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CONFIDENCE INTERVALS FOR THE RATIO OF TWO MEANS USING THE DISTRIBUTION OF THE QUOTIENT OF TWO NORMALS

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ABSTRACT

In various scientific fields such as medicine, biology and bioassay, several ratio quantities assumed to be Normal, are of potential interest. The estimator of the ratio of two means is a ratio of two random variables normally or asymptotically normally distributed. The present paper shows the importance of considering the real distribution of the estimator of the ratio of two means, because generally the approximation to Normal is not satisfied. The estimated asymptotic cumulative and density function of the estimator of the ratio is presented, with several considerations on the skewness. Finally, a new method for building confidence intervals for the ratio of two means was proposed. In contrast to other parametric methods, this new method is worthy to be preferred because it considers the skewness in the distribution of the ratio estimator, and the confidence intervals are always bounded.

Key words: estimator of the ratio of two means, distribution of the ratio of two correlated normals, skewness, confidence intervals for the ratio, Fieller's theorem.

1. Introduction

In various scientific fields such as medicine, biology, biometry and bioassay, several ratio quantities assumed to be normal are of potential interest. Pearson (1910) reported the first application of the ratio of normal random variables (rv) in medicine with the use of the *opsonic index*. It is a measure of the number of bacteria destroyed by blood cells, expressed as the ratio of opsonin, i.e., a substance that marks foreign bodies in the infected patient's blood to the amount

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found in a healthy person's blood. In biology, an example of a ratio of Normal rvs is the so called *digestibility*, i.e., the ratio of the weight of a component of a plant to that of the whole plant. In bioassay and bioequivalence problems, the relative potency of a new drug to that of a standard drug is often expressed in terms of a ratio. The true potencies of the two drugs are the mean values (μ_1, μ_2) and the relative potency is the ratio of the potency of the new drug with respect to the potency of a standard one, i.e., μ_1 / μ_2.

The estimator of the ratio of two means is a ratio of two rvs normally or asymptotically normally distributed. Descriptive and inferential aspects of the ratio of two Normal rvs are complex. The first author who specifically considered the problem was Geary (1930), in his paper called "*The frequency distribution of the ratio of two Normal variates*". Subsequently, the distribution of the ratio of two normal random variables was studied by Fieller (1932), Marsaglia (1965, 2006), Frosini (1970) and Aroian and Oksoy (1986) and only few others.

In this paper, we present recent results on descriptive aspects on the distribution of the estimator of the ratio of two means. Finally, in the last paragraph we propose a new method to build confidence intervals based on the distribution of the estimator of the ratio of two means. Differently from other parametric methods, this new method is preferable because it considers the skewness in the distribution of the ratio estimator and the confidence intervals are always bounded.

2. The distribution of the ratio of two normals random variables

Let us consider a bivariate correlated normal (bcn) rv (X_1, X_2) having the following parameters:

$$E(X_1) = \mu_1;\ E(X_2) = \mu_2;\ Var(X_1) = \sigma^2{}_1;\ Var(X_2) = \sigma^2{}_2;\ Corr(X_1, X_2) = \rho .$$

Let us define the rv $W = \dfrac{X_1}{X_2}$, i.e., the ratio of two normal rvs, jointly distributes as a bcn.

The distribution of the ratio of two independent standardized normal rvs is the well-known case of a standard Cauchy rv with median value equal to zero and scale parameter equal to one (Mood, 1974 and Kotz, 1994). The Cauchy distribution has no mean, nor variance or higher moments exist.

The cumulative density function (cdf) of W, indicated as $F_W(w)$, with parameters ($\mu_1, \mu_2; \sigma_1,\ \sigma_2; \rho$), can be expressed involving the bivariate normal integral tabulated by the National Bureau of Standards (1959), as an extension of

Hinkley's results (1969). Aroian (1986) parameterised the cdf in a more convenient way and showed that the distribution of *W* depends on two parameters *a* and *b* and the variable t_W, as follows:

$$F_W(w) = L\left(\frac{a - b\,t_w}{\sqrt{1+t_w^2}}, -b, \frac{t_w}{\sqrt{1+t_w^2}}\right) + L\left(\frac{b\,t_w - a}{\sqrt{1+t_w^2}}, b, \frac{t_w}{\sqrt{1+t_w^2}}\right) \qquad w \in R$$

with

$$a = \sqrt{\frac{1}{1-\rho^2}}\left(\frac{\mu_1}{\sigma_1} - \rho\frac{\mu_2}{\sigma_2}\right) \tag{1}$$

$$b = \left(\frac{\mu_2}{\sigma_2}\right) \tag{2}$$

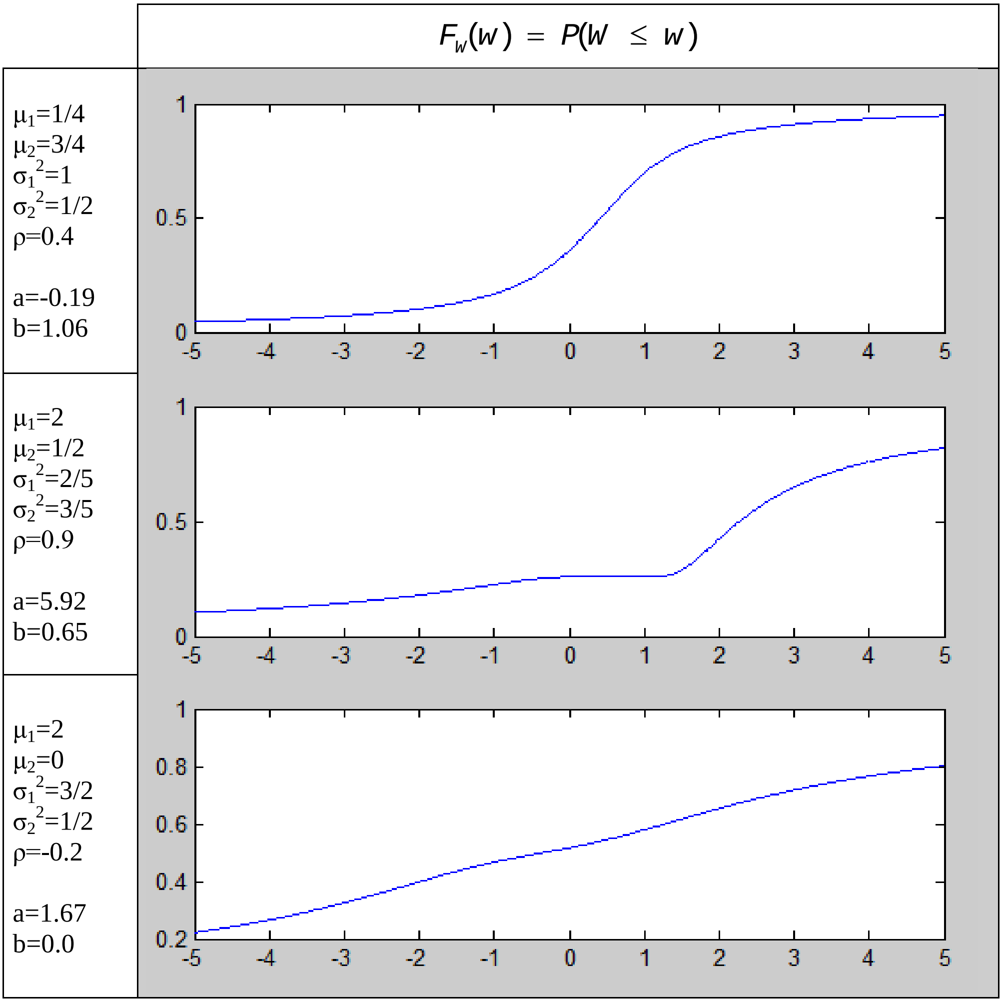
$$t_w = \sqrt{\frac{1}{1-\rho^2}}\left(\frac{\sigma_2}{\sigma_1}w - \rho\right) \tag{3}$$

and, *L(h,k,ρ)* is the bivariate normal integral according to the indication of Kotz et al. (2000), where

$$L(h,k,\rho) = \frac{1}{2\pi\sqrt{1-\rho^2}}\int_h^\infty\int_k^\infty \exp\left\{-\frac{1}{2\left(1-\rho^2\right)}(x_1^2 - 2\rho x_1 x_2 + x_2^2)\right\}dx_1 dx_2$$

In Figure 1 the cdf of the ratio of two normal rvs , $F_W(w)$, are reported for several selected values of the five parameters ($\mu_1, \mu_2; \sigma_1, \sigma_2; \rho$), and the corresponding *a* and *b*.

Figure 1. Cdf of W for selected values of the parameters



The probability density function (pdf) of W, indicated as $f_W(w)$, can be expressed as a function of the five parameters $(\mu_1, \mu_2; \sigma_1, \sigma_2; \rho)$ or, more conveniently, using the previously reported parameterization proposed by Aroian (1986), with a, b and t_w, as follows:

$$f_W(w) = \frac{\sigma_2}{\sigma_1}\sqrt{\frac{1}{1-\rho^2}}\, g(t) \qquad w \in R$$

where

$$g(t)=\frac{1}{\pi}e^{-\frac{1}{2}(a^2+b^2)}\frac{1}{\left(1+t^2\right)}\left\{1+c\int_0^q \varphi(u)du\right\}$$

$$q=\frac{b+at_w}{\sqrt{1+t_w^2}},\qquad c=q\left\{\varphi(q)\right\}^{-1},\qquad \varphi(u)=(2\pi)^{-\frac{1}{2}}e^{-\frac{u^2}{2}}$$

As reported in her PhD thesis (2007), Galeone showed that the pdf of W can be expressed as a finite non-standard mixture density (Everitt, 1996). In fact, the pdf is decomposable into two component densities (c=2) as follows:

$$f_W(w) = p\, f_1(w) + (1 - p) f_2(w)$$

with $0 \le p = e^{-\frac{1}{2}(a^2+b^2)} \le 1$

where *a* and *b* were defined in (1) and (2).

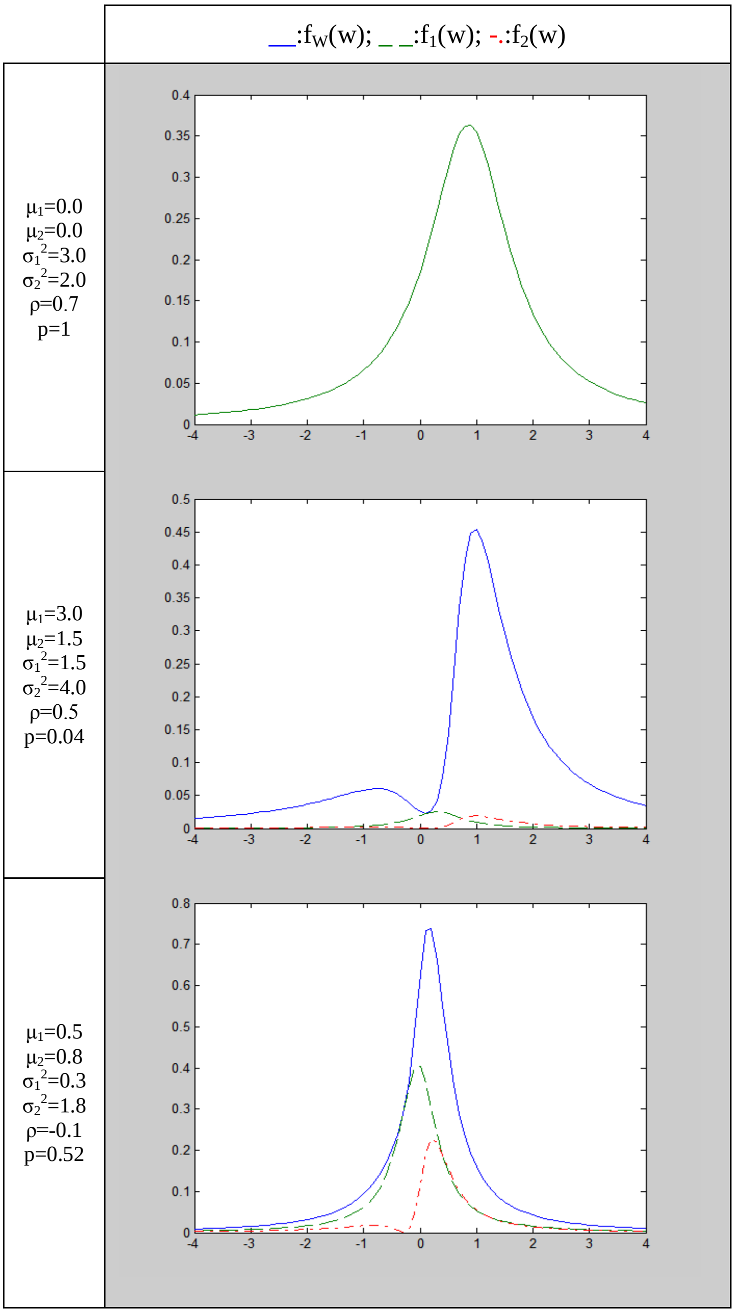
The first pdf, f_1, is a not central Cauchy rv. The second pdf is a complicate function that depends on *w* only through *q* and *t*, and is not referable to a well-known rv,

$$f_2(w) = \frac{\sigma_2 q\, e^{\frac{1}{2}q^2}\int_0^q e^{-\frac{1}{2}s^2}ds}{\pi\sigma_1\sqrt{1-\rho^2}\,(1+t^2)(e^{\frac{1}{2}(\mu_1^2+\mu_2^2)}-1)}$$

The pdf f_W and the two components of the mixture model f_1 and f_2, for selected values of the parameters are shown in Figure 2. Generally, the rv W is not symmetrically distributed, except in the case that the median value is equal to the ratio of the mean values μ_1 and μ_2 (Aroian Oksoy, 1986). In some cases, the pdf is bimodal.

The cdf of W can be computed as a function of *w* using Fortran+IMSL library or the scientific software package MATLAB or other libraries, especially those containing routines regarding the cdf of a bcn or other functions which can give the cdf of the bcn. In Appendix, we report the codes of the functions implemented in MATLAB to compute the cdf and the pdf of the ratio of two normal rvs. We have used these functions for all the graphs reported in the article.

Figure 2. Pdf $f_W(w)$ of the ratio of two Normal rvs and of the two components $f_1(w)$ and $f_2(w)$ of the mixture model, for selected values of the parameters. The first case is the pdf of central Cauchy random variable, where $f_2(w)=0$



3. The distribution of the estimator of the ratio of two means

Let us suppose we have drawn a simple random sample of *n* elements and we have obtained the observations (x_{1i}, x_{2i}) *(i=1,…,n).*

If (X_1, X_2) is a bcn or if *n* is large, the rv $(\bar{X}_1, \bar{X}_2)$ tends to a bcn with the following parameters:

$$E(\bar{X}_1) = \mu_1;\ E(\bar{X}_2) = \mu_2;\ Var(\bar{X}_1) = \frac{\sigma_1^2}{n};\ Var(\bar{X}_2) = \frac{\sigma_2^2}{n};\ Corr(\bar{X}_1, \bar{X}_2) = \rho .$$

Keeping into account the results obtained by Aroian (1986) reported in the previous paragraph, we can obtain the cdf of the rv $W_n = \frac{\bar{X}_1}{\bar{X}_2}$, indicated by $F_{W_n}(w)$. Often $W_n = \frac{\bar{X}_1}{\bar{X}_2}$ is used as the estimator of $R = \frac{\mu_1}{\mu_2}$.

The pdf of W_n can be expressed as a function of the five parameters $\left(\mu_1, \mu_2, \frac{\sigma_1^2}{n}, \frac{\sigma_2^2}{n}, \rho\right)$ or, more conveniently, using the previously reported parameterization proposed by Aroian (1986) based on a_n and b_n as follows:

$$f_{W_n}(w) = \frac{\sigma_2}{\sigma_1}\sqrt{\frac{1}{1-\rho^2}}\ g(t_w)$$

where

$$g(t_w) = \frac{1}{\pi}\ e^{-\frac{1}{2}\left(a_n^2 + b_n^2\right)}\ \frac{1}{\left(1+t_w^2\right)}\left\{1 + c\int_0^q \varphi(u)du\right\},$$

$$q = \frac{b_n + a_n t_w}{\sqrt{1+t_w^2}}, \qquad c = q\{\varphi(q)\}^{-1},$$

and

$$a_n = \sqrt{\frac{n}{1-\rho^2}}\left(\frac{\mu_1}{\sigma_1} - \rho\frac{\mu_2}{\sigma_2}\right) \qquad b_n = \sqrt{n}\left(\frac{\mu_2}{\sigma_2}\right) \qquad t_w = \sqrt{\frac{1}{1-\rho^2}}\left(\frac{\sigma_2}{\sigma_1}w - \rho\right)$$

As shown in Figure 2, generally the rv *W* is not symmetrically distributed. Mood et al. (1963) defined a rv *X* symmetrically distributed about a constant *C* if the rv ($X - C$) has the same distribution of the rv $-(X - C)$. In order to study the distribution of the estimator of *R*, we want to verify if the rv $(W_n - Me)$ is distributed as the rv $-(W_n - Me)$, where *Me* is the median of the distribution. If this is true, we expect that $f_{W_n}(Me - w) = f_{W_n}(Me + w)$ (MacGillivray, 1985) .

This implies that

$$t_{Me-w} = \sqrt{\frac{1}{1-\rho^2}}\left(\frac{\sigma_2}{\sigma_1}(Me - w) - \rho\right)$$

is equal to

$$t_{Me+w} = \sqrt{\frac{1}{1-\rho^2}}\left(\frac{\sigma_2}{\sigma_1}(Me + w) - \rho\right)$$

Being $t_{Me-w} \neq t_{Me+w}$, except in some degenerate case, it is easy to check that $f_{W_n}(w - Me) \neq f_{W_n}(Me + w)$.

As a consequence (Frosini ,1971), it is evident that $F_{W_n}(Me - w) \neq 1 - F_{W_n}(Me + w)$.

The measures of the asymmetry of a distribution is usually based on the traditional indices based on the moments of the distribution such as the third standardized moment (MacGillivray, 1986). Unfortunately, this approach cannot be used to study the shape of the distribution of the estimator of the ratio because no moment of the rv W_n exists. For these reasons, we have studied the shape by means of the median and percentiles of the distribution that cannot be obtained analytically but numerical calculations have to be done for each particular case.

First of all, we consider the index proposed by Bowley in 1901 (Brentari, 1990, Groeneveld, 1998)

$$sk\ (0.25) = \frac{Q_3 + Q_1 - 2Me}{Q_3 - Q_1}$$

where *Me* is the median, Q_1 and Q_3 are respectively the first and the third quartile. The index *sk(0.25)* varies in the interval [-1,1] and so it is easily interpretable.

Then, we use a more analytic index based on the asymmetry of points suggested by David F.N. and Johnson in 1956 (Brentari,1990); for a continuous rv it is defined as

$$sk(p) = \frac{x(1-p) + x(p) - 2Me}{x(1-p) - x(p)} \qquad 0 \le p < \frac{1}{2}$$

where $x(p) = F^{-1}(p)$ is the p^{th} quantile.

The index *sk(p)* is the difference of the distance of the $(1\text{-}p)^{th}$ quantile from the median and the distance of the median from the p^{th} quantile divided by the distance from the $(1\text{-}p)^{th}$ quantile and the p^{th} quantile. The index $sk(p)$ is normalized due to $-1 \le sk(p) \le 1$.

The cdf of W_n, indicated as $F_{W_n}(w)$, may be estimated by substituting in it the maximum likelihood (ML) estimates of $(\mu_1, \mu_2; \sigma_1, \sigma_2; \rho)$. The ML estimates of the means μ_1 and μ_2 are indicated respectively by $\bar{x}_1$ and $\bar{x}_2$. The ML estimates of σ_1^2, σ_2^2 and ρ are respectively given by

$$s_1^2 = \sum_{i=1}^{n} (x_{1i} - \bar{x}_1)^2 / n \qquad s_2^2 = \sum_{i=1}^{n} (x_{2i} - \bar{x}_2)^2 / n$$

$$r = \sum_{i=1}^{n} (x_{1i} - \bar{x}_1)(x_{2i} - \bar{x}_2) / \sqrt{\sum_{i=1}^{n} (x_{1i} - \bar{x}_1)^2 \sum_{i=1}^{n} (x_{2i} - \bar{x}_2)^2}$$

We can estimate the cdf of W_n as follows:

$$\hat{F}_{W_n}(w) = L\left(\frac{a_n - b_n t_w}{\sqrt{1+t_w^2}}, -b_n, \frac{t_w}{\sqrt{1+t_w^2}}\right) + L\left(\frac{b_n t_w - a_n}{\sqrt{1+t_w^2}}, b_n, \frac{t_w}{\sqrt{1+t_w^2}}\right)$$

where

$$a_n = \sqrt{\frac{n}{1-r^2}}\left(\frac{\overline{x}_1}{s_1} - r\frac{\overline{x}_2}{s_2}\right) \qquad b_n = \sqrt{n}\left(\frac{\overline{x}_2}{s_2}\right) \qquad t_w = \sqrt{\frac{1}{1-r^2}}\left(\frac{s_2}{s_1}w - r\right)$$

As reported by Cochran (1977), when *n* is not too small, the variance of the estimator $W_n = \frac{\overline{X}_1}{\overline{X}_2}$ is approximately equal to:

$$Var(W_n) \cong \frac{R^2}{n}\left\{CV_1^2 + CV_2^2 - 2\rho CV_1 CV_2\right\}$$

with $$CV_1 = \frac{\sigma_1}{\mu_1}, CV_2 = \frac{\sigma_2}{\mu_2}$$

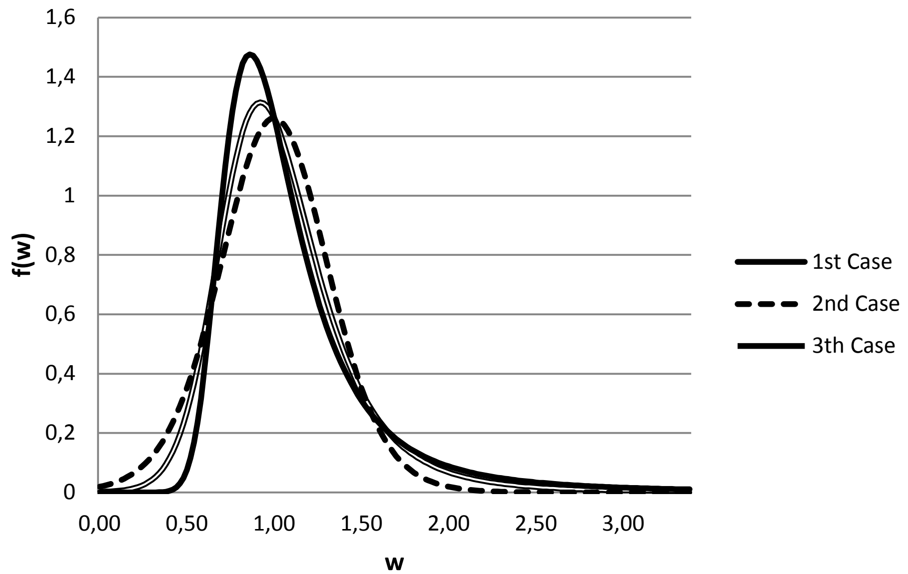
By means of this result, Cochran suggested to use the above approximate variance to build confidence intervals based on the Normal distribution. However, the Normal approximation is not always acceptable, as shown in several situations reported in paragraph 3.2.

3.1. Examples regarding the asymmetry of the distribution of the estimator

In order to understand the influences of the parameters of the rv W_n on the shape of the pdf, we report three situations fixing $\mu_1 = \mu_2 = 1$ and choosing σ_1, σ_2 and ρ in order to obtain the same asymptotic variance of W_n. For each situation, we report the pdf *f(w)* and the relative functions $sk(p)$ of the rv W_n.

Figure 3. Pdf (f_W) and asymmetry indexes (sk(p)) in three situation with asymptotic variance equal to $Var(W_n) = 0.01$ (sample size *n=30*)

The first case has $CV_1^2 = 1$, $CV_2^2 = 4$, $\rho = 0.5$
The second case has $CV_1^2 = 4$, $CV_2^2 = 1$, $\rho = 0.5$
The third case has $CV_1^2 = 2.5$, $CV_2^2 = 2.5$, $\rho = 0.4$



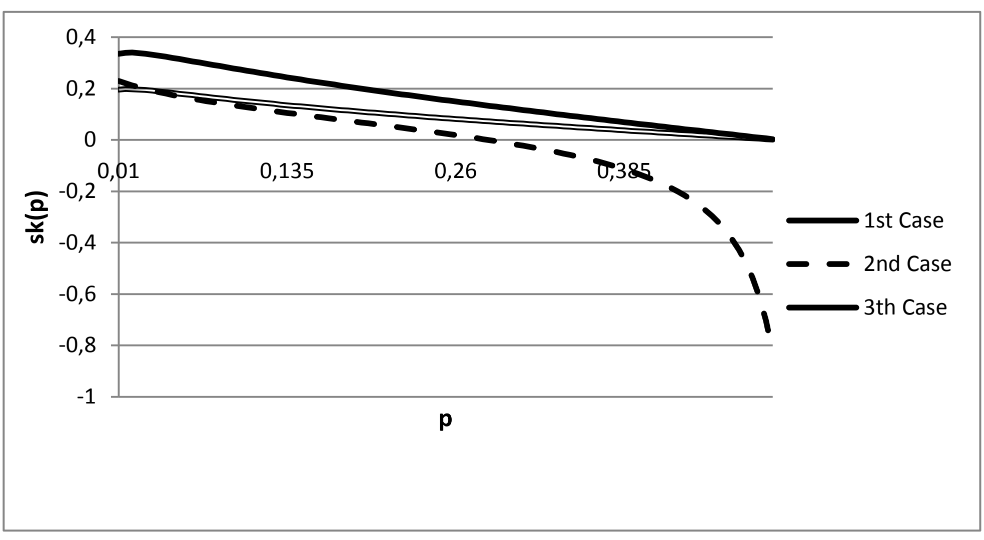


Figure 4. Pdf (f_W) and asymmetry indexes (sk(p)) in three situation with asymptotic variance equal to $Var(W_n) = 0.0047$ (sample size *n=30*)

The first case has $CV_1^2 = 0.1$, $CV_2^2 = 0.4$, $\rho = 0.9$
The second case has $CV_1^2 = 0.4$, $CV_2^2 = 0.1$, $\rho = 0.9$
The third case has $CV_1^2 = 0.25$, $CV_2^2 = 0.25$, $\rho = 0.72$

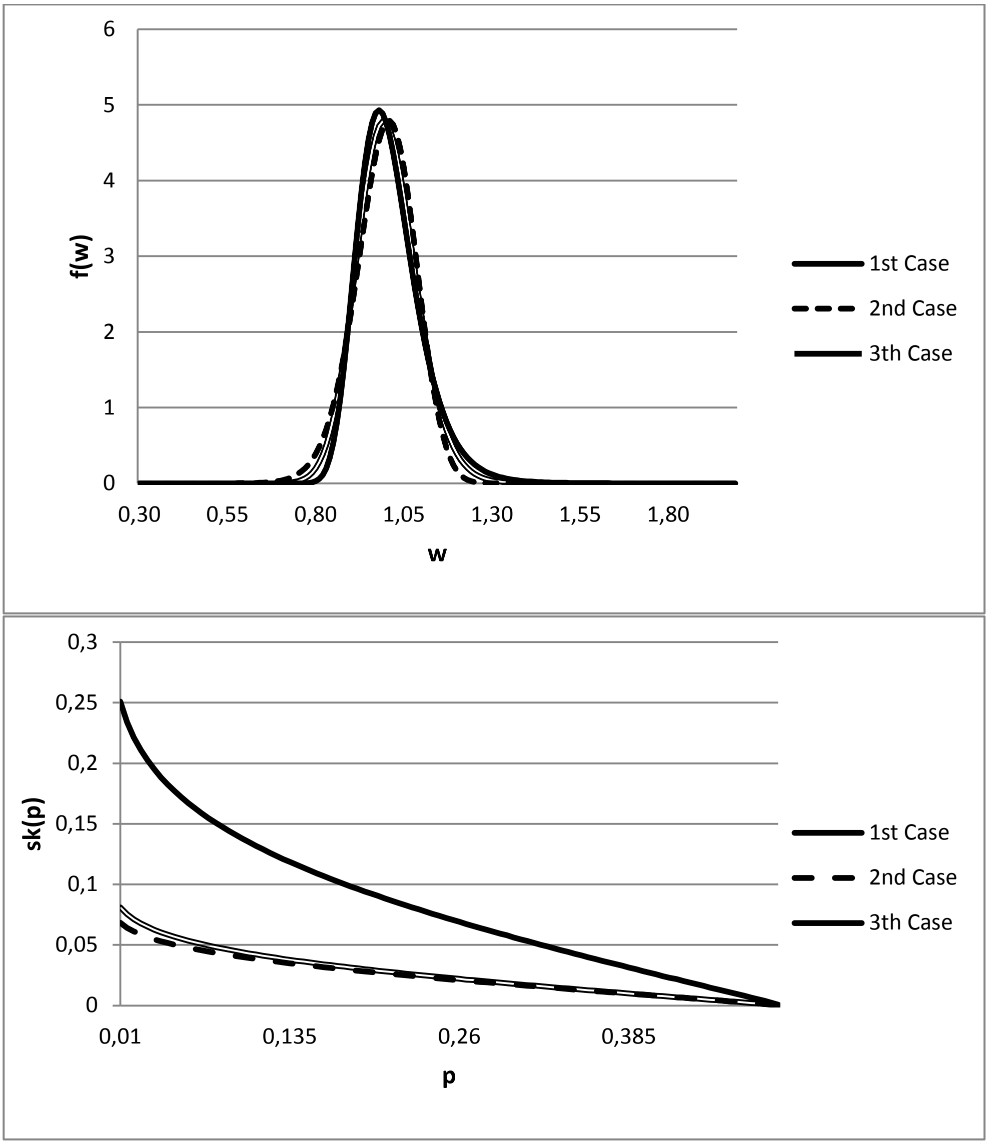
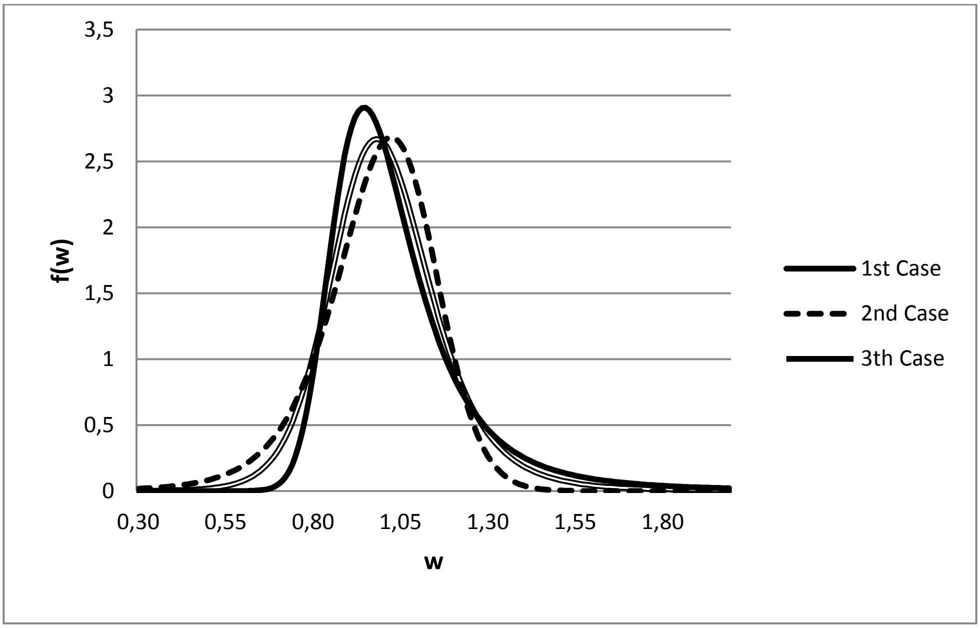
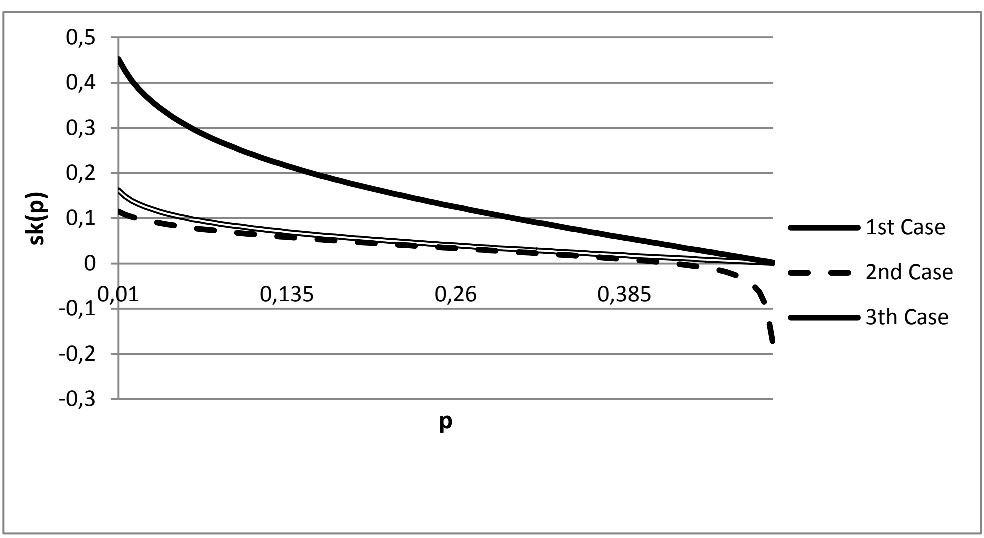


Figure 5. Pdf (f_W) and asymmetry indexes (sk(p)) in three situation with asymptotic variance equal to $Var(W_n) = 0.01515$ (sample size *n=30*)

The first case has $CV_1^2 = 1$, $CV_2^2 = 2$, $\rho = 0.9$
The second case has $CV_1^2 = 2$, $CV_2^2 = 1$, $\rho = 0.9$
The third case has $CV_1^2 = 1.5$, $CV_2^2 = 1.5$, $\rho = 0.8485$





In each figure considered above, the asymptotic variance $Var(W_n)$ was the same obtained with difference values of σ_1, σ_2 and ρ, and the shapes of the relative pdf were different.

3.2. Examples of comparison of the distribution of the estimator with the normal distribution

We fix the mean values equal to one, $\mu_1 = \mu_2 = 1$, and we compute the areas under the right and left tails of the exact distribution of W_n, in different sets of parameters, as follows:

$Pr(W_n < 0.8) = F_{W_n}(0.8)$ and $Pr(W_n > 1.2) = 1 - F_{W_n}(1.2)$

In Table 1, these areas under the tails were compared to them obtained considering a rv $Y \sim N(R, Var(W_n))$, as follows:

$Pr(Y < 0.8) = Pr(Y > 1.2) = F_Y(0.8)$

From the values of the differences between the left and the right tails of the true distribution of the rv W_n and of the normal distribution, it is evident that the distribution of the rv W_n is skewness and the normal approximation is not appropriate. For this reason, the confidence intervals based on the normal distribution, as suggested by Cochran (1977), are not always convenient.

Table 1. Area under the tails of the pdf of W_n and *Y* in several sets of parameters with same asymptotic variance $Var(W_n)$.

Differences between left tails (DLT) =$F_Y(0.8) - F_{W_n}(0.8)$
Differences between right tails (DRT) =$F_Y(0.8) - (1 - F_{W_n}(1.2))$

1) *n*=20 $Var(W_n) \cong 0.025$

σ^2_1	σ^2_2	ρ	$F_Y(0.8)$	$F_{W_n}(0.8)$	1- $F_{W_n}(1.2)$	*DLT*	DRT
0.1	0.4	0.0	0.1030	0.0678	0.1273	0.0352	-0.0243
0. 25	0.25	0.0	0.1030	0.0818	0.1203	0.0212	-0.0173
0.4	0.1	0.0	0.1030	0.0943	0.1106	0.0087	-0.0076

2) *n*=20 $Var(W_n) \cong 0.015$

σ^2_1	σ^2_2	ρ	$F_Y(0.8)$	$F_{W_n}(0.8)$	1- $F_{W_n}(1.2)$	*DLT*	DRT
0.1	0.4	0.5	0.0512	0.0218	0.0843	0.0294	-0.0331
0.25	0.25	0.4	0.0512	0.0369	0.0699	0.0143	-0.0187
0.4	0.1	0.5	0.0512	0.0524	0.0524	-0.0012	-0.0012

Table 1. Area under the tails of the pdf of W_n and Y in several sets of parameters with same asymptotic variance $Var(W_n)$ (cont.)

3) n=20 $Var(W_n) \cong 0.07$

σ^2_1	σ^2_2	ρ	$F_Y(0.8)$	$F_{W_n}(0.8)$	1- $F_{W_n}(1.2)$	*DLT*	DRT
0.1	0.4	0.9	0.0084	0.0003	0.0346	0.0081	-0.0262
0.25	0.25	0.72	0.0084	0.0052	0.0170	0.0032	-0.0086
0.4	0.1	0.9	0.0084	0.0165	0.0038	-0.0081	0.0046

4) n=30 $Var(W_n) \cong 0.0167$

σ^2_1	σ^2_2	ρ	$F_Y(0.8)$	$F_{W_n}(0.8)$	1- $F_{W_n}(1.2)$	*DLT*	DRT
0.1	0.4	0.0	0.1226	0.0942	0.1475	0.0284	-0.0249
0.25	0.25	0.0	0.1226	0.1054	0.1395	0.0172	0.0865
0.4	0.1	0.0	0.1226	0.1160	0.1298	0.0066	-0.0072

5) n=30 $Var(W_n) \cong 0.01$

σ^2_1	σ^2_2	ρ	$F_Y(0.8)$	$F_{W_n}(0.8)$	1- $F_{W_n}(1.2)$	*DLT*	DRT
0.1	0.4	0.5	0.0668	0.0397	0.0481	0.0271	0.0187
0.25	0.25	0.4	0.0668	0.0538	0.0826	-0.0531	-0.0158
0.4	0.1	0.5	0.0676	0.0668	0.0676	0.0008	0

6) n=30 $Var(W_n) \cong 0.0047$

σ^2_1	σ^2_2	ρ	$F_Y(0.8)$	$F_{W_n}(0.8)$	1- $F_{W_n}(1.2)$	*DLT*	DRT
0.1	0.4	0.9	0.0141	0.0022	0.0382	0.0119	-0.0241
0.25	0.25	0.72	0.0141	0.01	0.0221	-0.0041	-0.008
0.4	0.1	0.9	0.0141	0.0220	0.0085	-0.0079	0.0056

4. The confidence interval for *R* based on the exact distribution of the estimator

As discussed previously, none of the moments of W_n exists, and thus it is impossible to infer from the mean value $E(W_n)$ and variance $Var(W_n)$.

Cochran (1977), in order to built the confidence intervals for R, used a normal distribution having asymptotic expected value R and $Var(W_n)$. Several authors (Fieller, 1932; Hinkley, 1969; Frosini, 1970) showed that the ratio of two normal rvs is approximately normal when the coefficient of variation of the denominator is negligible. Consequently, the rv W_n is approximately normal also when n is large. However, this condition is not always satisfied, especially in the practical situations, as discussed in the previous paragraph. An alternative approach to obtain the confidence interval for the ratio of the means in a bivariate normal distribution was proposed by Fieller (1940; 1954), and it is always called as

"Fieller's theorem". The calculation of the confidence interval is relatively simple and this approach has been used as a touchstone by several authors (Finney 1964, Rao 1965, Kendall and Stuart 1961), because of its importance in examining the general techniques for constructing confidence intervals using resampling techniques, such as the jackknife or bootstrapping. However, the existence of a bounded (1-α)% confidence interval for *R* with the Fieller's theorem is not always guaranteed and in these cases the practical interpretation of the results is impossible. Gardiner at al. (2001) proved that the confidence interval is bounded if and only if the estimated $\bar{X}_2$ is significantly different from zero at level α.

In her PhD thesis (2007), Galeone proposed a new approach, called the exact distribution method, to built confidence interval for *R*, based on the inverse cdf of W_n. This approach always guarantees the existence of bounded confidence intervals, since the cdf is a monotonic non-decreasing function that can be inverted with computational methods. The (1-α) confidence interval of *R*, obtained by inversing cdf of W_n, is given by

$$P\left\{W_{\alpha/2} \leq R \leq W_{1-\alpha/2}\right\} = 1-\alpha$$

where $W_{\alpha/2}$ and $W_{1-\alpha/2}$ are the estimators (Galeone and Pollastri, 2008) of $(\alpha/2)^{th}$ and the $(1-\alpha/2)^{th}$ quantile of the rv W_n.

The implementation of procedures and functions to built confidence intervals with the exact distribution method and with the Fieller's theorem is available in Matlab, and the codes are reported in Appendix.

Simulation study

Monte Carlo experiment was used to assess the performances of the Fieller's theorem and the exact distribution method for computing 90% confidence intervals for *R*, by differing levels of correlation between numerator and denominator. We have started using a simulated population with known means (0.25, 1.20) and variances (9, 16) of $\bar{X}_1$ and $\bar{X}_2$, respectively, known correlations between rvs (0, |0.3|, |0.6|, |0.9|) and a known *R*. The sample size varied from 25 to 1600 with the rule of the doubling technique. Overall, there were 49 combinations of simulation parameters. For each combination of parameters, we have simulated 5000 independent samples for each treatment group from this population. The criterions used to evaluate the performances of the methods were the probability of coverage of the intervals (denoted as $(1-\hat{\alpha})$), the average width of the intervals (denoted as *Amp*) and the symmetric miscoverage of the intervals (denoted as *%ds*).

Simulation results

The performances of the two methods for the construction of 90% confidence intervals for *R* for $\rho = 0.3$ were reported in Table 2. For small values of *n* (*n*≤200), the confidence intervals constructed with the Fieller's theorem were not always bounded. For this reason the corresponding average widths were denoted as "-", i.e., there was at least one unbounded confidence interval that yielded the average widths not to be expressed as a real number. Consequently, the corresponding coverage probabilities were very low. For elevated values of *n*, the performances of the confidence intervals based on the Fieller's theorem and the exact distribution method were very close.

Table 2. Simulation study - Performances of the two methods for the construction of 90% confidence interval with ρ=0.3.

		Fieller's theorem	Exact distribution method
n			
	$(1-\hat{\alpha})$	0.3941	0.9267
25	%ds	0.5619	0.6178
	Amp	-	5.0478
	$(1-\hat{\alpha})$	0.5947	0.9196
50	%ds	0.3476	0.5463
	Amp	-	3.0029
	$(1-\hat{\alpha})$	0.8192	0.9101
100	%ds	0.2367	0.5222
	Amp	-	1.5692
	$(1-\hat{\alpha})$	0.8639	0.8968
200	%ds	0.6352	0.5368
	Amp	-	0.7281
	$(1-\hat{\alpha})$	0.8974	0.8972
400	%ds	0.4815	0.4805
	Amp	0.4338	0.4326
	$(1-\hat{\alpha})$	0.9018	0.9010
800	%ds	0.5173	0.5192
	Amp	0.2905	0.2901
	$(1-\hat{\alpha})$	0.9008	0.9006
1600	%ds	0.4980	0.4976
	Amp	0.2002	0.2001

$(1-\hat{\alpha})$: probability of coverage of the intervals

%ds : symmetric miscoverage of the intervals
Amp*:* average width of the intervals

Extending the simulation results to all other values of ρ considered, the Fieller's theorem always failed for $n \leq 50$, with corresponding non-acceptable coverage probabilities. For ρ equal to -0.6 and -0.9, the Fieller's theorem failed also for *n* equal to 100, but in these cases the coverage probabilities were higher as referred to those for $n<100$. For other values of ρ, i.e., equal to –0.3, 0 and 0.6, the Fieller's theorem failed also for *n* equal to 200. The simulation results highlighted that the Fieller's theorem less frequently produces unbounded confidence intervals for *R* with increasing values of *n*. Finally, the performances of the two methods were satisfactory and very close to each other for high values of *n*.

5. Conclusions

The present paper shows the importance of considering the real distribution of the estimator of the ratio of two means W_n, because generally the approximation to normal is not satisfied. For this reason, building the confidence intervals with the Cochran approach is not always appropriate. The Fieller's theorem is a general procedure to construct confidence interval for the ratio of the means in a bivariate normal distribution. The calculation of the confidence interval is relatively simple and this approach has been used as a touchstone by several authors. However, there are several cases, i.e., the estimated $\overline{X}_2$ is significantly different from zero at level α, for which the confidence interval is not bounded. In this paper, the authors propose an alternative method to compute the confidence interval, based on the inverse cdf of W_n, called the exact distribution method. Although the calculus of the confidence intervals by means of the exact distribution method is more complicated, since this involves the calculation of the inverse of a cdf that can be obtained only by a computer support, the novel method proposed always allows one to obtain bounded confidence intervals, also when the Fieller's theorem produces unbounded intervals. Besides theoretical interest, this may be useful in several applications. For example, the problem to treat the cost-effectiveness ratio in the equivalence studies, i.e., when the difference in effectiveness between the new treatment and the control treatment is close to zero, has recently arisen in the cost-effectiveness analysis. In these cases the confidence intervals for the cost-effectiveness ratio cannot be obtained with the Fieller's theorem and in medical literature there are no satisfactory parametric methods to construct confidence intervals. Therefore, the exact distribution method would be valuable. In order to encourage the dissemination of the novel method, in Appendix we have reported the codes of procedures and functions, with relative descriptions, to build confidence intervals with the exact distribution method in the scientific software package MATLAB. For completeness, we have also reported the code for building confidence intervals with the Fieller's theorem.

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APPENDIX

Procedures and functions implemented in MATLAB, useful to construct confidence intervals with the exact distribution method and the Fieller's theorem

Function 1	Cumulative density function: F(w)
Function 2	Probability density function: f(w)
Function 3	Fieller's theorem for the construction of confidence intervals for R
Function 4	Exact distribution method for the construction of confidence intervals for R

Function 1

```
% Definition Function: cdf  F(W) of the ratio of two normal random variables (w=x1/x2)
function fcum=cdfratio(media1,media2,var1,var2,r,w)

% Insert parameters: means (media1, media2), variances (var1,var2), coefficient of
correlation (r) and range of W (w)
```

```
sqm1=sqrt(var1);
sqm2=sqrt(var2);

raprho=1/(sqrt(1-r.^2));
b=media2/sqm2;
a=((media1/sqm1)-(r*b))*raprho;

t=((((sqm2.*w)/sqm1))-r).*raprho;
rq=sqrt(1+t.^2);
rho=t./rq;
x=(b.*t-a)./rq;
xg=-b;
xs=-x;

pt=zeros(length(w),1);
pp=zeros(length(w),1);
fcum=zeros(length(w),1);

for i=1:length(w)
   pt(i) = bivnormcdf(x(i),b,rho(i));
   pp(i)= bivnormcdf(xs(i),xg,rho(i));

   fcum(i)=pt(i)+pp(i); %cdf

end
```

Function 2

```
% Definition Function: pdf  f(W) of the ratio of two normal random variables (w=x1/x2)
function fden = pdfratio(media1,media2,var1,var2,r,w)

% Insert parameters: means (media1, media2), variances (var1,var2), coefficient of
correlation (r) and range of W (w)

sqm1=sqrt(var1);
sqm2=sqrt(var2);

raprho=1/(sqrt(1-r.^2));
b=media2/sqm2;
a=((media1/sqm1)-(r*b))*raprho;

costa=(sqm2/sqm1)*raprho;
gg=(1/pi)*exp(-0.5*(a^2+b^2));
t=(((sqm2/sqm1).*w)-r)*raprho;

q=(b+a.*(t))./(sqrt(1+(t.^2)));
pc=1./(1+t.^2) ;

funq=(1/sqrt(2*pi))*exp(-0.5*q.^2);
cc=q./funq;
dn=normcdf(q)-0.5;
```

```
og=(1+cc.*dn);

fden=(costa.*gg.*pc.*og); % pdf
```

Function 3

% Fieller method for the construction of confidence intervals for the ratio of means of Normal random variables ($R=\mu_1/\mu_2$)

```
function [visa]=idcfieller(mcamp1,mcamp2,vcampm1,vcampm2,rhocamp,t,nv)
```

% Insert parameters: sample means (mcamp1, mcamp2), sample variances of means (vcampm1,vcampm2), sample coefficient of correlation (rhocamp), Student's percentile point with n-1 df (t) and number of repetitions (nv)

```
 for i=1:nv
   co(i)=rhocamp(i)*(sqrt(vcampm1(i)*vcampm2(i)));
   an(i)=(mcamp2(i)^2)-((t^2)*(vcampm2(i)));
   bn(i)=(mcamp2(i)*mcamp1(i))-((t^2)*(co(i)));
   cn(i)=(mcamp1(i)^2)-((t^2*vcampm1(i)));

   inf(i)=(bn(i)-sqrt((bn(i)^2)-(an(i).*cn(i))))/(an(i));
   sup(i)=(1/an(i))*(bn(i)+sqrt((bn(i)^2)-(an(i).*cn(i))));

   visa=[inf;sup]';

 end
```

Function 4

% Exact distribution method for the construction of confidence intervals for the ratio of means of Normal random variables ($R=\mu_1/\mu_2$)

```
function [visa]=idcinv(mcamp1,mcamp2,vcampm1,vcampm2,rhocamp,x0,alfa,beta,nv)
```

% Insert parameters: sample means (mcamp1, mcamp2), sample variances of means (vcampm1,vcampm2), sample coefficient of correlation (rhocamp), x0=0, $\alpha/2$ value (α), 1- $\alpha/2$ value (β) and number of repetitions (nv)

```
 for i=1:nv

        wmin(i)=fzero(@cdfrp,x0,[],mcamp1(i),mcamp2(i),vcampm1(i),vcampm2(i),rho
        camp(i),alfa);

        wmax(i)=fzero(@cdfrp,x0,[],mcamp1(i),mcamp2(i),vcampm1(i),vcampm2(i),rho
        camp(i),beta);

    visa=[wmin;wmax]';

 end
```