejection region for endpoint k, and $(Y_{j,1}, Y_{j,2}) \sim BiBin(N_j, p_{j,1}, p_{j,2}, \gamma_j)$ follows the bivariate binomial distribution.

The correlation bounds are automatically checked using corrbound2Binary.

Value

A data frame with the following columns:

n1	Sample size for group 1
n2	Sample size for group 2
p11, p12, p21, p22	Response probabilities
rho1, rho2	Correlations
alpha	One-sided significance level
Test	Testing method used
power1	Power for the first endpoint alone
power2	Power for the second endpoint alone
powerCoprimary	Exact power for both co-primary endpoints

References

Homma, G., & Yoshida, T. (2025). Exact power and sample size in clinical trials with two co-primary binary endpoints. *Statistical Methods in Medical Research*, 34(11), 2183-2201.

Examples

```
# Exact power calculation using Boschloo test
power2BinaryExact(
  n1 = 100,
  n2 = 50,
  p11 = 0.5,
  p12 = 0.4,
  p21 = 0.3,
  p22 = 0.2,
  rho1 = 0.7,
  rho2 = 0.7,
  alpha = 0.025,
  Test = 'Boschloo'
)

# Exact power with Fisher exact test
power2BinaryExact(
  n1 = 80,
  n2 = 80,
  p11 = 0.6,
  p12 = 0.5,
  p21 = 0.4,
  p22 = 0.3,
  rho1 = 0.5,
  rho2 = 0.5,
  alpha = 0.025,
  Test = 'Fisher'
)
```

```
# Larger sample sizes (computationally intensive)
power2BinaryExact(
  n1 = 200,
  n2 = 100,
  p11 = 0.5,
  p12 = 0.4,
  p21 = 0.3,
  p22 = 0.2,
  rho1 = 0.6,
  rho2 = 0.6,
  alpha = 0.025,
  Test = 'Chisq'
)
```

`power2Continuous` *Power Calculation for Two Co-Primary Continuous Endpoints*

Description

Calculates the power for a two-arm superiority trial with two co-primary continuous endpoints, as described in Sozu et al. (2011).

Usage

```
power2Continuous(
  n1,
  n2,
  delta1,
  delta2,
  sd1,
  sd2,
  rho,
  alpha,
  known_var = TRUE,
  nMC = 10000
)
```

Arguments

`n1`	Sample size for group 1 (test group)
`n2`	Sample size for group 2 (control group)
`delta1`	Mean difference for the first endpoint
`delta2`	Mean difference for the second endpoint
`sd1`	Common standard deviation for the first endpoint

sd2	Common standard deviation for the second endpoint
rho	Common correlation between the two outcomes
alpha	One-sided significance level (typically 0.025 or 0.05)
known_var	Logical value indicating whether variance is known (TRUE) or unknown (FALSE). If TRUE, power is calculated analytically; otherwise, Monte Carlo simulation is used for unknown variance
nMC	Number of Monte Carlo simulations when known_var = FALSE (default is 10000)

Details

For known variance, the power is calculated using the bivariate normal distribution as described in Sozu et al. (2011). The test statistics are:

$$Z_k = \frac{\delta_k}{\sigma_k \sqrt{1/n_1 + 1/n_2}}$$

for k = 1, 2. The co-primary power is:

$$1 - \beta = \Phi_2 \left(-z_{1-\alpha} + Z_1, -z_{1-\alpha} + Z_2 \mid \rho \right)$$

where Φ_2 is the cumulative distribution function of the bivariate standard normal distribution.

For unknown variance, Monte Carlo simulation is used with Wishart-distributed correlation matrices of the standardized endpoints to account for variance estimation uncertainty, following equation (6) in Sozu et al. (2011):

$$\text{Power} = E_W \left[\Phi_2(-c_1^* \sqrt{w_{11}}, -c_2^* \sqrt{w_{22}} | \rho) \right]$$

where $c_k^* = t_{\alpha,\nu} \sqrt{\frac{1}{\nu}} - \frac{Z_k}{\sqrt{w_{kk}}}$ and W follows a Wishart distribution with $\nu = n_1 + n_2 - 2$ degrees of freedom and the correlation matrix of the standardized endpoints as its scale matrix, so that $\sqrt{w_{kk}/\nu}$ is the ratio of the estimated to the true standard deviation of endpoint k.

The Monte Carlo step draws random numbers, so results for `known_var = FALSE` vary between calls unless a seed is set with `set.seed` beforehand.

Value

A data frame with the following columns:

n1	Sample size for group 1
n2	Sample size for group 2
delta1	Mean difference for endpoint 1
delta2	Mean difference for endpoint 2
sd1	Standard deviation for endpoint 1
sd2	Standard deviation for endpoint 2
rho	Correlation between endpoints
alpha	One-sided significance level

known_var	Variance assumption
nMC	Number of Monte Carlo simulations (NA if known_var = TRUE)
power1	Power for the first endpoint alone
power2	Power for the second endpoint alone
powerCoprimary	Power for both co-primary endpoints

References

Sozu, T., Sugimoto, T., & Hamasaki, T. (2011). Sample size determination in superiority clinical trials with multiple co-primary correlated endpoints. *Journal of Biopharmaceutical Statistics*, 21(4), 650-668.

Examples

```
# Example parameters for comparison across methods
n1_ex <- 100
n2_ex <- 100
delta1_ex <- 0.5
delta2_ex <- 0.5
sd1_ex <- 1
sd2_ex <- 1
rho_ex <- 0.3
alpha_ex <- 0.025

# Power calculation with known variance
power2Continuous(
  n1 = n1_ex,
  n2 = n2_ex,
  delta1 = delta1_ex,
  delta2 = delta2_ex,
  sd1 = sd1_ex,
  sd2 = sd2_ex,
  rho = rho_ex,
  alpha = alpha_ex,
  known_var = TRUE
)


# Power calculation with unknown variance (Monte Carlo)
power2Continuous(
  n1 = n1_ex,
  n2 = n2_ex,
  delta1 = delta1_ex,
  delta2 = delta2_ex,
  sd1 = sd1_ex,
  sd2 = sd2_ex,
  rho = rho_ex,
  alpha = alpha_ex,
  known_var = FALSE,
  nMC = 10000
)
```

`power2MixedContinuousBinary` *Power Calculation for Two Co-Primary Mixed Endpoints*

Description

Calculates the power for a two-arm superiority trial with two co-primary endpoints where one is continuous and one is binary, as described in Sozu et al. (2012).

Usage

```
power2MixedContinuousBinary(
  n1,
  n2,
  delta,
  sd,
  p1,
  p2,
  rho,
  alpha,
  Test,
  nMC = 10000
)
```

Arguments

`n1`	Sample size for group 1 (test group)
`n2`	Sample size for group 2 (control group)
`delta`	Mean difference for the continuous endpoint (group 1 - group 2)
`sd`	Common standard deviation for the continuous endpoint
`p1`	Probability of response in group 1 for the binary endpoint (0 < p1 < 1)
`p2`	Probability of response in group 2 for the binary endpoint (0 < p2 < 1)
`rho`	Biserial correlation between the latent continuous variable underlying the binary endpoint and the observed continuous endpoint
`alpha`	One-sided significance level (typically 0.025 or 0.05)
`Test`	Statistical testing method for the binary endpoint. One of: • `"AN"`: Asymptotic normal method without continuity correction • `"ANc"`: Asymptotic normal method with continuity correction • `"AS"`: Arcsine method without continuity correction • `"ASc"`: Arcsine method with continuity correction • `"Fisher"`: Fisher's exact test (Monte Carlo simulation required)
`nMC`	Number of Monte Carlo replications when Test = "Fisher" (default: 10000)

Details

This function implements the power calculation for mixed endpoints (one continuous and one binary) as described in Sozu et al. (2012). The method assumes that the binary variable is derived from a latent continuous variable via dichotomization at a threshold point.

For Fisher's exact test, Monte Carlo simulation is used because exact calculation is computationally intensive. The continuous endpoint is analyzed using t-test, and the binary endpoint uses Fisher's exact test.

For asymptotic methods (AN, ANc, AS, ASc), analytical formulas are used based on bivariate normal approximation. The correlation between test statistics depends on the biserial correlation rho and the specific testing method.

Biserial Correlation: The biserial correlation rho represents the correlation between the latent continuous variable underlying the binary endpoint and the observed continuous endpoint. This is not the same as the point-biserial correlation observed in the data.

The Monte Carlo step of `Test = "Fisher"` draws random numbers, so results vary between calls unless a seed is set with `set.seed` beforehand. The sequential search for the sample size compares a simulated power against the target, so the returned sample size can differ by a subject or two between runs; increasing `nMC` reduces that variation.

Value

A data frame with the following columns:

`n1`	Sample size for group 1
`n2`	Sample size for group 2
`delta`	Mean difference for continuous endpoint
`sd`	Standard deviation for continuous endpoint
`p1`	Response probability in group 1 for binary endpoint
`p2`	Response probability in group 2 for binary endpoint
`rho`	Biserial correlation
`alpha`	One-sided significance level
`Test`	Testing method used for binary endpoint
`nMC`	Number of Monte Carlo replications (NA if Test != "Fisher")
`powerCont`	Power for the continuous endpoint alone
`powerBin`	Power for the binary endpoint alone
`powerCoprimary`	Power for both co-primary endpoints

References

Sozu, T., Sugimoto, T., & Hamasaki, T. (2012). Sample size determination in clinical trials with multiple co-primary endpoints including mixed continuous and binary variables. *Biometrical Journal*, 54(5), 716-729.

Examples

```
# Power calculation using asymptotic normal method
power2MixedContinuousBinary(
  n1 = 100,
  n2 = 100,
  delta = 0.5,
  sd = 1,
  p1 = 0.6,
  p2 = 0.4,
  rho = 0.5,
  alpha = 0.025,
  Test = 'AN'
)


# Power calculation with Fisher's exact test (computationally intensive)
power2MixedContinuousBinary(
  n1 = 50,
  n2 = 50,
  delta = 0.5,
  sd = 1,
  p1 = 0.6,
  p2 = 0.4,
  rho = 0.5,
  alpha = 0.025,
  Test = 'Fisher',
  nMC = 5000
)
```

---

power2MixedCountContinuous

Power Calculation for Two Co-Primary Endpoints (Count and Continuous)

Description

Calculates the power for a two-arm superiority trial with one overdispersed count co-primary endpoint and one continuous co-primary endpoint, as described in Homma and Yoshida (2024).

Usage

```
power2MixedCountContinuous(
  n1,
  n2,
  r1,
  r2,
  nu,
```

```
  t,
  mu1,
  mu2,
  sd,
  rho1,
  rho2,
  alpha
)
```

Arguments

n1	Sample size for group 1 (test group)
n2	Sample size for group 2 (control group)
r1	Mean rate (events per unit time) for the treatment group (count endpoint)
r2	Mean rate (events per unit time) for the control group (count endpoint)
nu	Common dispersion parameter for the negative binomial distribution (nu > 0)
t	Common follow-up time period
mu1	Mean for group 1 (continuous endpoint)
mu2	Mean for group 2 (continuous endpoint)
sd	Common standard deviation for the continuous endpoint
rho1	Correlation between count and continuous outcomes for treatment group
rho2	Correlation between count and continuous outcomes for control group
alpha	One-sided significance level (typically 0.025 or 0.05)

Details

The formulas below are those of Homma and Yoshida (2024), written in the indexing used throughout this package: group 1 is the treatment group and group 2 is the control group, and $\kappa = n_1/n_2$ is the argument r. The source article indexes the control group by 0 instead.

The test statistics are (equation 7 in Homma and Yoshida 2024):

$$Z_1 = \frac{\hat{\beta}_1}{\sqrt{Var(\hat{\beta}_1)}}, \quad Z_2 = \frac{\hat{\delta}}{\sigma\sqrt{(1+\kappa)/(\kappa n_2)}}$$

The joint distribution of (Z1, Z2) follows an asymptotic bivariate normal distribution with correlation gamma (equation 11):

$$\gamma = \sum_{j=1}^{2} \frac{n_2 \rho_j \sqrt{1+\lambda_j/\nu}}{n_j \sqrt{\lambda_j V_a}\sqrt{(1+\kappa)/\kappa}}$$

where $\lambda_j = r_j \times t$ is the mean count in group j, r_j is the event rate per unit time, which is distinct from the allocation ratio r, and V_a is the variance component of equation 8, $(1/t)(1/r_2 + 1/(\kappa r_1)) + (1+\kappa)/(\nu\kappa)$, so that $Var(\hat{\beta}_1) = V_a/n_2$.

The correlation bounds are automatically checked using corrbound2MixedCountContinuous.

Value

A data frame with the following columns:

n1	Sample size for group 1
n2	Sample size for group 2
r1	Mean rate in group 1 for count endpoint
r2	Mean rate in group 2 for count endpoint
nu	Dispersion parameter
t	Follow-up time
mu1	Mean in group 1 for continuous endpoint
mu2	Mean in group 2 for continuous endpoint
sd	Standard deviation for continuous endpoint
rho1	Correlation for group 1
rho2	Correlation for group 2
alpha	One-sided significance level
powerCount	Power for the count endpoint alone
powerCont	Power for the continuous endpoint alone
powerCoprimary	Power for both co-primary endpoints

References

Homma, G., & Yoshida, T. (2024). Sample size calculation in clinical trials with two co-primary endpoints including overdispersed count and continuous outcomes. *Pharmaceutical Statistics*, 23(1), 46-59.

Examples

```
# Power calculation with moderate correlation
power2MixedCountContinuous(
  n1 = 300,
  n2 = 300,
  r1 = 1.0,
  r2 = 1.25,
  nu = 0.8,
  t = 1,
  mu1 = -50,
  mu2 = 0,
  sd = 250,
  rho1 = 0.5,
  rho2 = 0.5,
  alpha = 0.025
)

# Power calculation with no correlation
power2MixedCountContinuous(
  n1 = 350,
```

```
  n2 = 350,
  r1 = 1.0,
  r2 = 1.5,
  nu = 1,
  t = 1,
  mu1 = -40,
  mu2 = 0,
  sd = 200,
  rho1 = 0,
  rho2 = 0,
  alpha = 0.025
)

# Unbalanced design
power2MixedCountContinuous(
  n1 = 400,
  n2 = 200,
  r1 = 1,
  r2 = 1.25,
  nu = 1,
  t = 1,
  mu1 = -50,
  mu2 = 0,
  sd = 250,
  rho1 = 0.6,
  rho2 = 0.6,
  alpha = 0.025
)
```

`print.twoCoprimary` *Print Method for twoCoprimary Objects*

Description

Provides a clean, formatted display of sample size and power calculation results from the twoCoprimary package.

Usage

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

Arguments

`x`	An object of class "twoCoprimary"
`...`	Additional arguments (currently unused)

Details

This print method provides a formatted output that displays key parameters and results in an easy-to-read format. The specific format adapts to the type of calculation (sample size vs power) and the type of endpoints involved.

Value

Invisibly returns the original object

---

print.twoCoprimary_table *Print Method for twoCoprimary_table Objects*

Description

Provides a clean display of design comparison tables

Usage

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

Arguments

x	An object of class "twoCoprimary_table"
...	Additional arguments passed to print.data.frame

Value

Invisibly returns the original object

---

rr1Binary *Rejection Region for Two-Arm Trials with a Single Binary Endpoint*

Description

Calculates the rejection region for two-arm trials with a single binary endpoint using various exact statistical tests, as described in Homma and Yoshida (2025).

Usage

```
rr1Binary(n1, n2, alpha, Test, n_grid = 100)
```

Arguments

n1	Sample size for group 1 (test group)
n2	Sample size for group 2 (control group)
alpha	One-sided significance level (typically 0.025)
Test	Type of statistical test. One of: • "Chisq": One-sided Pearson chi-squared test • "Fisher": Fisher exact test • "Fisher-midP": Fisher mid-p test • "Z-pool": Z-pooled exact unconditional test • "Boschloo": Boschloo exact unconditional test
n_grid	Number of grid points used to maximize the null tail probability over the nuisance parameter in the two exact unconditional tests, that is "Z-pool" and "Boschloo" (default is 100). The other three tests read their p-values off a distribution and ignore this argument. A finer grid locates the maximum more accurately at a proportionally higher computational cost, and the default reproduces the results of earlier versions of the package.

Details

This function computes the rejection region for five different one-sided tests:

Chi-squared test: Uses the asymptotic normal approximation of the chi-squared statistic.

Fisher exact test: Uses the hypergeometric distribution to calculate exact p-values conditional on the total number of successes.

Fisher mid-p test: Modification of Fisher's exact test that adds half the probability of the observed outcome to reduce conservatism.

Z-pooled test: Exact unconditional test that maximizes p-values over all possible values of the nuisance parameter (common success probability under H0).

Boschloo test: Exact unconditional test similar to Z-pooled but based on Fisher's exact p-values, maximizing over the nuisance parameter.

For the two exact unconditional tests the outcomes are ordered from the most extreme to the least extreme value of the ordering statistic, and the null tail probability is accumulated along that order before being maximized over the nuisance parameter. Outcomes that share the same value of the ordering statistic form a tie group, and since the tail event is the set of outcomes at least as extreme as the observed one, every member of a tie group receives the tail probability accumulated up to the last member of that group. This makes the p-value independent of the order in which tied outcomes happen to be sorted.

Value

A logical matrix of dimensions (n1+1) x (n2+1), where TRUE indicates rejection of the null hypothesis. Rows correspond to the number of responders in group 1 (0 to n1), and columns correspond to the number of responders in group 2 (0 to n2).

References

Homma, G., & Yoshida, T. (2025). Exact power and sample size in clinical trials with two co-primary binary endpoints. *Statistical Methods in Medical Research*, 34(11), 2183-2201.

Examples

```
# Simple example with small sample sizes
n1 <- 5
n2 <- 5
alpha <- 0.025
RR <- rr1Binary(n1, n2, alpha, Test = 'Chisq')
print(dim(RR))  # Should be (6, 6)

# Fisher exact test
RR_fisher <- rr1Binary(n1 = 10, n2 = 10, alpha = 0.025, Test = 'Fisher')


# More computationally intensive: Boschloo test
n1 <- 20
n2 <- 10
alpha <- 0.025
RR <- rr1Binary(n1, n2, alpha, Test = 'Boschloo')
print(RR)
```

`ss1BinaryApprox` *Sample Size Calculation for a Single Binary Endpoint*

Description

Calculates the required sample size for a two-arm superiority trial with a single binary endpoint using various statistical testing methods.

Usage

```
ss1BinaryApprox(p1, p2, r, alpha, beta, Test = "AN")
```

Arguments

`p1`	True probability of responders in group 1 ($0 < p1 < 1$). Must be greater than `p2`, since the design is a superiority trial
`p2`	True probability of responders in group 2 ($0 < p2 < 1$)
`r`	Allocation ratio of group 1 to group 2 (group 1:group 2 = r:1, where $r > 0$)
`alpha`	One-sided significance level (typically 0.025)
`beta`	Target type II error rate (typically 0.1 or 0.2)
`Test`	Statistical testing method. One of:

- "AN": Asymptotic normal method without continuity correction (default)
- "ANc": Asymptotic normal method with continuity correction
- "AS": Arcsine transformation without continuity correction
- "ASc": Arcsine transformation with continuity correction
- "Fisher": Fisher's exact test with iterative sample size determination

Details

This function implements sample size calculations for single binary endpoint trials using five different methods.

Important: This function is designed for a **single binary endpoint**. For co-primary endpoints, use ss2BinaryApprox (for approximate methods) or ss2BinaryExact (for exact methods).

Notation:

- r = n1/n2: allocation ratio (group 1 to group 2)
- kappa = 1/r = n2/n1: inverse allocation ratio
- p1, p2: response probabilities
- theta1 = 1 - p1, theta2 = 1 - p2: non-response probabilities
- delta = p1 - p2: treatment effect

All four asymptotic methods return the smallest n_2 whose realized group sizes reach the target power under power2BinaryApprox with both endpoints set to the same marginal. The closed forms below give the starting value of that search. They are not used as the answer, because they assume that n_1 is exactly rn_2, whereas n_1 is rounded up to an integer, and because for the two continuity corrected methods the correction depends on the sample size being solved for.

AN (Asymptotic Normal) Method: Uses the standard normal approximation with pooled variance under H0:

$$n_2 = \left\lceil \frac{(1+\kappa)}{(\pi_1-\pi_2)^2}\left(z_{1-\alpha}\sqrt{\bar{\pi}(1-\bar{\pi})} + z_{1-\beta}\sqrt{\kappa\pi_1\theta_1+\pi_2\theta_2}\right)^2/\kappa \right\rceil$$

where $\bar{\pi} = (r\pi_1+\pi_2)/(1+r)$ is the pooled proportion.

ANc Method: Adds Yates's continuity correction to the AN method.

AS (Arcsine) Method: Uses the variance-stabilizing arcsine transformation:

$$n_2 = \left\lceil \frac{(z_{1-\alpha}+z_{1-\beta})^2(1+\kappa)}{4(\sin^{-1}\sqrt{\pi_1}-\sin^{-1}\sqrt{\pi_2})^2} \right\rceil$$

ASc Method: Applies continuity correction to the arcsine method. The correction moves the two arms toward each other, and the variance is adjusted for the corrected proportions following Sozu et al. (2010).

Fisher Method: Fisher's exact test does not have a closed-form sample size formula. This method:

1. Starts with the AN method's sample size as initial value
2. Incrementally increases n2 by 1
3. Calculates exact power by summing the binomial probabilities over the rejection region

4. Stops when power is greater than or equal to 1 - beta
5. Steps back down while the target is still met, so that a starting value that already reached the target does not hide a smaller one

Note: Due to the saw-tooth nature of exact power (power does not increase monotonically with sample size), a sequential search approach is used. The incremental approach ensures the minimum sample size that achieves the target power.

Value

A data frame with the following columns:

p1	Probability of responders in group 1
p2	Probability of responders in group 2
r	Allocation ratio
alpha	One-sided significance level
beta	Type II error rate
Test	Testing method used
n1	Required sample size for group 1
n2	Required sample size for group 2
N	Total sample size (n1 + n2)

References

Sozu, T., Sugimoto, T., & Hamasaki, T. (2010). Sample size determination in clinical trials with multiple co-primary binary endpoints. *Statistics in Medicine*, 29(21), 2169-2179.

Examples

```
# Balanced design with 1:1 allocation (AN method)
ss1BinaryApprox(p1 = 0.6, p2 = 0.4, r = 1, alpha = 0.025, beta = 0.1, Test = "AN")

# Unbalanced design with 2:1 allocation (ANc method)
ss1BinaryApprox(p1 = 0.5, p2 = 0.3, r = 2, alpha = 0.025, beta = 0.2, Test = "ANc")

# Arcsine transformation method
ss1BinaryApprox(p1 = 0.55, p2 = 0.35, r = 1, alpha = 0.025, beta = 0.1, Test = "AS")

# Arcsine with continuity correction
ss1BinaryApprox(p1 = 0.65, p2 = 0.45, r = 1, alpha = 0.025, beta = 0.1, Test = "ASc")

# Fisher's exact test
ss1BinaryApprox(p1 = 0.6, p2 = 0.4, r = 2, alpha = 0.025, beta = 0.1, Test = "Fisher")
```

`ss1Continuous` *Sample Size Calculation for a Single Continuous Endpoint*

Description

Calculates the required sample size for a two-arm superiority trial with a single continuous endpoint using the standard formula for normally distributed outcomes.

Usage

```
ss1Continuous(delta, sd, r, alpha, beta)
```

Arguments

`delta`	Mean difference between treatment groups (treatment effect)
`sd`	Common standard deviation for the continuous endpoint
`r`	Allocation ratio of group 1 to group 2 (group 1:group 2 = r:1, where r > 0)
`alpha`	One-sided significance level (typically 0.025 or 0.05)
`beta`	Target type II error rate (typically 0.1 or 0.2)

Details

The required sample size for group 2 is calculated using the standard formula:

$$n_2 = \left\lceil \frac{(1 + 1/r)\sigma^2(z_\alpha + z_\beta)^2}{\delta^2} \right\rceil$$

where z_α and z_β are the quantiles of the standard normal distribution corresponding to the one-sided significance level α and type II error rate β, respectively. The sample size for group 1 is $n_1 = \lceil r \times n_2 \rceil$.

Value

A data frame with the following columns:

`delta`	Mean difference (treatment effect)
`sd`	Common standard deviation
`r`	Allocation ratio
`alpha`	One-sided significance level
`beta`	Type II error rate
`n1`	Required sample size for group 1
`n2`	Required sample size for group 2
`N`	Total sample size (n1 + n2)

Examples

```
# Balanced design with 1:1 allocation
ss1Continuous(delta = 0.4, sd = 1, r = 1, alpha = 0.025, beta = 0.1)

# Unbalanced design with 2:1 allocation
ss1Continuous(delta = 0.5, sd = 1.2, r = 2, alpha = 0.025, beta = 0.2)

# Large treatment effect
ss1Continuous(delta = 0.8, sd = 1, r = 1, alpha = 0.025, beta = 0.1)
```

---

ss1Count *Sample Size Calculation for a Single Count Endpoint (Negative Binomial)*

Description

Calculates the required sample size for a two-arm superiority trial with a single overdispersed count endpoint following a negative binomial distribution, as described in Homma and Yoshida (2024).

Usage

```
ss1Count(r1, r2, nu, t, r, alpha, beta)
```

Arguments

r1	Mean rate (events per unit time) for the treatment group, which must be less than r2, since a lower event rate is the treatment benefit of interest
r2	Mean rate (events per unit time) for the control group
nu	Common dispersion parameter for the negative binomial distribution (nu > 0)
t	Common follow-up time period
r	Allocation ratio (treatment:control = r:1, where r > 0)
alpha	One-sided significance level (typically 0.025 or 0.05)
beta	Target type II error rate (typically 0.1 or 0.2)

Details

The test statistic for the negative binomial rate ratio is:

$$Z_1 = \frac{\hat{\beta}_1}{\sqrt{Var(\hat{\beta}_1)}}$$

where $\hat{\beta}_1 = \log(\bar{Y}_1) - \log(\bar{Y}_2)$ and the variance is:

$$Var(\hat{\beta}_1) = \frac{1}{n_2}\left[\frac{1}{t}\left(\frac{1}{r_2} + \frac{1}{r \cdot r_1}\right) + \frac{1+r}{\nu \cdot r}\right]$$

This is equation (8) in Homma and Yoshida (2024).

Value

A data frame with the following columns:

r1	Mean rate for treatment group
r2	Mean rate for control group
nu	Dispersion parameter
t	Follow-up time
r	Allocation ratio
alpha	One-sided significance level
beta	Type II error rate
n1	Required sample size for treatment group
n2	Required sample size for control group
N	Total sample size (n2 + n1)

References

Homma, G., & Yoshida, T. (2024). Sample size calculation in clinical trials with two co-primary endpoints including overdispersed count and continuous outcomes. *Pharmaceutical Statistics*, 23(1), 46-59.

Examples

```
# Sample size for count endpoint with nu = 0.8
ss1Count(r1 = 1.0, r2 = 1.25, nu = 0.8, t = 1, r = 1,
         alpha = 0.025, beta = 0.1)

# Unbalanced design with 2:1 allocation
ss1Count(r1 = 1.0, r2 = 1.5, nu = 1.0, t = 1, r = 2,
         alpha = 0.025, beta = 0.2)

# Higher dispersion
ss1Count(r1 = 1.5, r2 = 2.0, nu = 3.0, t = 1, r = 1,
         alpha = 0.025, beta = 0.1)
```

---

ss2BinaryApprox *Sample Size Calculation for Two Co-Primary Binary Endpoints (Asymptotic Approximation)*

Description

Calculates the required sample size for a two-arm superiority trial with two co-primary binary endpoints using asymptotic normal approximation or arcsine transformation, as described in Sozu et al. (2010).

Usage

```
ss2BinaryApprox(p11, p12, p21, p22, rho1, rho2, r, alpha, beta, Test)
```

Arguments

p11	True probability of responders in group 1 for the first outcome (0 < p11 < 1)
p12	True probability of responders in group 1 for the second outcome (0 < p12 < 1)
p21	True probability of responders in group 2 for the first outcome (0 < p21 < 1)
p22	True probability of responders in group 2 for the second outcome (0 < p22 < 1)
rho1	Correlation between the two outcomes for group 1
rho2	Correlation between the two outcomes for group 2
r	Allocation ratio of group 1 to group 2 (group 1:group 2 = r:1, where r > 0)
alpha	One-sided significance level (typically 0.025 or 0.05)
beta	Target type II error rate (typically 0.1 or 0.2)
Test	Statistical testing method. One of: • "AN": Asymptotic normal method without continuity correction • "ANc": Asymptotic normal method with continuity correction • "AS": Arcsine method without continuity correction • "ASc": Arcsine method with continuity correction

Details

This function uses a sequential search algorithm (Homma and Yoshida 2025, Algorithm 1) to find the minimum sample size:

Step 1: Initialize with sample sizes from single endpoint formulas.

Step 2: Use sequential search:

- Calculate power at initial sample size
- If power >= target: decrease n2 until power < target, then add 1 back
- If power < target: increase n2 until power >= target

Step 3: Return final sample sizes.

The asymptotic normal (AN) and arcsine (AS) methods use normal approximation with or without continuity correction. For small sample sizes or extreme probabilities, consider using exact methods via ss2BinaryExact.

Value

A data frame with the following columns:

p11, p12, p21, p22	Response probabilities
rho1, rho2	Correlations
r	Allocation ratio

alpha	One-sided significance level
beta	Type II error rate
Test	Testing method used
n1	Required sample size for group 1
n2	Required sample size for group 2
N	Total sample size (n1 + n2)

References

Sozu, T., Sugimoto, T., & Hamasaki, T. (2010). Sample size determination in clinical trials with multiple co-primary binary endpoints. *Statistics in Medicine*, 29(21), 2169-2179.

Homma, G., & Yoshida, T. (2025). Exact power and sample size in clinical trials with two co-primary binary endpoints. *Statistical Methods in Medical Research*, 34(11), 2183-2201.

Examples

```
# Sample size calculation using asymptotic normal method
ss2BinaryApprox(
  p11 = 0.5,
  p12 = 0.4,
  p21 = 0.3,
  p22 = 0.2,
  rho1 = 0.5,
  rho2 = 0.5,
  r = 1,
  alpha = 0.025,
  beta = 0.2,
  Test = 'AN'
)

# With continuity correction
ss2BinaryApprox(
  p11 = 0.5,
  p12 = 0.4,
  p21 = 0.3,
  p22 = 0.2,
  rho1 = 0.5,
  rho2 = 0.5,
  r = 1,
  alpha = 0.025,
  beta = 0.2,
  Test = 'ANc'
)

# Using arcsine transformation
ss2BinaryApprox(
  p11 = 0.5,
  p12 = 0.4,
  p21 = 0.3,
  p22 = 0.2,
```

```
  rho1 = 0.5,
  rho2 = 0.5,
  r = 1,
  alpha = 0.025,
  beta = 0.2,
  Test = 'AS'
)
```

`ss2BinaryExact` *Exact Sample Size Calculation for Two Co-Primary Binary Endpoints*

Description

Calculates the required sample size for a two-arm superiority trial with two co-primary binary endpoints using exact methods, as described in Homma and Yoshida (2025).

Usage

```
ss2BinaryExact(
  p11,
  p12,
  p21,
  p22,
  rho1,
  rho2,
  r,
  alpha,
  beta,
  Test,
  n_grid = 100
)
```

Arguments

`p11`	True probability of responders in group 1 for the first outcome (0 < p11 < 1)
`p12`	True probability of responders in group 1 for the second outcome (0 < p12 < 1)
`p21`	True probability of responders in group 2 for the first outcome (0 < p21 < 1)
`p22`	True probability of responders in group 2 for the second outcome (0 < p22 < 1)
`rho1`	Correlation between the two outcomes for group 1
`rho2`	Correlation between the two outcomes for group 2
`r`	Allocation ratio of group 1 to group 2 (group 1:group 2 = r:1, where r > 0)
`alpha`	One-sided significance level (typically 0.025 or 0.05)
`beta`	Target type II error rate (typically 0.1 or 0.2)
`Test`	Statistical testing method. One of:

- "Chisq": One-sided Pearson chi-squared test
- "Fisher": Fisher exact test
- "Fisher-midP": Fisher mid-p test
- "Z-pool": Z-pooled exact unconditional test
- "Boschloo": Boschloo exact unconditional test

n_grid Number of grid points used to maximize the null tail probability over the nuisance parameter in the two exact unconditional tests, that is "Z-pool" and "Boschloo" (default is 100). The other three tests read their p-values off a distribution and ignore this argument. A finer grid locates the maximum more accurately at a proportionally higher computational cost, and the default reproduces the results of earlier versions of the package.

Details

This function uses a sequential search algorithm to find the minimum sample size that achieves the target power:

Step 1: Initialize with sample size from approximate method (AN). This provides a good starting point for the exact calculation.

Step 2: Use sequential search algorithm (Homma and Yoshida 2025, Algorithm 1):

- Calculate power at initial sample size
- If power >= target: decrease n2 until power < target, then add 1 back
- If power < target: increase n2 until power >= target

Step 3: Return final sample sizes.

Note: Due to the saw-tooth nature of exact power (power does not increase monotonically with sample size), this sequential search ensures the minimum sample size that achieves the target power.

Value

A data frame with the following columns:

p11, p12, p21, p22	Response probabilities
rho1, rho2	Correlations
r	Allocation ratio
alpha	One-sided significance level
beta	Type II error rate
Test	Testing method used
n1	Required sample size for group 1
n2	Required sample size for group 2
N	Total sample size (n1 + n2)

References

Homma, G., & Yoshida, T. (2025). Exact power and sample size in clinical trials with two co-primary binary endpoints. *Statistical Methods in Medical Research*, 34(11), 2183-2201.

Examples

```
# Quick example with Chi-squared test (faster)
ss2BinaryExact(
  p11 = 0.6,
  p12 = 0.5,
  p21 = 0.4,
  p22 = 0.3,
  rho1 = 0.3,
  rho2 = 0.3,
  r = 1,
  alpha = 0.025,
  beta = 0.2,
  Test = "Chisq"
)


# More computationally intensive example with Fisher test
ss2BinaryExact(
  p11 = 0.5,
  p12 = 0.4,
  p21 = 0.3,
  p22 = 0.2,
  rho1 = 0.5,
  rho2 = 0.5,
  r = 1,
  alpha = 0.025,
  beta = 0.2,
  Test = "Fisher"
)
```

---

ss2Continuous *Sample Size Calculation for Two Co-Primary Continuous Endpoints (Approximate)*

Description

Calculates the required sample size for a two-arm superiority trial with two co-primary continuous endpoints using sequential search algorithm.

Usage

```
ss2Continuous(
  delta1,
  delta2,
  sd1,
  sd2,
  rho,
```

```
  r,
  alpha,
  beta,
  known_var = TRUE,
  nMC = 10000
)
```

Arguments

delta1	Mean difference for the first endpoint
delta2	Mean difference for the second endpoint
sd1	Common standard deviation for the first endpoint
sd2	Common standard deviation for the second endpoint
rho	Common correlation between the two outcomes
r	Allocation ratio of group 1 to group 2 (group 1:group 2 = r:1, where r > 0)
alpha	One-sided significance level (typically 0.025 or 0.05)
beta	Target type II error rate (typically 0.1 or 0.2)
known_var	Logical value indicating whether variance is known (TRUE) or unknown (FALSE). If TRUE, power is calculated analytically; if FALSE, Monte Carlo simulation is used
nMC	Number of Monte Carlo simulations when known_var = FALSE (default is 10000)

Details

This function uses a sequential search algorithm (Homma and Yoshida 2025, Algorithm 1) for both known and unknown variance cases:

Step 1: Initialize with sample sizes from single endpoint formulas.

Step 2: Use sequential search:

- Calculate power at initial sample size
- If power >= target: decrease n2 until power < target, then add 1 back
- If power < target: increase n2 until power >= target

Step 3: Return final sample sizes.

For known variance, the standardized test statistics are:

$$Z_k = \frac{\delta_k}{\sigma_k \sqrt{1/n_1 + 1/n_2}}$$

For unknown variance, t-statistics with $\nu = n_1 + n_2 - 2$ degrees of freedom are used, and power is calculated using Monte Carlo simulation following Sozu et al. (2011).

Value

A data frame with the following columns:

`delta1`, `delta2`	Mean differences
`sd1`, `sd2`	Standard deviations
`rho`	Correlation
`r`	Allocation ratio
`alpha`	One-sided significance level
`beta`	Type II error rate
`known_var`	Variance assumption
`nMC`	Number of Monte Carlo simulations (NA if known_var = TRUE)
`n1`	Required sample size for group 1
`n2`	Required sample size for group 2
`N`	Total sample size (n1 + n2)

References

Sozu, T., Sugimoto, T., & Hamasaki, T. (2011). Sample size determination in superiority clinical trials with multiple co-primary correlated endpoints. *Journal of Biopharmaceutical Statistics*, 21(4), 650-668.

Homma, G., & Yoshida, T. (2025). Exact power and sample size in clinical trials with two co-primary binary endpoints. *Statistical Methods in Medical Research*, 34(11), 2183-2201.

Examples

```
# Sample size calculation with known variance
ss2Continuous(
  delta1 = 0.2,
  delta2 = 0.2,
  sd1 = 1,
  sd2 = 1,
  rho = 0.5,
  r = 1,
  alpha = 0.025,
  beta = 0.1,
  known_var = TRUE
)

# Sample size calculation with unequal allocation
ss2Continuous(
  delta1 = 0.3,
  delta2 = 0.25,
  sd1 = 1,
  sd2 = 1,
  rho = 0.3,
  r = 2,
  alpha = 0.025,
```

```
  beta = 0.2,
  known_var = TRUE
)


# Sample size calculation with unknown variance (uses sequential search)
ss2Continuous(
  delta1 = 0.5,
  delta2 = 0.4,
  sd1 = 1,
  sd2 = 1,
  rho = 0.4,
  r = 1,
  alpha = 0.025,
  beta = 0.1,
  known_var = FALSE,
  nMC = 10000
)
```

`ss2MixedContinuousBinary` *Sample Size Calculation for Two Co-Primary Endpoints: One Continuous and One Binary*

Description

Determines the sample size for a two-arm superiority trial with two co-primary endpoints where one is continuous and one is binary, to achieve a specified power at a given significance level.

Usage

```
ss2MixedContinuousBinary(
  delta,
  sd,
  p1,
  p2,
  rho,
  r,
  alpha,
  beta,
  Test,
  nMC = 10000
)
```

Arguments

delta	Mean difference for the continuous endpoint (group 1 - group 2)
sd	Common standard deviation for the continuous endpoint
p1	Probability of response in group 1 for the binary endpoint (0 < p1 < 1)
p2	Probability of response in group 2 for the binary endpoint (0 < p2 < 1)
rho	Biserial correlation between the latent continuous variable underlying the binary endpoint and the observed continuous endpoint
r	Allocation ratio n1/n2 where n1 is sample size for group 1
alpha	One-sided significance level (typically 0.025 or 0.05)
beta	Type II error rate (typically 0.1 or 0.2). Power = 1 - beta
Test	Statistical testing method for the binary endpoint. One of: • "AN": Asymptotic normal method without continuity correction • "ANc": Asymptotic normal method with continuity correction • "AS": Arcsine method without continuity correction • "ASc": Arcsine method with continuity correction • "Fisher": Fisher's exact test (uses sequential search)
nMC	Number of Monte Carlo replications when Test = "Fisher" (default: 10000)

Details

This function implements the sample size calculation for mixed continuous-binary co-primary endpoints following the methodology in Sozu et al. (2012).

The sequential search algorithm (Homma and Yoshida 2025, Algorithm 1) is used for all testing methods:

Step 1: Initialize with sample sizes from single endpoint formulas.

Step 2: Use sequential search:

- Calculate power at initial sample size
- If power >= target: decrease n2 until power < target, then add 1 back
- If power < target: increase n2 until power >= target

Step 3: Return final sample sizes.

Biserial Correlation: The biserial correlation rho represents the correlation between the latent continuous variable underlying the binary endpoint and the observed continuous endpoint. This is not the same as the point-biserial correlation observed in the data.

The Monte Carlo step of `Test = "Fisher"` draws random numbers, so results vary between calls unless a seed is set with `set.seed` beforehand. The sequential search for the sample size compares a simulated power against the target, so the returned sample size can differ by a subject or two between runs; increasing `nMC` reduces that variation.

Value

A data frame with the following columns:

delta	Mean difference for continuous endpoint
sd	Standard deviation for continuous endpoint
p1	Response probability in group 1 for binary endpoint
p2	Response probability in group 2 for binary endpoint
rho	Biserial correlation
r	Allocation ratio
alpha	One-sided significance level
beta	Type II error rate
Test	Testing method used for binary endpoint
nMC	Number of Monte Carlo replications (NA if Test != "Fisher")
n1	Required sample size for group 1
n2	Required sample size for group 2
N	Total sample size (n1 + n2)

References

Sozu, T., Sugimoto, T., & Hamasaki, T. (2012). Sample size determination in clinical trials with multiple co-primary endpoints including mixed continuous and binary variables. *Biometrical Journal*, 54(5), 716-729.

Homma, G., & Yoshida, T. (2025). Exact power and sample size in clinical trials with two co-primary binary endpoints. *Statistical Methods in Medical Research*, 34(11), 2183-2201.

Examples

```
# Sample size calculation using asymptotic normal method
ss2MixedContinuousBinary(
  delta = 0.5,
  sd = 1,
  p1 = 0.6,
  p2 = 0.4,
  rho = 0.5,
  r = 1,
  alpha = 0.025,
  beta = 0.1,
  Test = 'AN'
)

# With continuity correction
ss2MixedContinuousBinary(
  delta = 0.5,
  sd = 1,
  p1 = 0.6,
  p2 = 0.4,
```

```
  rho = 0.5,
  r = 1,
  alpha = 0.025,
  beta = 0.1,
  Test = 'ANc'
)


# Fisher's exact test (computationally intensive)
ss2MixedContinuousBinary(
  delta = 0.5,
  sd = 1,
  p1 = 0.6,
  p2 = 0.4,
  rho = 0.5,
  r = 1,
  alpha = 0.025,
  beta = 0.1,
  Test = 'Fisher',
  nMC = 5000
)
```

`ss2MixedCountContinuous` *Sample Size Calculation for Two Co-Primary Endpoints: One Count and One Continuous*

Description

Determines the sample size for a two-arm superiority trial with two co-primary endpoints where one is a count (negative binomial) and one is continuous (normal), to achieve a specified power at a given significance level.

Usage

```
ss2MixedCountContinuous(
  r1,
  r2,
  nu,
  t,
  mu1,
  mu2,
  sd,
  r,
  rho1,
  rho2,
  alpha,
```

```
  beta
)
```

Arguments

r1	Mean count rate in group 1 for the count endpoint
r2	Mean count rate in group 2 for the count endpoint
nu	Dispersion parameter for the negative binomial distribution (nu > 0). Smaller values indicate greater overdispersion
t	Follow-up time period
mu1	Mean for group 1 for the continuous endpoint
mu2	Mean for group 2 for the continuous endpoint
sd	Common standard deviation for the continuous endpoint
r	Allocation ratio n1/n2 where n1 is sample size for group 1
rho1	Correlation between count and continuous endpoints in group 1
rho2	Correlation between count and continuous endpoints in group 2
alpha	One-sided significance level (typically 0.025 or 0.05)
beta	Type II error rate (typically 0.1 or 0.2). Power = 1 - beta

Details

This function implements the sample size calculation for mixed count-continuous co-primary endpoints following the methodology in Homma and Yoshida (2024).

The sequential search algorithm (Homma and Yoshida 2025, Algorithm 1) is used:

Step 1: Initialize with sample sizes from single endpoint formulas.

Step 2: Use sequential search:

- Calculate power at initial sample size
- If power >= target: decrease n2 until power < target, then add 1 back
- If power < target: increase n2 until power >= target

Step 3: Return final sample sizes.

Negative Binomial Distribution: The count endpoint follows a negative binomial distribution NB(lambda, nu) where:

- lambda_j = r_j * t is the mean count in group j, where r_j is the event rate per unit time and t the follow-up period. Note that r_j is distinct from the allocation ratio r = n1/n2
- nu is the dispersion parameter
- Variance = lambda + lambda^2 / nu

Correlation: The correlations rho1 and rho2 must satisfy feasibility constraints that depend on the parameters. Use `corrbound2MixedCountContinuous` to check valid correlation bounds.

Value

A data frame with the following columns:

r1, r2	Count rates
nu	Dispersion parameter
t	Follow-up time
mu1, mu2	Means for continuous endpoint
sd	Standard deviation for continuous endpoint
r	Allocation ratio
rho1, rho2	Correlations
alpha	One-sided significance level
beta	Type II error rate
n1	Required sample size for group 1
n2	Required sample size for group 2
N	Total sample size (n1 + n2)

References

Homma, G., & Yoshida, T. (2024). Sample size calculation in clinical trials with two co-primary endpoints including overdispersed count and continuous outcomes. *Pharmaceutical Statistics*, 23(1), 46-59.

Homma, G., & Yoshida, T. (2025). Exact power and sample size in clinical trials with two co-primary binary endpoints. *Statistical Methods in Medical Research*, 34(11), 2183-2201.

Examples

```
# Sample size calculation for count and continuous endpoints
ss2MixedCountContinuous(
  r1 = 1.0,
  r2 = 1.25,
  nu = 0.8,
  t = 1,
  mu1 = -50,
  mu2 = 0,
  sd = 250,
  r = 1,
  rho1 = 0.4,
  rho2 = 0.4,
  alpha = 0.025,
  beta = 0.2
)


# With different dispersion parameter (more overdispersion). The sequential
# search reaches several hundred subjects per group, so this is kept out of
# the routinely executed examples.
ss2MixedCountContinuous(
```

```
  r1 = 1.0,
  r2 = 1.25,
  nu = 0.5,
  t = 1,
  mu1 = -50,
  mu2 = 0,
  sd = 250,
  r = 1,
  rho1 = 0.4,
  rho2 = 0.4,
  alpha = 0.025,
  beta = 0.2
)
```

`twoCoprimary2BinaryApprox` *Unified Interface for Two Co-Primary Binary Endpoints (Approximate Methods)*

Description

This function provides a unified interface for both power calculation and sample size determination for two co-primary binary endpoints using asymptotic normal approximation methods.

Usage

```
twoCoprimary2BinaryApprox(
  n1 = NULL,
  n2 = NULL,
  p11,
  p12,
  p21,
  p22,
  rho1,
  rho2,
  power = NULL,
  r = NULL,
  alpha = 0.025,
  Test = "AN"
)
```

Arguments

`n1`	Sample size for group 1 (treatment group). If NULL, will be calculated.
`n2`	Sample size for group 2 (control group). If NULL, will be calculated.
`p11`	True response probability for endpoint 1 in group 1

p12	True response probability for endpoint 2 in group 1
p21	True response probability for endpoint 1 in group 2
p22	True response probability for endpoint 2 in group 2
rho1	Correlation between endpoints 1 and 2 in group 1
rho2	Correlation between endpoints 1 and 2 in group 2
power	Target power (1 - beta). If NULL, will be calculated.
r	Allocation ratio (n1/n2). Required when calculating sample size.
alpha	One-sided significance level (typically 0.025 or 0.05)
Test	Test method: "AN" (asymptotic normal), "ANc" (with continuity correction), "AS" (arcsine), or "ASc" (arcsine with continuity correction)

Details

This function serves as a unified interface similar to `power.prop.test()`. The function determines the operation mode based on which parameters are NULL.

Exactly one of {(n1, n2), (power, r)} must be NULL.

Value

An object of class "twoCoprimary" containing either:

- Power calculation results (when n1 and n2 are specified)
- Sample size calculation results (when power and r are specified)

Examples

```
# Calculate power given sample sizes
twoCoprimary2BinaryApprox(
  n1 = 200, n2 = 100,
  p11 = 0.5, p12 = 0.4,
  p21 = 0.3, p22 = 0.2,
  rho1 = 0.7, rho2 = 0.7,
  alpha = 0.025, Test = "AN"
)

# Calculate sample size given target power
twoCoprimary2BinaryApprox(
  p11 = 0.5, p12 = 0.4,
  p21 = 0.3, p22 = 0.2,
  rho1 = 0.7, rho2 = 0.7,
  power = 0.8, r = 1,
  alpha = 0.025, Test = "AN"
)
```

`twoCoprimary2BinaryExact` *Unified Interface for Two Co-Primary Binary Endpoints (Exact Methods)*

Description

This function provides a unified interface for both power calculation and sample size determination for two co-primary binary endpoints using exact inference methods.

Usage

```
twoCoprimary2BinaryExact(
  n1 = NULL,
  n2 = NULL,
  p11,
  p12,
  p21,
  p22,
  rho1,
  rho2,
  power = NULL,
  r = NULL,
  alpha = 0.025,
  Test = "Fisher",
  n_grid = 100
)
```

Arguments

`n1`	Sample size for group 1 (treatment group). If NULL, will be calculated.
`n2`	Sample size for group 2 (control group). If NULL, will be calculated.
`p11`	True response probability for endpoint 1 in group 1
`p12`	True response probability for endpoint 2 in group 1
`p21`	True response probability for endpoint 1 in group 2
`p22`	True response probability for endpoint 2 in group 2
`rho1`	Correlation between endpoints 1 and 2 in group 1
`rho2`	Correlation between endpoints 1 and 2 in group 2
`power`	Target power (1 - beta). If NULL, will be calculated.
`r`	Allocation ratio (n1/n2). Required when calculating sample size.
`alpha`	One-sided significance level (typically 0.025 or 0.05)
`Test`	Test method: "Chisq" (one-sided Pearson chi-squared test), "Fisher" (Fisher's exact test), "Fisher-midP" (Fisher's mid-p test), "Z-pool" (Z-pooled exact unconditional test), or "Boschloo" (Boschloo's exact unconditional test)

`n_grid` Number of grid points used to maximize the null tail probability over the nuisance parameter in the two exact unconditional tests, that is `"Z-pool"` and `"Boschloo"` (default is 100). The other three tests read their p-values off a distribution and ignore this argument. A finer grid locates the maximum more accurately at a proportionally higher computational cost, and the default reproduces the results of earlier versions of the package.

Details

This function serves as a unified interface similar to `power.prop.test()`. The function determines the operation mode based on which parameters are NULL.

Exactly one of {(n1, n2), (power, r)} must be NULL.

Note: Exact methods are computationally intensive and may take considerable time, especially for large sample sizes.

Value

An object of class "twoCoprimary" containing either:

- Power calculation results (when n1 and n2 are specified)
- Sample size calculation results (when power and r are specified)

Examples

```
# Calculate power given sample sizes
twoCoprimary2BinaryExact(
  n1 = 50, n2 = 50,
  p11 = 0.5, p12 = 0.4,
  p21 = 0.3, p22 = 0.2,
  rho1 = 0.5, rho2 = 0.5,
  alpha = 0.025, Test = "Fisher"
)

# Calculate sample size given target power
twoCoprimary2BinaryExact(
  p11 = 0.5, p12 = 0.4,
  p21 = 0.3, p22 = 0.2,
  rho1 = 0.5, rho2 = 0.5,
  power = 0.8, r = 1,
  alpha = 0.025, Test = "Chisq"
)
```

`twoCoprimary2Continuous` *Unified Interface for Two Co-Primary Continuous Endpoints*

Description

This function provides a unified interface for both power calculation and sample size determination for two co-primary continuous endpoints. Depending on which parameters are provided (sample sizes or power), the function automatically determines whether to calculate power or sample size.

Usage

```
twoCoprimary2Continuous(
  n1 = NULL,
  n2 = NULL,
  delta1,
  delta2,
  sd1,
  sd2,
  rho,
  power = NULL,
  r = NULL,
  alpha = 0.025,
  known_var = TRUE,
  nMC = 10000
)
```

Arguments

`n1`	Sample size for group 1 (treatment group). If NULL, will be calculated.
`n2`	Sample size for group 2 (control group). If NULL, will be calculated.
`delta1`	Mean difference for the first endpoint
`delta2`	Mean difference for the second endpoint
`sd1`	Common standard deviation for the first endpoint
`sd2`	Common standard deviation for the second endpoint
`rho`	Common correlation between the two outcomes
`power`	Target power (1 - beta). If NULL, will be calculated.
`r`	Allocation ratio (n1/n2). Required when calculating sample size.
`alpha`	One-sided significance level (typically 0.025 or 0.05)
`known_var`	Logical indicating whether variance is known (TRUE) or unknown (FALSE). Default is TRUE.
`nMC`	Number of Monte Carlo simulations when known_var = FALSE. Default is 10000.

Details

This function serves as a unified interface similar to `power.prop.test()`. The function determines the operation mode based on which parameters are NULL:

- If n1 and n2 are provided and power is NULL: calculates power
- If power and r are provided and n1/n2 are NULL: calculates sample size

Exactly one of {(n1, n2), (power, r)} must be NULL.

Value

An object of class "twoCoprimary" containing either:

- Power calculation results (when n1 and n2 are specified)
- Sample size calculation results (when power and r are specified)

Examples

```
# Calculate power given sample sizes
twoCoprimary2Continuous(
  n1 = 100, n2 = 100,
  delta1 = 0.5, delta2 = 0.5,
  sd1 = 1, sd2 = 1,
  rho = 0.3, alpha = 0.025,
  known_var = TRUE
)

# Calculate sample size given target power
twoCoprimary2Continuous(
  delta1 = 0.5, delta2 = 0.5,
  sd1 = 1, sd2 = 1,
  rho = 0.3, power = 0.8,
  r = 1, alpha = 0.025,
  known_var = TRUE
)
```

`twoCoprimary2MixedContinuousBinary` *Unified Interface for Mixed Continuous and Binary Co-Primary Endpoints*

Description

This function provides a unified interface for both power calculation and sample size determination for trials with one continuous and one binary co-primary endpoint.

Usage

```
twoCoprimary2MixedContinuousBinary(
  n1 = NULL,
  n2 = NULL,
  delta,
  sd,
  p1,
  p2,
  rho,
  power = NULL,
  r = NULL,
  alpha = 0.025,
  Test = "AN",
  nMC = 10000
)
```

Arguments

n1	Sample size for group 1 (treatment group). If NULL, will be calculated.
n2	Sample size for group 2 (control group). If NULL, will be calculated.
delta	Mean difference for the continuous endpoint
sd	Common standard deviation for the continuous endpoint
p1	True response probability for the binary endpoint in group 1
p2	True response probability for the binary endpoint in group 2
rho	Biserial correlation between the continuous endpoint and the latent continuous variable underlying the binary endpoint
power	Target power (1 - beta). If NULL, will be calculated.
r	Allocation ratio (n1/n2). Required when calculating sample size.
alpha	One-sided significance level (typically 0.025 or 0.05)
Test	Test method for the binary endpoint: "AN" (asymptotic normal), "ANc" (with continuity correction), "AS" (arcsine), "ASc" (arcsine with continuity correction), or "Fisher" (Fisher's exact test)
nMC	Number of Monte Carlo simulations when Test = "Fisher". Default is 10000.

Details

This function serves as a unified interface similar to `power.prop.test()`. The function determines the operation mode based on which parameters are NULL.

Exactly one of {(n1, n2), (power, r)} must be NULL.

The biserial correlation rho represents the correlation between the observed continuous endpoint and the latent continuous variable underlying the binary endpoint.

Value

An object of class "twoCoprimary" containing either:

- Power calculation results (when n1 and n2 are specified)
- Sample size calculation results (when power and r are specified)

Examples

```
# Calculate power given sample sizes
twoCoprimary2MixedContinuousBinary(
  n1 = 100, n2 = 100,
  delta = 0.5, sd = 1,
  p1 = 0.6, p2 = 0.4,
  rho = 0.5,
  alpha = 0.025, Test = "AN"
)

# Calculate sample size given target power
twoCoprimary2MixedContinuousBinary(
  delta = 0.5, sd = 1,
  p1 = 0.6, p2 = 0.4,
  rho = 0.5,
  power = 0.8, r = 1,
  alpha = 0.025, Test = "AN"
)
```

---

twoCoprimary2MixedCountContinuous

Unified Interface for Mixed Count and Continuous Co-Primary Endpoints

---

Description

This function provides a unified interface for both power calculation and sample size determination for trials with one count endpoint (modeled by negative binomial distribution) and one continuous endpoint.

Usage

```
twoCoprimary2MixedCountContinuous(
  n1 = NULL,
  n2 = NULL,
  r1,
  r2,
  nu,
  t,
  mu1,
```

```
  mu2,
  sd,
  rho1,
  rho2,
  power = NULL,
  r = NULL,
  alpha = 0.025
)
```

Arguments

n1	Sample size for group 1 (treatment group). If NULL, will be calculated.
n2	Sample size for group 2 (control group). If NULL, will be calculated.
r1	Event rate per unit time for the count endpoint in group 1
r2	Event rate per unit time for the count endpoint in group 2
nu	Dispersion parameter for the negative binomial distribution (nu > 0). When nu approaches infinity, the distribution converges to Poisson.
t	Follow-up period (time unit)
mu1	Mean for the continuous endpoint in group 1
mu2	Mean for the continuous endpoint in group 2
sd	Common standard deviation for the continuous endpoint
rho1	Correlation between count and continuous endpoints in group 1
rho2	Correlation between count and continuous endpoints in group 2
power	Target power (1 - beta). If NULL, will be calculated.
r	Allocation ratio (n1/n2). Required when calculating sample size.
alpha	One-sided significance level (typically 0.025 or 0.05)

Details

This function serves as a unified interface similar to `power.prop.test()`. The function determines the operation mode based on which parameters are NULL.

Exactly one of {(n1, n2), (power, r)} must be NULL.

The count endpoint is modeled using a negative binomial distribution to account for overdispersion. The dispersion parameter nu controls the variance: Var = lambda + lambda^2/nu.

Value

An object of class "twoCoprimary" containing either:

- Power calculation results (when n1 and n2 are specified)
- Sample size calculation results (when power and r are specified)

Examples

```
# Calculate power given sample sizes
twoCoprimary2MixedCountContinuous(
  n1 = 300, n2 = 300,
  r1 = 1.0, r2 = 1.25,
  nu = 0.8, t = 1,
  mu1 = -50, mu2 = 0, sd = 250,
  rho1 = 0.5, rho2 = 0.5,
  alpha = 0.025
)

# Calculate sample size given target power
twoCoprimary2MixedCountContinuous(
  r1 = 1.0, r2 = 1.25,
  nu = 0.8, t = 1,
  mu1 = -50, mu2 = 0, sd = 250,
  rho1 = 0.5, rho2 = 0.5,
  power = 0.8, r = 1,
  alpha = 0.025
)
```

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