

Tolerance limits for a ratio of normal random variables

Lanju Zhang¹, Thomas Mathew², Harry Yang¹,
K. Krishnamoorthy³ and Iksung Cho¹

¹Department of Biostatistics
MedImmune, Inc.
One MedImmune Way, Gaithersburg, MD, 20878

²Department of Mathematics and Statistics
University of Maryland Baltimore County
Baltimore, MD, 21250

³Department of Mathematics
University of Louisiana at Lafayette
Lafayette, LA, 70504

Abstract. The problem of deriving an upper tolerance limit for a ratio of two normal random variables is addressed, when the random variables follow a bivariate normal distribution, or when they are independent. 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 bioassay. Such an example is used to illustrate our results. Numerical results are also reported regarding the performance of the proposed tolerance limit.

Keywords: Bioassay; Generalized confidence interval; 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. 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, Lin and Iyer (2006), and the references therein), etc. In the present article, we take up 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), the investigation in the present 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 in the manufacture of FluMist[®], a trivalent influenza vaccine produced from three strains of attenuated live viruses. Most retroviruses do not produce morphological transformation or cytopathogenesis in cell culture, thus they would not be detected using in vitro cell culture assays. The RNA-dependent DNA polymerase (RT) enzyme is an essential component of all replication competent retrovirus. RT enzyme activities can be indicated by the presence of Mn^{++} -requiring RNA dependent DNA polymerase. Since the presence of Mn^{++} directly correlates with the RT enzyme activities, a large amount of Mn^{++} would be indicative of retroviral contamination. However, DNA from test sample might also produce high amount of Mn^{++} , potentially resulting in false positive outcome. As a remedy, specific DNA is added to the RT enzymatic reaction mixture to suppress non-specific activity by

providing an alternative template for the DNA polymerases. The RT enzyme activity is thus quantitated as the ratio of Mn^{++} measurements from RNA and DAN templates.

For a test sample to be negative, this ratio needs to be smaller than a pre-specified cutoff value. Because the ratio is a random variable, an upper tolerance limit for the ratio can be chosen to be the limit, so that the condition is met for a large percent of retrovirus-free lots, with a high confidence. The historical data showed that the Mn^{++} from RNA and DNA templates followed a bivariate normal distribution. Thus we have the problem of obtaining an upper tolerance limit for the ratio of two random variables, distributed as bivariate normal.

In this article, we shall 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) θ , and if $\hat{\theta}$ is an estimator of θ , then an upper tolerance limit for X having content β and confidence level $1 - \alpha$ is a function of $\hat{\theta}$, say $g(\hat{\theta})$, satisfying

$$P_{\hat{\theta}} \left(P_X(X \leq g(\hat{\theta}) | \hat{\theta}) \geq \beta \right) = 1 - \alpha.$$

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

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

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

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

If we solve $h(\hat{\theta}, t) = \beta$, it is easily seen that the solution $t = g(\hat{\theta})$ 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 set up, $h(\hat{\theta}, t)$ is an increasing function of t , and hence the solution to $h(\hat{\theta}, t) = \beta$ 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 shall also consider the simpler case when X_1 and X_2 are independent univariate normal random variables. The problem is briefly discussed in Yang, Zhang and Cho (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 above, we shall 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 above 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 set up, 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 $\boldsymbol{\Sigma} = \begin{pmatrix} \sigma_{11} & \sigma_{12} \\ \sigma_{12} & \sigma_{22} \end{pmatrix}$. Suppose $(X_{1j}, X_{2j})', j = 1, \dots, n$, is a random sample from the bivariate normal distribution. Let $\bar{X}_i = \sum_{j=1}^n X_{ij}/n, i = 1, 2$ and

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

Clearly, $(\bar{X}_1, \bar{X}_2)' \sim N_2(\boldsymbol{\mu}, \frac{1}{n}\Sigma)$ and $\mathbf{A} \sim W_2(\Sigma, n-1)$, 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 shall comment on how small $\sqrt{\sigma_{22}}/\mu_2$ should be. Under the above assumptions, we have

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

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 CV of X_2 , namely $\sqrt{\sigma_{22}}/\mu_2$, is small. Here we shall 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 shall now construct a $100(1-\alpha)\%$ upper confidence limit for $u(\boldsymbol{\theta}, t)$ using the generalized confidence interval idea. Towards this, let \bar{x}_i denote the observed value of \bar{X}_i , $i = 1, 2$, and let \mathbf{a} denote the observed value of the Wishart matrix \mathbf{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) is used. A GPQ is a function of the random variables \mathbf{A} and $(\bar{X}_1, \bar{X}_2)'$, and the observed data \mathbf{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 \mathbf{A} and \bar{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} 's and K_{ij} 's defined in (8) and (9) in the appendix. In addition, define

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

and let

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

where the V_{ij} 's and the K_{ij} 's are defined in (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} 's, \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} 's and the K_{ij} 's. 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 shall 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

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

where

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

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 shall now do away with this assumption. For this we shall 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

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

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

and

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

A GPQ for $F(t)$ is now easily obtained using GPQs for d_1, d_2, d_3 and $b(t)$. These quantities being 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 above, 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

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

where $f(x_2; \mu_2, \sigma_{22})$ is the normal density with mean μ_2 and variance σ_{22} and $\phi(z)$ is the standard normal density. To get the second equation above, 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 (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

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

where $Z_{0i} = \frac{\bar{X}_i - \mu_i}{\sqrt{\sigma_{ii}/n}} \sim N(0, 1)$ 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 $P(X_1/X_2 \leq t)$. 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 $\boldsymbol{\Sigma}$, generate $(\bar{x}_1, \bar{x}_2)'$ from $N_2(\boldsymbol{\mu}, \boldsymbol{\Sigma}/n)$ where n is the sample size, and generate $\mathbf{a} \sim W_2(\boldsymbol{\Sigma}, n - 1)$. Keeping $(\bar{x}_1, \bar{x}_2)'$ and \mathbf{a} fixed, and for a fixed value of t , generate values of T_{11} and T_{12} in (3), and T_{21} in (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. 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 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 (8) or (9) for Σ .

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 (5). For this, we used a subroutine provided by Drezner and Wesolowsky (1990). The numerical results appear in Table 2. 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 shall 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 $\hat{F}(t)$ 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 $\hat{F}(t)$, 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 $\hat{F}(t)$ 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 Mn^{++} values from RNA and DNA templates were accumulated in previous RT assays, denoted by $(X_{1j}, X_{2j})'$, $j = 1, \dots, 45$. The Shapiro-Wilk normality test showed 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 the Mn^{++} values from the DNA template 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, for $1 - \alpha = 0.95$, and $\beta = 0.95$ and 0.99.

The results in Table 3 show that the GPQs (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 (8) and (9) result in nearly the same coverage probability. Also note that the 1000 repeated calculations of the upper tolerance limits resulted in a rather small standard deviation.

5 Concluding Remarks

This work appears to be the first attempt to derive a 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 under the additional assumption that one of the random variables has a small coefficient of variation. Numerical results are reported on the performance of the proposed tolerance limit, and a bioassay example is used to illustrate the results. Note that our methodology does not naturally generalize to produce two-sided tolerance intervals. In fact the problem of deriving a two-sided tolerance interval for the ratio of two normal random variables remains open.

6 Acknowledgement

The authors wish to thank Dr. Wendy Chen for her valuable insight on the RT assay.

References

- Bebu, I. and Mathew, T. (2008). Comparing the means and variances of a bivariate log-normal distribution. *Statistics in Medicine* (to appear).
- Drezner, Z. and Wesolowsky, G. O. (1990). On the computation of the bivariate normal integral. *Journal of Statistical Computation and Simulation*, **35**, 101-107.
- Efron, B. and Tibshirani, R. J. (1993). *An Introduction to the Bootstrap*, New York: Chapman & Hall.

- Gamage, J., Mathew, T. and Weerahandi, S. (2004). Generalized p-values and generalized confidence regions for the multivariate Behrens-Fisher problem. *Journal of Multivariate Analysis*, **88**, 177-189.
- Guo, H. and Krishnamoorthy, K. (2004). New approximate inferential methods for the reliability parameter in a stress-strength model: the normal case. *Communication in Statistics – Theory and Methods*, **33**, 1715-1731.
- Guttman, I. (1970), *Statistical Tolerance Regions: Classical and Bayesian*, London: Griffin.
- Hall, I. J. and Sampson, C. B. (1973). Tolerance limits for the distribution of the product and quotient of normal random variates. *Biometrics*, **29**, 109-119.
- Hinkley, D. V. (1969). On the ratio of two correlated normal random variables. *Biometrika*, **56**, 635-639.
- Krishnamoorthy, K. and Mathew, T. (2004). One-Sided tolerance limits in balanced and unbalanced one-way random models based on generalized confidence limits. *Technometrics*, **46**, 44-52.
- Liao, C. T., Lin, T. Y. and Iyer, H. K. (2005). One- and two-sided tolerance intervals for general balanced mixed models and unbalanced one-way random models. *Technometrics*, **47**, 323-335.
- Mathew, T. and Webb, D. W. (2005). Generalized p values and confidence intervals for variance components: applications to Army test and evaluation. *Technometrics*, **47**, 312–322.
- Weerahandi, S. (1993). Generalized confidence intervals. *Journal of the American Statistical Association*, **88**, 899-905.
- Weerahandi, S. (1995). *Exact Statistical Methods for Data Analysis*. New York: Springer-Verlag.
- Weerahandi, S. (2004). *Generalized Inference in Repeated Measures: Exact Methods in MANOVA and Mixed Models*. New York: Wiley.
- Yang, H., Zhang, L. and Cho, I. (2006). Evaluating parallelism testing methods in immunoassay. *Proceedings of the American Statistical Association, Biometrics Section*, 191-197.

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 $(\bar{X}_1, \bar{X}_2)' \sim N_2(\boldsymbol{\mu}, \frac{1}{n}\boldsymbol{\Sigma})$ and $\mathbf{A} \sim W_2(\boldsymbol{\Sigma}, n-1)$, as defined in the first part of Section 2. Furthermore, let \bar{x}_i denote the observed value of \bar{X}_i , $i = 1, 2$, and let \mathbf{a} denote the observed value of \mathbf{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) is used. A GPQ is a function of the random variables \mathbf{A} and $(\bar{X}_1, \bar{X}_2)'$, and the observed data \mathbf{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 \mathbf{A} and \bar{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 shall exhibit a GPQ for the entire parameter set $(\boldsymbol{\mu}, \boldsymbol{\Sigma})$. 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, Mathew and Weerahandi (2004), Mathew and Webb (2005) and Bebu and Mathew (2008).

We shall first construct a GPQ for $\boldsymbol{\Sigma}$; we shall in fact give two different constructions. Since $\mathbf{A} \sim W_2(\boldsymbol{\Sigma}, n-1)$, we have the following well known properties of the Wishart distribution.

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

where χ_s^2 denotes a central chisquare distribution with s degrees of freedom, A_{ij} and σ_{ij} denote the (ij) th elements of \mathbf{A} and $\boldsymbol{\Sigma}$, respectively, $A_{11.2} = A_{11} - A_{12}^2/A_{22}$, and $\sigma_{11.2} = \sigma_{11} - \sigma_{12}^2/\sigma_{22}$. 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

$$V_{22} = \frac{\sigma_{22}}{A_{22}} a_{22} = \frac{a_{22}}{U_{22}}$$

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

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

$$\mathbf{V} = \begin{pmatrix} V_{11} & V_{12} \\ V_{12} & V_{22} \end{pmatrix} \quad (8)$$

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

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

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

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

$$\mathbf{H}^{-1} = \mathbf{K} = \begin{pmatrix} K_{11} & K_{12} \\ K_{12} & K_{22} \end{pmatrix}. \quad (9)$$

is also a GPQ for Σ .

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

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

where

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

and \mathbf{L} is the matrix \mathbf{V} in (8) or the matrix \mathbf{K} in (9). It is now easy to verify that $(Y_1, Y_2)'$ given above

is a GPQ for $\boldsymbol{\mu}$.

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 3.1 for $\mu_1 = 40$ and $\sigma_{11} = 100$; (I) and (II) in the table refer to the GPQ construction given in (8) and (9) respectively, and the independent case corresponds to X_1 and X_2 being independent.

			$\rho=-.8$	$\rho=.2$	$\rho=0.8$	Independent case			
$n = 20$									
μ_2	σ_{22}	t	(I)	(II)	(I)	(II)	(I)	(II)	
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

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 3.2 for $\mu_1 = 10$ and $\sigma_{11} = 25$; (I) and (II) in the table refer to the GPQ construction given in (8) and (9) respectively, and the independent case corresponds to X_1 and X_2 being independent.

			$\rho=-.8$		$\rho=.2$		$\rho=0.8$		Independent case
			$n = 20$						
μ_2	σ_{22}	t	(I)	(II)	(I)	(II)	(I)	(II)	
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

Table 3. Upper tolerance limits for the example with $1 - \alpha = 0.95$; the entries are the mean (SD) based on 1000 repetitions.

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