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TOLERANCE LIMITS FOR A RATIO OF NORMAL RANDOM VARIABLES

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The problem of deriving an upper tolerance limit for a ratio of two normally distributed random variables is addressed, when the random variables follow a bivariate normal distribution, or when they are independent normal. The derivation uses the fact that an upper tolerance limit for a random variable can be derived from a lower confidence limit for the cumulative distribution function (cdf) of the random variable. The concept of a generalized confidence interval is used to derive the required lower confidence limit for the cdf. In the bivariate normal case, a suitable representation of the cdf of the ratio of the marginal normal random variables is also used, coupled with the generalized confidence interval idea. In addition, a simplified derivation is presented in the situation when one of the random variables has a small coefficient of variation. The problem is motivated by an application from a reverse transcriptase assay. Such an example is used to illustrate our results. Numerical results are also reported regarding the performance of the proposed tolerance limit.

Key Words: Content; Generalized confidence interval; Reverse transcriptase assay; Upper tolerance limit.

1. INTRODUCTION AND MOTIVATION

In many practical applications, intervals that capture a specified proportion of a population, with a given confidence level, are required. Such intervals are referred to as tolerance intervals. This is in contrast to a confidence interval that provides information on a population parameter only. The theory of tolerance intervals is well developed for the normal distribution; we refer to the monograph by Guttman (1970) for a detailed discussion. However, practical applications do call for the computation of tolerance intervals for other distributions and setups: for example, for the difference between two normal random variables (Guo and Krishnamoorthy, 2004), for the one-way random model setup (Krishnamoorthy and Mathew, 2004; Liao et al., 2005); and the references therein), etc. In this article, we take up

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the problem of computing tolerance limits for the ratio of two normal random variables, independent, as well as correlated. For the case of independent normal random variables, the problem has been addressed by Hall and Sampson (1973), who gave an approximate solution assuming that the coefficient of variations are small. These authors also gave an application related to drug development. Apart from the motivation and applications given in Hall and Sampson (1973), inference concerning the ratio of bivariate normal means and tolerance intervals for ratios of bivariate normal random variables have a number of important applications. While comparing a test treatment and a reference treatment regarding their costs and health benefits, the cost-effectiveness ratio (CER) is a parameter that represents the additional cost of the test treatment for each additional unit of health benefit. Interval estimation of the CER reduces to that for a ratio of bivariate normal means, where the bivariate normality could result from asymptotic considerations; see Gardiner et al. (2001). Though not addressed in the CER literature, the tolerance interval problem could also be relevant here, for obtaining information on the population consisting of the ratio of the relevant random variables. The investigation in this paper is also motivated by the following specific application.

The reverse transcriptase (RT) assay is used as a screening tool to detect potential retroviral contamination in the raw materials used for manufacture of FluMist, an influenza vaccine. Most retroviruses do not produce pathological changes in cell cultures, and, as such, their presence in raw materials for FluMist cannot be detected using assays dependent on pathological changes. However, the presence of a particular enzyme, RNA directed DNA polymerase, can be used as a reliable indicator for presence of retrovirus in a test sample (Baltimore, 1970). In the RT assay, the larger amount of this enzyme in the sample will induce a larger radioactivity count. A negative control is usually included in the assay to calibrate the radioactivity count resulting from the cell culture itself. One necessary condition for a sample to be classified as negative is that the ratio of radioactivity count induced from the sample (signal + noise) to radioactivity count induced from the negative control (noise) be less than some prespecified limit. Since this limit will apply to future assays to decide whether a sample is positive or negative, a tolerance limit is used to ensure that a given proportion (say, 95%) of the future assay results will be less than the limit with a given confidence level, if the process is in control.

Historical in-control data show that the radioactivity count from the sample and that from the negative control are both normally distributed. They are evidently dependent. Thus we have the problem of deriving an upper tolerance limit for the ratio of two random variables following a bivariate normal distribution.

In this article, we denote by β and $1-\alpha$, respectively, the *content* and the *confidence level* of the tolerance interval. Thus, if X is a random variable whose distribution depends on a parameter (vector) $\boldsymbol{\theta}$, and if $\hat{\boldsymbol{\theta}}$ is an estimator of $\boldsymbol{\theta}$, then an upper tolerance limit for X having content β and confidence level $1-\alpha$ is a function of $\hat{\boldsymbol{\theta}}$, say, $g(\hat{\boldsymbol{\theta}})$, satisfying

$$P_{\hat{\theta}}\big(P_X(X \leq g(\hat{\boldsymbol{\theta}}) \mid \hat{\boldsymbol{\theta}}) \geq \beta\big) = 1-\alpha$$

We refer to $g(\hat{\boldsymbol{\theta}})$ as a $(\beta, 1-\alpha)$ upper tolerance limit. If x_β is the βth percentile of X, then the preceding definition is equivalent to

$$P_{\hat{\theta}}(g(\hat{\boldsymbol{\theta}}) \geq x_\beta) = 1 - \alpha \tag{1}$$

i.e., $g(\hat{\boldsymbol{\theta}})$ is a $100(1-\alpha)\%$ upper confidence limit for x_β. Now consider the cumulative distribution function (cdf) $P(X \leq t)$ as a function of t and $\boldsymbol{\theta}$. Let $h(\hat{\boldsymbol{\theta}}, t)$ be a $100(1-\alpha)\%$ lower confidence limit for $P(X \leq t)$. That is,

$$P_{\hat{\theta}}\big(P_X(X \leq t) \geq h(\hat{\boldsymbol{\theta}}, t)\big) = 1 - \alpha$$

If we solve $h(\hat{\boldsymbol{\theta}}, t) = \beta$, it is easily seen that the solution $t = g(\hat{\boldsymbol{\theta}})$ is a $(\beta, 1-\alpha)$ upper tolerance limit for X. In other words, an upper tolerance limit for X can be obtained based on a lower confidence limit for the cdf. In our setup, $h(\hat{\boldsymbol{\theta}}, t)$ is an increasing function of t, and hence the solution to $h(\hat{\boldsymbol{\theta}}, t) = \beta$ will be unique.

Our problem is that of computing an upper tolerance limit for X_1/X_2 when (X_1, X_2) follows a bivariate normal distribution. We also consider the simpler case when X_1 and X_2 are independent univariate normal random variables. The problem is briefly discussed in Yang et al. (2006). As noted by these authors, it appears that a simple or direct approach is not possible for solving such a tolerance interval problem. As noted earlier, we first tackle the problem of computing a lower confidence limit for the cdf of X_1/X_2. Our derivations are based on the concept of a *generalized confidence interval* due to Weerahandi (1993); see also Weerahandi (1995, 2004).

The paper is organized as follows. In Section 2, we discuss the computation of an upper tolerance limit for X_1/X_2, based on a lower confidence limit for the cdf of X_1/X_2. It is noted that when X_2 is known to have a small coefficient of variation (CV), and when the sign of the mean of X_2 is known, it is possible to use an approximation to the cdf of $P(X_1/X_2 \leq t)$, along with the generalized confidence interval idea. In the general case where the previous assumption concerning the coefficient of variation does not hold, we use an expression for the cdf of X_1/X_2 due to Hinkley (1969), along with the generalized confidence interval procedure. In Section 3, we have reported simulation results on the performance of our approximate limits. The RT assay example is discussed in Section 4 of the paper to demonstrate our methods. A final section contains some concluding remarks. The generalized confidence interval idea, as it applies to the present setup, is briefly explained in an appendix.

2. UPPER TOLERANCE LIMITS FOR X_1/X_2

Suppose $(X_1, X_2)' \sim N_2(\boldsymbol{\mu}, \boldsymbol{\Sigma})$, a bivariate normal distribution with mean $\boldsymbol{\mu} = (\mu_1, \mu_2)'$ and covariance matrix $\boldsymbol{\Sigma} = \left(\begin{smallmatrix}\sigma_{11} & \sigma_{12} \\ \sigma_{12} & \sigma_{22}\end{smallmatrix}\right)$. Suppose $(X_{1j}, X_{2j})'$, $j = 1, \ldots, n$, is a random sample from the bivariate normal distribution. Let $\overline{X}_i = \sum_{j=1}^n X_{ij}/n$, $i = 1, 2$ and

$$\boldsymbol{A} = \sum_{j=1}^n \begin{pmatrix} X_{1j} - \overline{X}_1 \\ X_{2j} - \overline{X}_2 \end{pmatrix} \begin{pmatrix} X_{1j} - \overline{X}_1 \\ X_{2j} - \overline{X}_2 \end{pmatrix}' = \begin{pmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{pmatrix}$$

Clearly, $(\overline{X}_1, \overline{X}_2)' \sim N_2(\boldsymbol{\mu}, \frac{1}{n}\Sigma)$ and $\boldsymbol{A} \sim W_2(\Sigma, n-1)$, the bivariate Wishart distribution with scale matrix Σ and degrees of freedom $n-1$.

2.1. Tolerance Limits Based on an Approximation to the cdf of X_1/X_2

The approximation that we shall consider is for the case where $\mu_2 > 0$ and the coefficient of variation of X_2, namely, $\sqrt{\sigma_{22}}/\mu_2$, is small; later we comment on how small $\sqrt{\sigma_{22}}/\mu_2$ should be. Under the assumptions just described, we have

$$P\left(\frac{X_1}{X_2} \le t\right) = P\left(\frac{X_1}{X_2} \le t, X_2 > 0\right) + P\left(\frac{X_1}{X_2} \le t, X_2 < 0\right) \approx P(X_1 \le tX_2)$$
$$= \Phi\left(\frac{-(\mu_1 - t\mu_2)}{\sqrt{\sigma_{11} - 2t\sigma_{12} + t^2\sigma_{22}}}\right) = \Phi(-u(\boldsymbol{\theta}, t))$$

where

$$u(\boldsymbol{\theta}, t) = \frac{(\mu_1 - t\mu_2)}{\sqrt{\sigma_{11} - 2t\sigma_{12} + t^2\sigma_{22}}}$$

and $\Phi(\cdot)$ is the cdf of the standard normal distribution. This approximation is also discussed in Hinkley (1969). A similar approximation can also be developed when $\mu_2 < 0$ and the coefficient of variance (CV) of X_2, namely, $\sqrt{\sigma_{22}}/\mu_2$, is small. Here we discuss the case of $\mu_2 > 0$, along with the CV being small; the other case is similar.

Now we need to find a $100(1-\alpha)\%$ upper confidence limit for $u(\boldsymbol{\theta}, t)$, say, $h(\hat{\boldsymbol{\theta}}, t)$, where $\hat{\boldsymbol{\theta}}$ is an estimator of $\boldsymbol{\theta}$. Then $\Phi(-h(\hat{\boldsymbol{\theta}}, t))$ is a $100(1-\alpha)\%$ lower confidence limit for $\Phi(-u(\boldsymbol{\theta}, t))$. We can solve $\Phi(-h(\hat{\boldsymbol{\theta}}, t)) = \beta$, or equivalently

$$h(\hat{\boldsymbol{\theta}}, t) = -z_\beta \tag{2}$$

to obtain $t = g(\hat{\boldsymbol{\theta}})$, the upper $(\beta, 1-\alpha)$-tolerance limit for X_1/X_2. Here z_β is such that $\Phi(z_\beta) = \beta$.

We now construct a $100(1-\alpha)\%$ upper confidence limit for $u(\boldsymbol{\theta}, t)$ using the generalized confidence interval idea. Toward this, let $\bar{x}_i$ denote the observed value of $\overline{X}_i$, $i = 1, 2$, and let $\boldsymbol{a}$ denote the observed value of the Wishart matrix $\boldsymbol{A}$. In order to construct a $100(1-\alpha)\%$ generalized confidence interval for $u(\boldsymbol{\theta}, t)$, the percentiles of a *generalized pivotal quantity* (GPQ) are used. A GPQ is a function of the random variables $\boldsymbol{A}$ and $(\overline{X}_1, \overline{X}_2)'$ and of the observed data $\boldsymbol{a}$ and $(\bar{x}_1, \bar{x}_2)'$, satisfying two conditions: (i) Given the observed data, the distribution of the generalized pivotal quantity is free of any unknown parameters, and (ii) when the random variables $\boldsymbol{A}$ and $\overline{X}_i$ are replaced by the corresponding observed values, the generalized pivotal quantity becomes equal to the parameter of interest, namely, $u(\boldsymbol{\theta}, t)$. The derivation of the GPQ is briefly explained in the appendix. In particular, we shall use the quantities V_{ij} and K_{ij} defined in Eqs. (8) and (9) in the appendix. In addition, define

$$Z_1 = \frac{(\overline{X}_1 - t\overline{X}_2) - (\mu_1 - t\mu_2)}{\sqrt{(\sigma_{11} - 2t\sigma_{12} + t^2\sigma_{22})/n}} \sim N(0, 1)$$

and let

$$
\begin{aligned}
T_{11} &= \frac{\bar{x}_1 - t\bar{x}_2}{\sqrt{V_{11} - 2tV_{12} + t^2V_{22}}} - \frac{(\overline{X}_1 - t\overline{X}_2) - (\mu_1 - t\mu_2)}{\sqrt{(\sigma_{11} - 2t\sigma_{12} + t^2\sigma_{22})/n}} \frac{1}{\sqrt{n}} \\
&= \frac{\bar{x}_1 - t\bar{x}_2}{\sqrt{V_{11} - 2tV_{12} + t^2V_{22}}} - \frac{Z_1}{\sqrt{n}} \\
T_{12} &= \frac{\bar{x}_1 - t\bar{x}_2}{\sqrt{K_{11} - 2tK_{12} + t^2K_{22}}} - \frac{(\overline{X}_1 - t\overline{X}_2) - (\mu_1 - t\mu_2)}{\sqrt{(\sigma_{11} - 2t\sigma_{12} + t^2\sigma_{22})/n}} \frac{1}{\sqrt{n}} \\
&= \frac{\bar{x}_1 - t\bar{x}_2}{\sqrt{K_{11} - 2tK_{12} + t^2K_{22}}} - \frac{Z_1}{\sqrt{n}} \qquad (3)
\end{aligned}
$$

where the V_{ij} and the K_{ij} are defined in Eqs. (8) and (9) in the appendix. It is readily verified that both T_{11} and T_{12} are GPQs for $u(\boldsymbol{\theta}, t)$. Keeping the observed values (the a_{ij}, $\bar{x}_1$, and $\bar{x}_2$) fixed, we can easily estimate the percentiles of T_{11} or T_{12} by Monte Carlo simulation; see the appendix regarding the generation of the V_{ij} and the K_{ij} terms. The $100(1-\alpha)$th percentile of T_{11} (or that of T_{12}) so obtained gives a $100(1-\alpha)\%$ generalized upper confidence limit for $u(\boldsymbol{\theta}, t)$, which in turn gives an approximate $(\beta, 1-\alpha)$ upper tolerance limit for X_1/X_2. We later report numerical results regarding the performance of the solutions so obtained.

Note that in the independent case (i.e., when $\sigma_{12} = 0$) we have $u(\boldsymbol{\theta}, t) = \frac{\mu_1 - t\mu_2}{\sqrt{\sigma_{11} + t^2\sigma_{22}}}$, and a GPQ for $u(\boldsymbol{\theta}, t)$ is now given by

$$
T_{21} = \frac{\bar{x}_1 - t\bar{x}_2}{\sqrt{V_{11} + t^2V_{22}}} - \frac{Z_2}{\sqrt{n}} \qquad (4)
$$

where

$$
Z_2 = \frac{(\overline{X}_1 - t\overline{X}_2) - (\mu_1 - t\mu_2)}{\sqrt{(\sigma_{11} + t^2\sigma_{22})/n}} \sim N(0, 1)
$$

2.2. Tolerance Limits Based on the Exact cdf

The results in Section 2.1 have been derived under the assumption that the coefficient of variation of X_2 is small. We now do away with this assumption. For this we use a representation for the actual cdf of X_1/X_2, say, $F(t)$, due to Hinkley (1969): $F(t) = L(d_1, d_2; d_3) + L(-d_1, -d_2; d_3)$, where $L(p, q; \rho)$ is the standard bivariate normal integral

$$
L(p, q; \rho) = \frac{1}{2\pi\sqrt{1-\rho^2}} \int_p^\infty \int_q^\infty \exp\left\{-\frac{x^2 - 2\rho xy + y^2}{2(1-\rho^2)}\right\} dx\, dy \qquad (5)
$$

$$
d_1 = \frac{\mu_1 - t\mu_2}{\sqrt{\sigma_{11}\sigma_{22}}\, b(t)}, \quad d_2 = -\frac{\mu_2}{\sqrt{\sigma_{22}}}, \quad \text{and} \quad d_3 = \frac{t\sigma_{22} - \sigma_{12}}{\sqrt{\sigma_{11}}\sigma_{22} b(t)} \qquad (6)
$$

and

$$b(t) = \sqrt{\frac{t^2}{\sigma_{11}} - \frac{2t\sigma_{12}}{\sigma_{11}\sigma_{22}} + \frac{1}{\sigma_{22}}} \tag{7}$$

A GPQ for $F(t)$ is now easily obtained using GPQs for d_1, d_2, d_3, and $b(t)$. Because these quantities are functions of $\boldsymbol{\mu}$ and Σ, GPQs for d_1, d_2, d_3, and $b(t)$ can in turn be obtained using the GPQs for $\boldsymbol{\mu}$ and Σ derived in the appendix.

Note that the resulting GPQ for $F(t)$ has an integral form, which can be evaluated using numerical methods for evaluating the bivariate normal cdf. We have used a subroutine provided by Drezner and Wesolowsky (1990). The algorithm has a maximum error of 2×10^{-7}.

Apart from using Hinkley's (1969) representation for the cdf given earlier, a GPQ can also be obtained using yet another simple representation for the cdf of X_1/X_2. For this, note that the conditional distribution of X_1 given X_2 is $N(\mu_1 + \sigma_{12}\sigma_{22}^{-1}(X_2 - \mu_2), \sigma_{11.2})$.

Using this result, it is easy to see that

$$\begin{aligned}
P\left(\frac{X_1}{X_2} \le t\right) &= \int_0^{\infty} \Phi\left(\frac{x_2 t - \mu_1 - \sigma_{12}\sigma_{22}^{-1}(x_2 - \mu_2)}{\sqrt{\sigma_{11.2}}}\right) f(x_2; \mu_2, \sigma_{22}) dx_2 \\
&\quad + \int_{-\infty}^{0} \left[1 - \Phi\left(\frac{x_2 t - \mu_1 - \sigma_{12}\sigma_{22}^{-1}(x_2 - \mu_2)}{\sqrt{\sigma_{11.2}}}\right)\right] f(x_2; \mu_2, \sigma_{22}) dx_2 \\
&= \Phi\left(-\frac{\mu_2}{\sqrt{\sigma_{22}}}\right) + \int_{-\frac{\mu_2}{\sqrt{\sigma_{22}}}}^{\infty} \Phi\left(\frac{(\mu_2 + z\sqrt{\sigma_{22}})t - (\mu_1 + z\sigma_{12}/\sqrt{\sigma_{22}})}{\sqrt{\sigma_{11.2}}}\right)\phi(z) dz \\
&\quad - \int_{-\infty}^{-\frac{\mu_2}{\sqrt{\sigma_{22}}}} \Phi\left(\frac{(\mu_2 + z\sqrt{\sigma_{22}})t - (\mu_1 + z\sigma_{12}/\sqrt{\sigma_{22}})}{\sqrt{\sigma_{11.2}}}\right)\phi(z) dz
\end{aligned}$$

where $f(x_2; \mu_2, \sigma_{22})$ is the normal density with mean μ_2 and variance σ_{22}, $\phi(z)$ is standard normal density and $\sigma_{11.2} = \sigma_{11} - \sigma_{12}^2/\sigma_{22}$. To get the second equation just shown, we have used the transformation $z = (x_2 - \mu_2)/\sqrt{\sigma_{22}}$.

When X_1 and X_2 are independent, $\sigma_{12} = 0$ in Eqs. (6) and (7). Generalized pivotal quantities for σ_{11} and σ_{22} are obviously given by V_{11} and V_{22}. Generalized pivotal quantities for μ_1 and μ_2, say, W_1 and W_2, are given by

$$W_i = \bar{x}_i - \frac{\overline{X}_i - \mu_i}{\sqrt{\sigma_{ii}/n}}\sqrt{V_{ii}/n} = \bar{x}_i - Z_{0i}\sqrt{V_{ii}/n}$$

where $Z_{0i} = \frac{\overline{X}_i - \mu_i}{\sqrt{\sigma_{ii}/n}} \sim N(0, 1)$ and are independent for $i = 1, 2$. Using the generalized pivotal quantities for $\mu_1, \mu_2, \sigma_{11}$ and σ_{22}, we can easily obtain a generalized pivotal quantity for $F(t)$ in the independent case.

3. NUMERICAL RESULTS

In order to study the performance of the approximate upper tolerance limits, it is enough to study the performance of the generalized upper confidence limit for

Table 1 Simulated confidence levels of the 95% generalized confidence interval for $P(X_1/X_2 \leq t)$ using the approximation to the cdf given in Section 2.1 for $\mu_1 = 40$ and $\sigma_{11} = 100$

			$\rho = -.8$		$\rho = .2$		$\rho = 0.8$		Independent
μ_2	σ_{22}	t	(I)	(II)	(I)	(II)	(I)	(II)	case
					$n = 20$				
32	81	0.65	.946	.942	.926	.940	.927	.937	.945
		1.25	.952	.951	.954	.953	.953	.955	.956
		1.85	.956	.966	.963	.966	.958	.967	.963
50	225	0.65	.945	.951	.950	.949	.931	.943	.943
		1.25	.953	.961	.957	.960	.962	.963	.962
		1.85	.948	.959	.957	.968	.955	.968	.950
					$n = 60$				
32	81	0.65	.949	.942	.945	.950	.936	.942	.943
		1.25	.947	.951	.950	.952	.955	.952	.950
		1.85	.948	.960	.954	.954	.957	.953	.951
50	225	0.65	.948	.945	.946	.948	.939	.943	.948
		1.25	.952	.952	.952	.951	.955	.957	.958
		1.85	.951	.957	.953	.960	.946	.961	.953

Note. (I) and (II) in the table refer to the GPQ construction given in Eqs. (8) and (9), respectively, and the independent case corresponds to X_1 and X_2 being independent.

$P(X_1/X_2 \leq t)$. Thus, we have simulated the coverage probability of the generalized upper confidence limit for $P(X_1/X_2 \leq t)$. The simulation was carried out as follows.

First consider the approximation to the cdf discussed in Section 2.1. For specified values of the parameters $\boldsymbol{\mu}$ and Σ, generate $(\bar{x}_1, \bar{x}_2)'$ from $N_2(\boldsymbol{\mu}, \boldsymbol{\Sigma}/n)$ where n is the sample size, and generate $\boldsymbol{a} \sim W_2(\boldsymbol{\Sigma}, n-1)$. Keeping $(\bar{x}_1, \bar{x}_2)'$ and $\boldsymbol{a}$ fixed, and for a fixed value of t, generate values of T_{11} and T_{12} in Eq. (3), and T_{21} in Eq. (4), 5000 times by simulating the random variables involved in their definitions; see the appendix. The upper confidence limit for $P(X_1/X_2 \leq t)$ can then be estimated as the appropriate percentile of the GPQs T_{11}, T_{12}, or T_{21}. This process can be repeated 5000 times, and the coverage probability is the proportion of times $P(X_1/X_2 \leq t)$ is below the upper confidence limit.

The coverage probabilities so obtained are given in Table 1, corresponding to a nominal level of 95%, and for sample sizes 20 and 60. In Table 1, for each sample size, we have selected parameters $\mu_1, \mu_2, \sigma_{11}$, and σ_{22} such that the CV of X_2 is less than or equal to 30%. In the first case, $\mu_1 < \mu_2$, and in the second case, $\mu_1 > \mu_2$. We found that the approximation to the cdf, described in Section 2.1, is quite accurate if the coefficient of variation of X_2 is no more than 0.30. From the numerical results in Table 1, we conclude that the proposed generalized confidence interval for $P(X_1/X_2 \leq t)$ satisfactorily maintains the confidence level. In other words, the tolerance interval that we have constructed using the approximation to the cdf exhibits satisfactory performance. We note that the performance is equally satisfactory regardless of whether we use the GPQ of Eqs. (8) or (9) for Σ. For practical use, we can recommend either of the two GPQs. There appears to be no difference between the two, in terms of performance and in terms of computational advantage. This is also reinforced by the example in the next section.

Table 2 Simulated confidence levels of the 95% generalized confidence interval for $P(X_1/X_2 \leq t)$ based on the exact cdf given in Section 2.2 for $\mu_1 = 10$ and $\sigma_{11} = 25$

			$\rho = -.8$		$\rho = .2$		$\rho = 0.8$		Independent case
μ_2	σ_{22}	t	(I)	(II)	(I)	(II)	(I)	(II)	
					$n = 20$				
5	25	1.1	.912	.892	.921	.906	.918	.916	.917
		2.0	.906	.889	.925	.909	.926	.902	.921
		2.9	.907	.891	.927	.910	.925	.910	.918
20	225	1.1	.929	.922	.933	.933	.931	.936	.928
		2.0	.930	.936	.931	.934	.933	.935	.936
		2.9	.926	.928	.932	.936	.931	.938	.933
					$n = 60$				
5	25	1.1	.924	.923	.930	.929	.937	.928	.930
		2.0	.923	.917	.929	.926	.938	.927	.935
		2.9	.928	.925	.933	.926	.938	.926	.937
20	225	1.1	.932	.935	.939	.941	.940	.942	.941
		2.0	.934	.941	.939	.944	.936	.945	.943
		2.9	.934	.940	.942	.941	.943	.944	.943

Note. (I) and (II) in the table refer to the GPQ construction given in Eqs. (8) and (9), respectively, and the independent case corresponds to X_1 and X_2 being independent.

The simulation procedure can be similarly carried out for the tolerance interval that uses the exact cdf of X_1/X_2, as described in Section 2.2. However, here we need to numerically evaluate the double integral of Eq. (5). For this, we used a subroutine provided by Drezner and Wesolowsky (1990). The numerical results appear in Table 2. Here parameters are chosen such that the CV of X_2 is larger; one is 75% and the other 100%. Again $\mu_1 < \mu_2$ in one case and $\mu_1 > \mu_2$ in the other. We do notice some unsatisfactory coverages, especially for $n = 20$. One possibility to improve the coverage is to use a bootstrap calibration, at the expense of more numerical work; see Efron and Tibshirani (1993, Chapter 18). We now explain this in the context of computing a 95% lower confidence limit for the exact cdf $F(t)$ of X_1/X_2, given in Section 2.2. Based on a given sample, the bootstrap calibration, carried out parametrically, can be described as follows.

1. Estimate the bivariate normal parameters using the given sample, and also compute $F(t)$ for the given t using the estimated parameters. Let $\widehat{F}(t)$ denote the estimate so obtained.
2. Now generate M_1 samples from the bivariate normal distribution with estimated parameters. For each sample, compute the lower confidence limit for $\widehat{F}(t)$, following the generalized confidence interval methodology, and for a range of values of the nominal confidence level $1 - \alpha$ in the interval $0.95 - 0.99$ (say).
3. For each value of the nominal level $1 - \alpha$, compute the proportion of times $\widehat{F}(t)$ exceeds the generalized lower confidence limit, and select the value of $1 - \alpha$, say $1 - \alpha_0$, for which this proportion is closest to 0.95.
4. Use the nominal level of $1 - \alpha_0$ to compute a lower confidence limit for $F(t)$, based on the original sample.

5. The coverage probability of the resulting procedure can be evaluated by specifying values of the bivariate normal parameters, generating M_2 samples from the resulting bivariate normal distribution, and repeating steps 1–4 for each generated sample.

We carried out steps 1–5 for $n = 20$ and $60, t = 1.1, \mu_1 = 10, \mu_2 = 5, \sigma_{11} = 25, \sigma_{22} = 25$, and $\rho = -0.8$. For $M_1 = 1000$ and $M_2 = 200$, and for $n = 20$, the coverage probability after calibration turned out to be 0.91, and it was 0.89 before the calibration. For $n = 60$, the calibration improved the coverage probability from 0.92 to 0.955. While carrying this out, we estimated the generalized lower confidence limit using 2000 simulated values of the GPQ.

All simulation programs, and the program for the next section, were written in R and are available upon request.

4. AN EXAMPLE

In this section we use the example mentioned in Section 1 to demonstrate our methods. Forty-five pairs of radioactivity counts of negative controls and samples were accumulated in previous in-control RT assays, denoted by $(X_{1j}, X_{2j})'$, $j = 1, \ldots, 45$. The Shapiro–Wilk normality test revealed that the data were distributed as bivariate normal. Furthermore, the sample data gave the observed values $\bar{x}_1 = 38.1$, $s_{11} = a_{11}/44 = 56.3$, $\bar{x}_2 = 38.9$, $s_{22} = a_{22}/44 = 35.1$, and $\hat{\rho} = 0.81$. Since the estimated coefficient of variation of radioactivity counts from samples is 0.15, we decided to use the approximation method of Section 3.1.

In order to construct a $(\beta, 1-\alpha)$ upper tolerance limit for X_1/X_2, we first constructed a $100(1-\alpha)\%$ generalized lower confidence limit for $P(X_1/X_2 \leq t)$, using 5000 simulations, and then equated the limit to β to solve for t. (We searched for t such that the difference between the lower confidence limit and β is less than 0.001, using a bi-section search). The solution so obtained is the required upper tolerance limit, as explained in the introduction. We repeated this process 1000 times. The mean and standard deviation (SD) of the tolerance limits so obtained are reported in Table 3, based on the GPQs of Eqs. (8) and (9) for Σ, for $1-\alpha = 0.95$, and for $\beta = 0.95$ and 0.99.

The results in Table 3 show that the GPQs of Eqs. (8) and (9) both resulted in practically the same upper tolerance limits. This is consistent with the numerical results in Table 1, which show that both Eqs. (8) and (9) result in nearly the same

Table 3 Upper tolerance limits for the example with $1-\alpha = 0.95$

β	(I)	(II)
0.95	1.233 (0.0009)	1.230 (0.0009)
0.99	1.346 (0.0013)	1.343 (0.0011)

Note. The entries are the mean (SD) based on 1000 repetitions ((I) and (II) in the table refer to the GPQ construction given in Eqs. (8) and (9), respectively).

coverage probability. Also note that the 1000 repeated calculations of the upper tolerance limits resulted in a rather small standard deviation.

5. CONCLUDING REMARKS

Tolerance intervals are used in practical applications to obtain information on a specified proportion or more of a given population. This proportion is referred to as the content of the tolerance interval. Tolerance intervals could be one-sided, having only an upper limit or a lower limit, or they could be two-sided. This work appears to be the first attempt to derive a one-sided tolerance limit for the ratio of two normal random variables in a bivariate normal setup, or in an independent setup, without imposing additional assumptions. The procedure is based on the observation that an upper tolerance limit for a random variable can be derived using a lower confidence limit for the corresponding cdf. In our context, such a lower confidence limit has been constructed using the generalized confidence interval idea. The derivation simplifies considerably, and the resultant tolerance interval provides desirable coverage probability, under the additional assumption that one of the random variables has a small coefficient of variation, which is true for many practical applications. Numerical results are reported on the performance of the proposed tolerance limit, and a bioassay example is used to illustrate the results. In some cases, the tolerance limit that we have derived turns out to be liberal—i.e., the actual coverage probability could be less than the assumed nominal level. A bootstrap calibration can remedy this problem to some extent, but not entirely. Overall, the procedures developed in the paper are computationally somewhat demanding. Of the two generalized pivotal quantities developed in the appendix, one does not provide any computational advantage over the other. It is certainly desirable to develop accurate approximations—a problem that needs more investigation.

Note that our methodology does not naturally generalize to produce two-sided tolerance intervals. The reason for this is that the two-sided tolerance interval problem does not reduce to the computation of confidence limits. In fact, the problem of deriving a two-sided tolerance interval for the ratio of two normal random variables remains open.

APPENDIX: THE GENERALIZED PIVOTAL QUANTITY (GPQ)

Based on a sample of size n from the bivariate normal distribution $N_2(\boldsymbol{\mu}, \boldsymbol{\Sigma})$, let $(\overline{X}_1, \overline{X}_2)' \sim N_2(\boldsymbol{\mu}, \frac{1}{n}\Sigma)$ and $\boldsymbol{A} \sim W_2(\Sigma, n-1)$, as defined in the first part of Section 2. Furthermore, let $\bar{x}_i$ denote the observed value of $\overline{X}_i$, $i = 1, 2$, and let $\boldsymbol{a}$ denote the observed value of $\boldsymbol{A}$. Consider $f(\boldsymbol{\theta})$, a scalar valued function of $\boldsymbol{\theta} = (\mu_1, \mu_2, \sigma_{11}, \sigma_{12}, \sigma_{22})'$. In order to construct a $100(1-\alpha)\%$ generalized confidence interval for $f(\boldsymbol{\theta})$, the percentiles of a generalized pivotal quantity (GPQ) are used. A GPQ is a function of the random variables $\boldsymbol{A}$ and $(\overline{X}_1, \overline{X}_2)'$, and the observed data $\boldsymbol{a}$ and $(\bar{x}_1, \bar{x}_2)'$, satisfying two conditions: (i) Given the observed data, the distribution of the generalized pivotal quantity is free of any unknown parameters, and (ii) when the random variables $\boldsymbol{A}$ and $\overline{X}_i$ are replaced by the corresponding observed values, the generalized pivotal quantity becomes equal to the parameter of interest, namely, $f(\boldsymbol{\theta})$. We exhibit a GPQ for the entire parameter set $(\boldsymbol{\mu}, \Sigma)$. A GPQ for a scalar valued function $f(\boldsymbol{\theta})$ can then be easily obtained by replacing the parameters in $f(\boldsymbol{\theta})$ by the corresponding GPQs. The procedure is described here very briefly, since GPQs in the context of the bivariate normal distribution have been constructed in Gamage et al. (2004), Mathew and Webb (2005), and Bebu and Mathew (2008).

We first construct a GPQ for Σ; in fact, we give two different constructions. Since $\boldsymbol{A} \sim \boldsymbol{W}_2(\boldsymbol{\Sigma}, n-1)$, we have the following well-known properties of the Wishart distribution:

$$U_{22} = \frac{A_{22}}{\sigma_{22}} \sim \chi^2_{n-1}, \quad U_{11.2} = \frac{A_{11.2}}{\sigma_{11.2}} \sim \chi^2_{n-2} \quad \text{and}$$
$$Z_2 = \left(A_{12} - \frac{\sigma_{12}}{\sigma_{22}} A_{22}\right) \Big/ \sqrt{\sigma_{11.2} A_{22}} \sim N(0, 1)$$

where χ^2_s denotes a central chi-square distribution with s degrees of freedom, and A_{ij} and σ_{ij} denote the (ij)th elements of $\boldsymbol{A}$ and Σ, respectively, with $A_{11.2} = A_{11} - A^2_{12}/A_{22}$, and $\sigma_{11.2} = \sigma_{11} - \sigma^2_{12}/\sigma_{22}$. Furthermore, the random variables U_{22}, $U_{11.2}$ and Z_2 are independently distributed. Let a_{ij} and $a_{11.2}$, respectively, denote the observed values of A_{ij} $(i, j = 1, 2)$, and $A_{11.2}$. Now define

$$\begin{aligned}
V_{22} &= \frac{\sigma_{22}}{A_{22}} a_{22} = \frac{a_{22}}{U_{22}} \\
V_{12} &= \frac{\sigma_{22}}{A_{22}} a_{12} - \left[\sqrt{a_{11.2} a_{22}} \frac{A_{12} - \frac{\sigma_{12}}{\sigma_{22}} A_{22}}{\sqrt{\sigma_{11.2} A_{11.2}}} \sqrt{\frac{\sigma_{11.2}}{A_{11.2}} \frac{\sigma_{22}}{A_{22}}}\right] \\
&= \frac{a_{12}}{U_{22}} - \left[\sqrt{a_{11.2} a_{22}} \frac{Z_2}{\sqrt{U_{11.2}}} \frac{1}{U_{22}}\right] \\
V_{11} &= \frac{\sigma_{11.2}}{A_{11.2}} a_{11.2} + \frac{V^2_{12}}{V_{22}} = \frac{a_{11.2}}{U_{11.2}} + \frac{V^2_{12}}{V_{22}}
\end{aligned}$$

The values of V_{11}, V_{12} and V_{22} at $A_{ij} = a_{ij}$ and $A_{11.2} = a_{11.2}$ are, respectively, σ_{11}, σ_{12}, and σ_{22}. Define

$$\boldsymbol{V} = \begin{pmatrix} V_{11} & V_{12} \\ V_{12} & V_{22} \end{pmatrix} \tag{8}$$

Then $\boldsymbol{V}$ is a GPQ for the entire matrix Σ.

A second GPQ for Σ can be obtained by noting that when the observed value $\boldsymbol{a}$ of $\boldsymbol{A}$ is fixed,

$$\boldsymbol{H} = \boldsymbol{a}^{-1/2}(\boldsymbol{a}^{-1/2}\boldsymbol{\Sigma}\boldsymbol{a}^{-1/2})^{-1/2}(\boldsymbol{a}^{-1/2}\boldsymbol{A}\boldsymbol{a}^{-1/2})(\boldsymbol{a}^{-1/2}\boldsymbol{\Sigma}\boldsymbol{a}^{-1/2})^{-1/2}\boldsymbol{a}^{-1/2} \sim W_2((\boldsymbol{a}^{-1}, n-1)$$

The value of $\boldsymbol{H}$ at $\boldsymbol{A} = \boldsymbol{a}$ is easily seen to be $\boldsymbol{\Sigma}^{-1}$. Thus

$$\boldsymbol{H}^{-1} = \boldsymbol{K} = \begin{pmatrix} K_{11} & K_{12} \\ K_{12} & K_{22} \end{pmatrix} \tag{9}$$

is also a GPQ for Σ.

In case of two independent normal variables, a GPQ for Σ can be obtained simply by letting $V_{12} = 0$ in Eq. (8).

In order to derive a GPQ for $\boldsymbol{\mu}$, let

$$\begin{pmatrix} Y_1 \\ Y_2 \end{pmatrix} = \begin{pmatrix} \bar{x}_1 \\ \bar{x}_2 \end{pmatrix} - \left(\frac{\boldsymbol{L}}{n}\right)^{1/2} \left(\frac{\boldsymbol{\Sigma}}{n}\right)^{-1/2} \begin{pmatrix} \overline{X}_1 - \mu_1 \\ \overline{X}_2 - \mu_2 \end{pmatrix}$$
$$= \begin{pmatrix} \bar{x}_1 \\ \bar{x}_2 \end{pmatrix} - \left(\frac{\boldsymbol{L}}{n}\right)^{1/2} \boldsymbol{Z} \tag{10}$$

where

$$\boldsymbol{Z} = \left(\frac{\boldsymbol{\Sigma}}{n}\right)^{-1/2} \begin{pmatrix} \overline{X}_1 - \mu_1 \\ \overline{X}_2 - \mu_2 \end{pmatrix} \sim N_2(\boldsymbol{0}, \boldsymbol{I}_2)$$

and $\boldsymbol{L}$ is the matrix $\boldsymbol{V}$ in Eq. (8) or the matrix $\boldsymbol{K}$ in Eq. (9). It is now easy to verify that $(Y_1, Y_2)'$ given here is a GPQ for $\boldsymbol{\mu}$.

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