Reliability Stress-Strength Models for Dependent Observations With Applications in Clinical Trials

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SUMMARY

We consider the applications of stress-strength models in studies involving clinical trials. When studying the effects and side effects of certain procedures (treatments), it is often the case that observations are correlated due to subject effect, repeated measurements and observing many characteristics simultaneously. We develop maximum likelihood estimator (MLE) and uniform minimum variance unbiased estimator (UMVUE) of the reliability which in clinical trial studies could be considered as the chances of increased side effects due to a particular procedure compared to another. The results developed apply to both univariate and multivariate situations. Also, for the univariate situations we develop simple to use lower confidence bounds for the reliability. Further, we consider the cases when both stress and strength constitute time dependent processes. We define the future reliability and obtain methods of constructing lower confidence bounds for this reliability. Finally, we conduct simulation studies to evaluate all the procedures developed and also to compare the MLE and the UMVUE.

Key Words: Stress-Strength Models; Reliability; Time Series; Confidence Intervals for $P(x < y)$; UMVUE; MLE

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1. Introduction:

Critically ill patients often require endotracheal intubation and mechanical ventilation. Endotracheal intubation is a procedure by which a tube that is attached to a ventilation machine is inserted into the trachea through the mouth of the patient, allowing oxygen to pass through the airway. The presence of the tube interferes with the mucociliary transport system – the normal mechanism by which respiratory tract secretions are removed (see Gray et al. (1990)). Thus, endotracheal suctioning is an important component of the mechanically ventilated patient's care. In the presence of pulmonary disease, infection or dehydration, respiratory secretions may become thick and tenacious, making removal by suctioning difficult. Therefore, instillation of normal saline solution (5-10 ml bolus of sterile-normal-saline) into the tube prior to suctioning is a common practice. This procedure is believed to aid in eliciting a cough and also liquefy and mobilize secretions. Several studies have been conducted to study the side effects of normal saline instillation (NSI) on variables such as gas exchange, respiratory system, etc. However, Gray et al. (1990) were the first to conduct a designed clinical study. Further, Jordan and Garrett (1991) conducted another clinical trial to study the effect of NSI on variables such as heart rate, ventilatory rate and $Sa0_2$ (the amount of oxygen content in hemoglobin). The effect of NSI can be studied in two ways: (i) compare these means of the variables with NSI and without NSI or (ii) estimate the chances that a patient gets worse (or better), in terms of these variables, by using NSI compared to not using NSI. Here, we are interested in the latter. For example, we may want to assess the chances of increased heart rate due to NSI procedure compared to without NSI procedure. In other words, if y_{1i} denotes the increase in the heart rate of the ith subject with NSI procedures, and y_{2i} denotes that without the NSI procedures, then we are interested in

$$R = P[Y_{1i} > Y_{2i}]. \tag{1}$$

This probability is usually known as the "reliability" in reliability stress-strength literature (see Johnson (1988), Guttman et al. (1988), Weerahandi and Johnson (1992) and the references therein). One may compare the means but as noted by Weerahandi and Johnson (1992) 'even when comparing two treatments, it may be more informative to study the unit free quantity, R, rather than comparing the means'. Especially when y_{1i} and y_{2i} are clinical variables that help measure risk of a particular procedure, R would be of much more interest.

Much of the work in the literature has been concentrated around situations where stress and strength are independent, univariate normal random variables (also see Church

and Harris (1970), Downtown (1971), Enis and Geisser (1971)). Owen, Craswell and Hanson (1964) developed upper nonparametric confidence bounds for the reliability by relaxing the distributional assumptions. Weerahandi and Johnson (1992) provided procedures for conducting a test such as $H_0 : R \leq R_0$. In the presence of explanatory variables, methods of constructing confidence intervals for R have been discussed in Guttman et al. (1988). Most of the applications considered in the literature have been from the industrial point of view. We feel that these reliability stress-strength results can also be applied to the clinical data just as easily. However, in clinical setting, it is often the case that stress and strength would be correlated because of the subject effect, repeated measurements and observing many characteristics simultaneously. For the cases when stress and strength follow a bivariate normal distribution, Owen et al. (1964) provided confidence intervals for the reliability via the non-central t-distribution. This of course includes the paired data sets, where stress and strength are the paired observations on various subjects.

In this paper we first consider the case of bivariate normal distribution (as in Owen et al. (1964)), and provide the maximum likelihood estimator (MLE) and also give a procedure of constructing UMVUE of R. Since MLE and UMVUE are not analytically comparable, we conduct simulation studies to compare their performance in terms of bias and mean square error (mse). It will be shown that UMVUE performs better when the true probability (i.e. reliability) is roughly between 0.25 and 0.75. We also give three easy to use approximations to construct $(1-\alpha)100\%$ most accurate lower bounds for R. Simulation studies are used to evaluate and compare the approximations in terms of their coverage probabilities. Based on the evaluations, we recommend a particular approximation which maintains the coverage almost identical to the specified coverage.

Next, we study the case when y and x are p-variate normal vectors observed on same patients using two different treatments or at two different time points using a single treatment (for example: before and after the treatment). Therefore, we allow y and x to be correlated. Once again, we provide the MLE and devise a procedure to obtain the UMVUE of R. Because of the multivariate nature of the problem, we do not get a closed form for the UMVUE. However, as long as the dimension of the vector is not too high, a simple program utilizing IMSL or NAG subroutines can be used to obtain the UMVUE. We compare MLE and UMVUE via simulation studies in terms of the bias and the mse. Simulation studies once again indicate that the UMVUE performs better than the MLE when the true probability is roughly between 0.25 and 0.75. Even though MLE has a closed form, and is easier to compute than the UMVUE, the advantages of UMVUE outweigh the complexity of its usage. For a good discussion on the advantages UMVUE in similar settings see Govindarajulu (1995).

Further, we deal with the situations when both stress and strength are observed simultaneously, at time points $1, 2, \ldots, n$, and they are time dependent. Assuming that the conditional joint distribution of (y_{n+1}, x_{n+1}), given all the past observations, depends only on the current observations y_n and x_n, we develop procedures to predict the reliability at time $(n+1)$. We also provide confidence intervals for the reliability at time $(n+1)$ conditional on the past observations.

Finally, we apply the results of the first two procedures to the clinical trials data provided by Jordan and Garrett (1991). We also provide examples for the third procedure.

2. Point and interval estimation of reliability, when stress and strength follow a bivariate normal distribution.

Assume that y and x jointly follow a bivariate normal distribution given by,

$$\begin{pmatrix} y \\ x \end{pmatrix} \sim N(\mu, \Sigma) \tag{2}$$

where μ is the mean vector and Σ is the variance covariance matrix.

We are interested in the reliability, defined by

$$R_1 = P[y > x] = P[y - x > 0]. \tag{3}$$

Let $c^T = (1, -1)$, then $R = \Phi(\delta)$, where Φ denotes the standard normal distribution function and $\delta = c'\mu/(c'\Sigma c)^{1/2}$. Let $\hat{\mu}$ and $\hat{\Sigma}$ denote the MLE's of μ and Σ, based on the observations $(y_1, \cdots, y_n)$ and $(x_1, \cdots, x_n)$. Then, the maximum likelihood estimator of R is given by

$$\hat{R}_1^m = \Phi(\hat{\delta}) \tag{4}$$

where $\hat{\delta}$ is δ with μ and Σ replaced by their MLE's, i.e $\hat{\delta} = c'\hat{\mu}/(c'\hat{\Sigma}c)^{1/2}$.

Now we derive the UMVUE of R_1. Let A denote an orthogonal matrix with its first two rows given by $a_1^T = (1 - \frac{1}{n}, -\frac{1}{n}, \ldots, -\frac{1}{n})$ and $a_2^T = (\frac{1}{n}, \frac{1}{n}, \ldots, \frac{1}{n})$. Also, define $I_{(y_1 - x_1)} = 1$ if $(y_1 - x_1) > 0$ and $I_{(y_1 - x_1)} = 0$ otherwise. Then, it is easy to see that $I_{(y_1 - x_1)}$ is an unbiased estimator of R_1. Now, by making an orthogonal transformation $y = Ax$, and using Rao-Blackwell Theorem (for properties of complete sufficient statistics) and Basu's Theorem (on ancillary statistics) (see Lehman (1983)) we obtain the UMVUE of R_1 given by

$$R_1^{\text{UMVUE}} = \int_{-\infty}^{\sqrt{n-1}\hat{\delta}} f(z)dz, \tag{5}$$

where

$$f(z) = \begin{cases} b_1(1 - \frac{nz^2}{n-1})^{\frac{n}{2}-2} & \text{if } |z| < \sqrt{\frac{n-1}{n}} \\ 0 & \text{otherwise,} \end{cases}$$

with $b_1 = \Gamma(\frac{n-1}{2})/(\Gamma(\frac{1}{2})\Gamma(\frac{n-2}{2}))$.

Lower confidence bounds for R_1:

Using the standard distribution theory (see Rohatgi (1976)), it can be shown that $c^T\hat{\mu} \sim N(c^T\mu, \frac{1}{n}c^T\Sigma c)$, $n\,(c^T\Sigma c)^{-1}(c^T\hat{\Sigma}c) \sim \chi^2_{n-1}$ and hence, $\sqrt{n-1}\hat{\delta} \sim t_{n-1}(\sqrt{n}\delta)$, where $t_{n-1}(\sqrt{n}\delta)$ denotes the non-central t-distribution with $(n-1)$ d.f. and non-centrality parameter $\sqrt{n}\delta$. If we use the unbiased estimator of Σ instead of the MLE, then $\sqrt{n}\hat{\delta} \sim t_{n-1}(\sqrt{n}\delta)$, where $\hat{\delta}$ is δ with μ and Σ replaced by their unbiased estimators.

Further, since constructing a lower bound on R_1 is equivalent to constructing a lower bound on δ, we obtain a lower bound on δ. A uniformly most accurate, scale invariant, $(1-\alpha)100\%$ lower confidence bound for δ is given by the solution of

$$F_{t_{n-1}(\sqrt{n}\delta)}(\sqrt{n}\hat{\delta}) = 1-\alpha, \tag{6}$$

where $F_{t_{n-1}(\sqrt{n}\delta)}(\cdot)$ denotes the distribution function of non-central t-distribution with $(n-1)$ d.f. and non-centrality parameter $\sqrt{n}\delta$. Note that in (6) we have used the unbiased estimator of Σ instead of MLE. If one uses MLE, one needs to adjust the constant accordingly.

Even though, solution of equation (6) is computationally tenable, a closed form approximation that is simple to use and satisfies the necessary coverage properties is desirable in practice. Therefore, we provide three different closed form approximations and obtain the approximate lower bound in each case.

Approximate lower confidence bounds:

(i) Using a well known approximation of a non-central t-distribution by a standard normal distribution (see Johnson and Kotz (1970)), we provide an approximate lower bound for δ given by

$$L_{A_1}(\hat{\delta}) = \hat{\delta}b_2 - z_\alpha\frac{1}{\sqrt{n}}\left[1+\frac{n}{n-1}\hat{\delta}^2 b_3\right]^{\frac{1}{2}} \tag{7}$$

where $b_2 = \sqrt{\frac{2}{n-1}}(\Gamma(\frac{n}{2})/\Gamma(\frac{n-1}{2}))$, $b_3 = (n-1)[1-\frac{2}{n-1}(\Gamma(\frac{n}{2})/\Gamma(\frac{n-1}{2}))^2]$, and $z_\alpha = \Phi^{-1}(1-\alpha)$. If we further approximate this using $\sqrt{2}(\Gamma(\frac{n}{2})/\Gamma(\frac{n-1}{2})) = \sqrt{n-1}$, our approximation of non-central t by standard normal reduces to the one used in Guttman et al. (1988, Section 2). However, we will use the lower bound in (7) as it is not difficult to use.

(ii) Another approximation is of the form

$$\left[\frac{1}{b_4}\sinh^{-1}\left(\frac{b_4\sqrt{n}\hat{\delta}}{b_5}\right) - \sinh^{-1}\left(\frac{b_4 E(\sqrt{n}\hat{\delta})}{b_5}\right)\right] \dot{\sim} N(0,1),$$

and hence the lower bound is given by

$$L_{A_2}(\hat{\delta}) = \left[\sinh\left(\frac{1}{b_4}\sinh^{-1}\left(\frac{b_4\sqrt{n}\hat{\delta}}{b_5}\right)\right) - z_\alpha\right] b_6, \tag{8}$$

where $b_4 = \Gamma(\frac{n-1}{2})\{2[(n-3)\Gamma^2(\frac{n-2}{2}) - 1]^{-1}\}^{\frac{1}{2}}$, $b_5 = \sqrt{(n-1)/(n-3)}$ and $b_6 = \frac{b_5}{b_4}\Gamma(\frac{n-1}{2})\{\Gamma(\frac{n-2}{2})\sqrt{2n(n-1)}\}^{-1}$.

(iii) A further approximation of the approximation in (ii) can be made to obtain a much simpler lower bound given by

$$L_{A_3}(\hat{\delta}) = \frac{1}{\sqrt{n}}\left[\sqrt{n-1}\sinh^{-1}\left(\frac{\sqrt{n}\hat{\delta}}{\sqrt{n-1}}\right) - z_\alpha\right]. \tag{9}$$

We should note that computation of the left hand side of the equation in (6) can be done via numerical integration without too much difficulty (as noted also by Guttman et al. (1988)). However, the approximations provide simple lower bounds that can be calculated easily and one only needs the standard normal distribution tables to compute the bounds. As it is clear that there is no direct analytical comparison between these three approximations, we conduct a simulation study and evaluate these approximations in terms of the coverage probability in the current setting.

Simulation Studies:

We generated random samples of sizes n=10,15,20,25,30, and 35 from normal distribution with various combinations of means and variances. For each simulation we computed the MLE, the UMVUE, and their respective biases. We also calculated the coverage probabilities using: equation in (6), approximation (i) , approximation (ii), and approximation (iii). At the end of 20,000 simulations, we find the averages and the standard deviations of these quantities. Further, we calculate the mean square error (mse) for both MLE and UMVUE. In Table I, we report the true probability, MLE, UMVUE. Biases, Standard deviations and the root mean square errors of MLE and UMVUE are also given in the same table. It is apparent from the results that UMVUE does better than MLE if the true probability is neither low or nor high (i.e. if true probability is roughly between 0.25 and 0.75), otherwise MLE seems to do better. This is not very surprising because, for instance, when the true probability is very low (or high), even though MLE is biased, the bias will not contribute a great deal to the mse. Whereas, when the true probability is neither high nor low, the bias plays an important role and hence UMVUE performs better in terms of bias and mse. When an unbiased estimator is of interest, one should choose UMVUE

regardless of the true probability because when it does have more mse than that of the MLE, the mse is marginally more. However, if one prefers to use the estimate only based on smaller mse, it helps if one has some knowledge of the true probability (in terms of low, medium, high). In practice, one can calculate $\hat{\delta}$ and if this value is a high positive (or high negative) number, that indicates that the true probability is probably high (or low). This knowledge can be utilized in deciding between the two estimators. In clinical studies, usually, the cases that are of most interest are when the true probabilities are neither too high nor too low. As for the ease of use, certainly MLE is easier to calculate than the UMVUE, however the calculation of the UMVUE in this case is not at all difficult.

INSERT TABLE I HERE

Further, the true coverage (confidence level) and the simulated coverages obtained by the four methods mentioned above are reported in Table II. From this, it is also clear that the simulated coverages obtained using (6) and using approximation (i) are very close to each other and to the true coverage. Approximation (ii) seems to be very conservative in the sense of having lot more coverage than the desired confidence. In other words, the lower bound obtained using this approximation is much smaller than the true lower bound, resulting in a wider interval than necessary. Approximation (iii) does very badly until the true probability gets to be around 0.25. And as the true probability increases beyond 0.75, this approximation turns out to be very conservative. Therefore, the practitioner can use either (6) or the approximation (i). We recommend the use of approximation (i), as it is very simple to use and needs only the knowledge of standard normal percentile points.

INSERT TABLE II HERE

3. Estimation of reliability for repeated multivariate observations

Let y_i and x_i denote the observation vectors (p-vectors) made on subject i at periods 1 and 2 respectively. y_i and x_i could also denote the observations on the same patients using two different treatments. Thus, y_i and x_i could be correlated. Assume that $y \sim N_1(\mu_1, \Sigma_1)$ and $x \sim N_1(\mu_2, \Sigma_2)$ and y_i and x_i may be correlated. Therefore, reliability is given by

$$R_2 = P[y > x + r] = P[y - x > r]. \tag{10}$$

Here x and y represents the p-variate random vector and r is a p-variate known quantity. The event $[y > x]$ represents that each component of y (i.e y_i) is greater than the corresponding component of x (i.e x_i). Without loss of generality we can assume that $r = 0$. Also, let $d = y - x$ and $d_i = y_i - x_i$, $i = 1, \ldots, n$, then $d \sim N_p(\mu_d, \Sigma_d)$, and $R_2 = P[d > 0]$.

Let $\hat{\mu}_d = \bar{d}$ and $\hat{\Sigma}_d = \frac{1}{n}\sum_{i=1}^{n}(d_i - \bar{d})(d_i - \bar{d})^T$ be the usual maximum likelihood estimators of μ_d and Σ_d. Then, the MLE of R_2 is given by

$$\hat{R}_2^m = P[d > 0]_{\mu_d = \hat{\mu}_d, \Sigma_d = \hat{\Sigma}_d}. \tag{11}$$

It is known (see Anderson (1984)) that $(\bar{d}, S_d)$ are the complete sufficient statistics for (μ_d, Σ_d), where $S_d = \frac{n}{n-1}\hat{\Sigma}_d$. Now, let $I_{(d_1>0)}$ be an indicator function such that $I_{(d_1>0)} = 1$, if $d_1 > 0$ and $= 0$ otherwise. Then using an orthogonal transformation, Rao-Blackwell Theorem and Basu's Theorem, we show (see Appendix for the sketch of proof) that, the UMVUE of R_2 is given by

$$\hat{R}_2^{\text{UMVUE}} = \int\int_{[d_1>0]}\int \; f(D)dD \tag{12}$$

where

$$D = \sqrt{\frac{n}{n-1}}\; S_d^{-\frac{1}{2}}\; (d_1 - \bar{d}),$$

$$f(D) = \begin{cases} b_7\,(1 - D^T D)^{\frac{n-p-3}{2}} & \text{if } 0 \le D^T D \le 1 \\ 0 & \text{otherwise,} \end{cases}$$

and $b_7 = \Gamma(\frac{n-1}{2})\left[\pi^{P/2} \cdot \Gamma(\frac{n-p-1}{2})\right]^{-1}$.

Obtaining UMVUE by (12) has to be done via numerical integration. A closed form estimate is not possible. However, since it has the desirable properties, namely, having the least variance among all the unbiased estimators, it is worth pursuing. We now conduct simulation studies to compare MLE and UMVUE of R_2.

Simulation Studies:

We generated random samples of sizes n=15,20,30, and 40, from bivariate normal distribution with several combinations of means, variances, and covariances. For each simulation, we calculated the MLE and UMVUE of R_2, and their respective biases. At the end of 20,000 simulations, average bias, standard deviation and root mean square error for both the estimators are calculated. These are reported in Table III. As in the univariate case, once again the UMVUE seems to perform better than the MLE when the true probability is roughly between 0.25 and 0.75. However, there are a few cases when UMVUE seems to do better even when the true probability is about 0.11. It should also be noted that the difference in the mse of the two estimators is quite small once the sample size is large. Therefore, for large sample sizes MLE is preferred because of the simplicity in the

use. And for small to moderate sample sizes one has to choose either one based on whether one wants an unbiased estimate. We have not reported the actual values of the means, the standard deviations and correlations used in our simulations. Many combinations were chosen to obtain the true probabilities. Our main interest, however, is in studying the properties of MLE and UMVUE in relation to the true probability. Since, we are dealing with a bivariate normal distribution, it is clear that R_2 would be around 0.25 if the means are zeros and the correlation is zero (as the mass would be equally distributed in all four quadrants). Also, if the means are positive and the correlation is a high positive, much of the mass will be located in the first quadrant resulting in high true probability (i.e. R_2). In practice, sample information available on means and correlations could be used in deciding whether to use MLE or UMVUE. Once again if one is interested in an estimator simple to calculate and that does quite well, MLE is the ideal choice. The computation of UMVUE for the bivariate case is quite simple, however, for higher dimensions it could take some time to calculate it, as it would involve integration of higher dimensions. With some programming knowledge one can calculate the UMVUE via subroutines from IMSL or NAG.

INSERT TABLE III HERE

4. Prediction interval for the future reliability when the observations on stress and strength are time dependent.

Let $(y_1, x_1), \cdots, (y_n, x_n)$ denote the observations on stress and strength at time points $1, 2, \cdots, n$, and are time dependent (see Section 5.2 for examples). We assume that y and x are independent, and that the conditional distribution of (y_{n+1}, x_{n+1}) given $y(n) = (y_1, \cdots, y_n)$ and $x(n) = (x_1, \cdots, x_n)$ depends only on y_n and x_n. This assumption basically implies that there is a first order correlation (i.e. autoregression of order one) for both the processes $\{x\}$ and $\{y\}$. We provide several examples (Section 5.2) to show that this assumption is satisfied easily. This assumption can be relaxed so that the conditional distribution depends on (y_{n-1}, y_n) and (x_{n-1}, x_n), if the autoregression is of order two. Now, assuming that the observations have normal distribution, the future reliability at time $(n+1)$ given the past observations up to time n, is given by

$$\begin{aligned} R_3(y_n, x_n) &= P\left[y_{n+1} > x_{n+1} \middle| y(n), x(n)\right] \\ &= \Phi[\delta(y_n, x_n, \theta)], \end{aligned} \tag{13}$$

where θ is a vector of all the parameters, and δ is some function of y_n, x_n and θ.

Now, assume that there is enough information available, other than (y_n, x_n), to estimate the parameter θ and denote that estimator by $\hat{\theta}$ (see Kulkarni and Kushary (1991)).

This assumption is mostly required for the analytical derivations. We need this to obtain the conditional distribution of $\hat{\delta} = \delta(y_n, x_n, \hat{\theta})$ conditional on y_n and x_n, which is a crucial factor in constructing a lower bound on δ. However, in practice one can use y_n and x_n also in the estimation of θ as they contribute highly to the prediction of y_{n+1} and x_{n+1}. This should result in better estimates and hence yielding more precise results.

Since reliability is conditional on y_n and x_n, we study the distribution of $\hat{\delta} = \delta(y_n, x_n, \hat{\theta})$ conditional on y_n and x_n. Now, using Taylor Series expansion of $\hat{\delta}$ as a function of $\hat{\theta}$, we have

$$\delta(y_n, x_n, \hat{\theta}) = \delta(y_n, x_n, \theta) + (\delta'(y_n, x_n, \theta))^T(\hat{\theta} - \theta) \tag{14}$$

where δ' denotes the derivative of δ w.r.t. θ.

Suppose there exists $\hat{\theta}$ such that

$$(\hat{\theta} - \theta) \dot{\sim} N(0, \Sigma_n(\theta)). \tag{15}$$

Then, the conditional distribution of $\hat{\delta}$ given x_n and y_n is given by

$$\delta(y_n, x_n, \hat{\theta}) \dot{\sim} N[\delta(y_n, x_n, \theta), \quad \sigma_n^2(\theta)] \tag{16}$$

where $\sigma_n^2(\theta) = [\delta'(y_n, x_n, \theta)]^T \Sigma_n(\theta)[\delta'(y_n, x_n, \theta)]$. Therefore, an $(1-\alpha)100\%$ lower prediction bound for $\delta(y_n, x_n, \theta)$, given y_n and x_n, is

$$L_n = \delta(y_n, x_n, \hat{\theta}) - z_\alpha \sigma_n(\hat{\theta}), \tag{17}$$

where $\sigma_n(\hat{\theta})$ is $\sigma_n(\theta)$ with θ replaced by $\hat{\theta}$ and is a consistent estimator of $\sigma_n(\theta)$.

5. Applications

5.1 Applications of procedures developed in Sections 2 and 3.

We consider the data in Jordan et al. (1991), part of which is reproduced here in Table IV. They selected 10 critically ill patients that needed mechanical ventilation. Both the procedures (i.e. with NSI and without NSI) were administered on the same patients. Observations on heart rate, and ventilatory rate were made among other things. They recorded the measurements just prior to administering a procedure, right after administration and, 10 minutes after the procedure was administered. However, the measurements that are really of interest are prior to administration and right after administration, because as more time is given patient's conditions usually return to normal. After the first

administration, they allowed at least 90 minutes before administering the second procedure. The order of assignment was random. Another important variable measured was the amount of secretions removed.

INSERT TABLE IV HERE

First, we consider estimating the chances of 'with NSI' being more effective in removing the secretions than 'without NSI' procedure. While the time allowed between the administration of the two procedures may have eliminated any carryover effects (from the previous procedure to the latter procedure), the patient effect is not removed. Therefore, the measurements made by the two procedures are paired observations. Let y and x denote the amount of secretions removed with and without NSI respectively. Then, for this data, $\hat{R}_1^m = 0.99686$ and $\hat{R}_1^{UMVUE} = 0.99988$. Since, both MLE and UMVUE are very high, difference between them seems negligible. Therefore, one can choose either as their point estimate. Further, we construct a 95% most accurate lower confidence bound for R_1 using all four methods. These are reported in Table V, along with the results for other two variables of interest, namely, ventilatory rate and heart rate. However, for these variables, we define y =(post administration measurement with NSI − pre administration measurement with NSI), and similarly x is defined for the without NSI procedure.

INSERT TABLE V HERE

Next, since all the variables are measured simultaneously on each subject, they constitute a multivariable observation vector. Therefore, it is of interest to estimate the chances of patient being worse off with NSI compared to without NSI. It is known from the past studies, and clear in this study as well, that the amount of secretions removed using NSI is significantly more than without NSI. This is the main reason to administer NSI. Therefore, we will not include this variable in our multivariate study. The main purpose of the study is to see if there are increased chances of side effects (due to NSI) such as higher heart rate and ventilatory rates among other things. Therefore, we only consider two variables heart rate and ventilatory rate in our multivariate vector. Then, using the results of Section 3, estimates of reliability are given by $\hat{R}_2^m$= 0.41820, $\hat{R}_2^{\text{UMVUE}} = 0.40864$. Therefore, there is a little over 40% chance that With NSI procedure results in elevated heart rate and ventilatory rate. In practice, just knowing the chance of increased heart rate and ventilatory rate may not be very informative as it does not say much about the magnitude of increase. If a physician determines that an increase of 'a' in the heart rate and an increase of 'b' in ventilatory rate might be dangerous, then one can calcuate the estimators according to that. Here we have simply calculated the chance of increased heart and ventilatory rate (i.e. a=b=0).

5.2 Examples for procedure in Section 4.

First, we give several models that satisfy the conditional distribution assumption made in Section 4.

Example 1: $AR(1)$ model.

Suppose y_n and x_n follow a stationary first order autoregressive model given by

$$y_n = \rho_1 y_{n-1} + u_n$$

and

$$x_n = \rho_2 x_{n-1} + v_n \tag{20}$$

where u_n and v_n are independent normal r.v.'s with means 0 and variances σ_1^2 and σ_2^2. It is easy to see that the conditional distribution of (y_{n+1}, x_{n+1}), given $(y(n), x(n))$ depends only on (y_n, x_n) and of course the parameters.

Example 2: Regression model with Autoregressive errors.

Consider the usual regression model with errors following a first order autoregression, for both y and x, given by

$$y_n = \beta_{01} + \beta_{11} C_{1n} + u_n, \quad u_n = \rho_1 u_{n-1} + \epsilon_{1n}$$

and

$$x_n = \beta_{02} + \beta_{12} C_{2n} + v_n, \quad v_n = \rho_2 v_{n-1} + \epsilon_{2n} \tag{21}$$

where ϵ_{1n} and ϵ_{2n} are independent normal random variables with means 0 and variances σ_1^2 and σ_2^2. This model also satisfies the condition that the conditional distribution of observations at time $n+1$ depends only on the observations at time n.

Example 3: First order autoregressive model with regressors.

This model is similar to the model in Example 2, however one is not a simple reparametrization of the other (see Kulkarni (1987)).

$$y_n = \rho_1 y_{n-1} + \beta_{11} C_{1n} + u_n$$

and

$$x_n = \rho_2 x_{n-1} + \beta_{12} C_{2n} + v_n, \tag{22}$$

where u_n and v_n are independent normal random variables with means 0 and variances σ_1^2 and σ_1^2. It can be verified that assumption is satisfied for this model as well.

Next, we consider the model in (22) and illustrate the results of Section 4. Note, however, that similar results can be obtained for other models as well. For a good discussion of these models and related models see Basawa et al. (1985) and Kulkarni (1987). For simplicity, assume that σ_1^2 and σ_2^2 are known and let $c_{1n} = c_{2n}$. Then,

$$\begin{aligned}\delta(y_n, x_n, \hat{\theta}) &= (\hat{\delta}_1 y_n + \hat{\beta}_1 c_{n+1} - \hat{\delta}_2 x_n - \hat{\beta}_2 c_{n+1})/\sqrt{\sigma_1^2 + \sigma_2^2} \\ &= \delta(y_n, x_n, \hat{\theta}) + m^T(\hat{\theta} - \theta)/\sqrt{\sigma_1^2 + \sigma_2^2}\end{aligned} \tag{23}$$

where $m^T = (-y_n, -c_{n+1}, -x_n, -c_{n+1})$, $\theta^T = (\delta, \beta_1, \delta_2, \beta_2) = (\theta_1^T, \theta_2^T)$, with $\theta_i^T = (\delta_i, \beta_i)$ and $\hat{\theta}_i$ is the MLE of θ obtained using $(y_1, x_1), \cdots, (y_{n-1}, x_{n-1})$. Notice that in (23) we did not have to use the Taylor series expansion as we could simply rewrite it in that form. If $c_{1n} \neq c_{2n}$, then we would have to use the Taylor Series expansion. Also, assumption of σ_1^2 and σ_2^2 being known is for simplicity. When they are unknown, we incorporate these also in θ and obtain the asymptotic distribution of $\sqrt{n-1}(\hat{\theta} - \theta)$, as only $(n-1)$ observations are used in the estimation (see Kulkarni and Kushary (1991)). It can be shown using results in Kulkarni (1987) that $(\hat{\theta}_i - \theta) \dot{\sim} N(0, \frac{1}{n-1}\Sigma_{in}(\theta_i))$, $i = 1, 2$, where

$$\Sigma_{in}(\theta_i) = \begin{bmatrix} \frac{\sigma_i^2}{1-\delta_2^2} & \sigma_{i,12} \\ \sigma_{i,12} & d\sigma_i^2 \end{bmatrix}$$

with $d = \frac{1}{n-1}\sum_{i=1}^{n-1} c_i^2$, $\sigma_{1,12} = \frac{1}{n-1}\sum_{i=1}^{n-1} y_{i-1}c_i$, and $\sigma_{2,12} = \frac{1}{n-i}\sum_{i=1}^{n-1} x_{i-1}c_i$. $\Sigma_{i=1}(\theta_i)$ is estimated consistently by replacing δ_i^2 by $\hat{\delta}_i^2$. Further, $(\hat{\delta} - \delta) \dot{\sim} N(\delta, \Sigma_n(\theta))$, where

$$\Sigma_n(\theta) = \begin{bmatrix} \Sigma_{1n}(\theta) & 0 \\ 0 & \Sigma_{2n}(\theta) \end{bmatrix}.$$

Using these results the conditional distribution of $\delta(y_n, x_n, \hat{\delta})$, conditional on (y_n, x_n), is

$$\delta(y_n, x_n, \hat{\delta}) \dot{\sim} N(\delta(y_n, x_n, \delta), \sigma_n^2(\theta)),$$

where $\sigma_n^2(\theta) = \frac{1}{n-1} m^T \Sigma_n(\theta) m$ and m is as in (23). Also, estimated variance of $\delta(y_n, x_n, \hat{\theta}_n)$ is given by $\sigma_n^2(\hat{\theta})$. As noted earlier, in practice one can use y_n and x_n also in estimating θ and replace $(n-1)$ in all the expressions above by n. This should result in more precise results.

At this point we should note that, even though a medical data set that would fit into our models is not presented here, the models described above are fairly common in medical research (see Diggle (1992)) and have broad applications.

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Appendix:

A sketch of the proof of the UMVUE for the p-variate normal case:

Let $x_1 \sim N_p(\mu_1, \Sigma_1)$ and $x_2 \sim N_p(\mu_2, \Sigma_2)$ and they may be are correlated. Consider, $p = P(x_1 - x_2 > 0) = P(y > 0)$, where $y = x_1 - x_2$. Now onword, we will concentrate on the random variable y only. Let $y \sim N_p(\mu, \Sigma)$ and let $\hat{\mu} = \bar{y} \quad \hat{\Sigma} = \frac{1}{n}\sum_{i=1}^{n}(y_i - \bar{y})(y_i - \bar{y})^T$ denote the maximum likelihood estimators. Hence MLE of p is $\hat{p} = P(y > 0)|_{\mu=\hat{\mu},\Sigma=\hat{\Sigma}}$. Let $\delta(y_1) = 1$, if $y_1 > 0$ and 0 otherwise. Since $(\bar{y}, S)$ are the complete sufficient statistics, where $S = \frac{n}{(n-1)}\hat{\Sigma}$, using Rao-Blackwell theorem $E(\delta(y_1)|\bar{y}, S)$ is the UMVUE. Therefore, we need to find the distribution of y_1 given $(\bar{y}, S)$.

Joint distribution of $y_1, \cdots, y_n$ is

$$f(y_1, \cdots, y_n) = \text{ Const } \cdot |\Sigma|^{-\frac{n}{2}} - \frac{1}{2}tr\left\{\Sigma^{-1}\sum_{i=1}^{n}(y_i - \mu)(y_i - \mu)^T\right\}.$$

Consider the joint distribution of $z_1, \cdots, z_n$ where $z_i = \sum_{j=1}^{n} C_{ij}y_j$, and $C_i^T = (C_{il}, \cdots, C_{in})$ is the ith row of an orthogonal matrix whose with first and second rows are given by $C_1^T = \frac{1}{\sqrt{n}}1^T$ and $C_2^T = c(1 - \frac{1}{n}, -\frac{1}{n}, \cdots, -\frac{1}{n})$ respectively. Here, c is a normalizing constant given by $c = (1 - \frac{1}{n})^{-\frac{1}{2}}$. Using Theorem 3.3.1 of Anderson (1984), it can be shown that $z_1, \cdots, z_n$ are independent. Since, $\sum_{i=1}^{n}(y_i - \mu)(y_i - \mu)^T = \sum_{i=2}^{n} z_i z_i^T + (z_1 - \sqrt{n}\mu)(z_1 - \sqrt{n}\mu)^T$, we have $\sum_{i=1}^{n}(y_i - \bar{y})(y_i - \bar{y})^T = \sum_{i=2}^{n} z_i z_i^T$. Thus,

$$
\begin{aligned}
S &= \sum_{i=3}^{n} z_i z_i^T + z_2 z_2^T \\
&= \sum_{i=3}^{n} z_i z_i^T + c^2 (y_1 - \bar{y})(y_1 - \bar{y})^T \\
&= S_{-1} + c^2 (y_1 - \bar{y})(y_1 - \bar{y})^T .
\end{aligned}
$$

Now the joint distribution of $z_1, \cdots, z_n$ is

$$
f(z_1, z_2, \cdots z_n) = \text{ Const} \cdot \exp\left\{ -\frac{1}{2} tr\left[\Sigma^{-1} \left[\sum_{i=2}^{n} z_i z_i^T + (z_1 - \sqrt{n}\mu)(z_1 \sqrt{n}\mu)^T \right] \right] \right\}.
$$

Hence, z_1, z_2, S_{-1} are independent with $z_1 \sim N(\sqrt{n}\mu, \Sigma)$, $z_2 \sim N(0, \Sigma)$, and $S_{-1} \sim W(n-2, \Sigma)$, where W denotes the Wishart distribution. Now, the joint distribution of S_{-1} and z_2 is

$$
\begin{aligned}
f(S_{-1}, z_2) = \text{ Const } \cdot |\Sigma|^{-\frac{(n-2)}{2}} |S_{-1}|^{(n-p-3)/2} \exp\{ -\tfrac{1}{2} tr(\Sigma^{-1} S_{-1}) \} |\Sigma|^{-\frac{1}{2}} \\
\exp\left\{ -\tfrac{1}{2} tr[\Sigma^{-1} z_2 z_2^T] \right\}.
\end{aligned}
$$

From this, we find the joint distribution of $S = S_{-1} + z_2 z_2^T$ and z_2 given by

$$
f(S, z_2) = \text{ Const } \cdot |\Sigma|^{-\frac{(n-1)}{2}} |S - z_2 z_2^T|^{(n-p-3)/2} \exp\left\{ -\frac{1}{2} tr[\Sigma^{-1} S] \right\}
$$

where $|S - z_2 z_2^T|$ is positive definite.

Further, the joint distribution of S and $D = S^{-\frac{1}{2}} z_2$ is

$$
\begin{aligned}
f(S, D) &= \text{ Const } \cdot |\Sigma|^{-\frac{(n-1)}{2}} \left[|S|(I - DD^T) \right]^{(n-p-3)/2} \exp\left\{ -\frac{1}{2} tr(\Sigma^{-1} S) \right\} |S|^{\frac{1}{2}} \\
&= \text{ Const } \cdot |\Sigma|^{-\frac{(n-1)}{2}} |S|^{\frac{(n-p-2)}{2}} \exp\left\{ -\frac{1}{2} tr(\Sigma^{-1} S) \right\} (1 - D^T D)^{(n-p-3)/2},
\end{aligned}
$$

implying that D is also independent of S. It can be seen that,

$$
f(D) = k(1 - D^T D)^{(n-p-3)/2} \quad , \quad 0 \le D^T D \le 1,
$$

where $k = \Gamma(\frac{n-1}{2})[\pi^{p/2} \Gamma(\frac{n-p-1}{2})]^{-1}$.

Therefore, the distribution of D is free of the parameters. Since, the UMVUE of p is $\hat{p} = P(y_1 > 0 | \bar{y}, S)$ but the distribution of $S^{-\frac{1}{2}}(y_1 - \bar{y})$ is independent of parameters, by Basu's theorem, conditional distribution of $S^{-\frac{1}{2}}(y_1 - \bar{y})$ is independent of $\bar{y}$ and S.

Hence,

$$
\hat{p} = \int \cdots \int_{y_1 > 0} f(D) dD.
$$

Table 1. Simulations results on mle (M) and UMVUE (U) with n=10

True Probability		Estimate	Bias	Std. dev.	Root mse
0.01222	M	0.01492	0.00270	0.02037	0.02054
	U	0.01225	0.00003	0.02190	0.02190
0.02275	M	0.02454	0.00179	0.02847	0.02853
	U	0.02241	-0.00034	0.03168	0.03168
0.04006	M	0.04088	0.00082	0.04071	0.04072
	U	0.04052	0.00046	0.04593	0.04593
0.06681	M	0.06394	-0.00287	0.05499	0.05506
	U	0.06635	-0.00046	0.06165	0.06165
0.10565	M	0.10006	-0.00559	0.07221	0.07243
	U	0.10636	0.00071	0.07898	0.07898
0.15866	M	0.14919	-0.00946	0.09077	0.09126
	U	0.15910	0.00045	0.09581	0.09581
0.22663	M	0.21463	-0.01199	0.10911	0.10977
	U	0.22655	-0.00007	0.11047	0.11047
0.30854	M	0.29653	-0.01201	0.12424	0.12482
	U	0.30759	-0.00095	0.12086	0.12087
0.40129	M	0.39639	-0.00490	0.13521	0.13530
	U	0.40294	0.00164	0.12775	0.12776
0.50000	M	0.50096	0.00096	0.13893	0.13893
	U	0.50093	0.00093	0.12989	0.12989
0.59871	M	0.60419	0.00548	0.13550	0.13562
	U	0.59760	-0.00111	0.12807	0.12807
0.69146	M	0.70348	0.01202	0.12382	0.12440
	U	0.69242	0.00096	0.12049	0.12049
0.77337	M	0.78529	0.01192	0.10935	0.11000
	U	0.77337	0.00000	0.11064	0.11064
0.84134	M	0.85218	0.01084	0.09047	0.09112
	U	0.84238	0.00104	0.09564	0.09565
0.89435	M	0.90059	0.00624	0.07172	0.07199
	U	0.89435	0.00000	0.07857	0.07857
0.93319	M	0.93613	0.00293	0.05462	0.05470
	U	0.93370	0.00051	0.06121	0.06122
0.95994	M	0.95970	-0.00024	0.04000	0.04000
	U	0.96014	0.00020	0.04512	0.04512
0.97725	M	0.97515	-0.00210	0.02903	0.02911
	U	0.97721	-0.00004	0.03233	0.03233
0.98778	M	0.98508	-0.00269	0.02026	0.02044
	U	0.98778	0.00001	0.02179	0.02179
0.99379	M	0.99133	-0.00246	0.01349	0.01371
	U	0.99391	0.00012	0.01362	0.01362

Table 2. Simulated coverages with true confidence 0.95.

True Probability	Using (6)	Aprx.(i)	Aprx.(ii)	Aprx.(iii)
n=10				
0.00620	0.95000	0.94745	1.00000	0.01855
0.01222	0.94810	0.94425	1.00000	0.07605
0.02275	0.95190	0.94965	1.00000	0.24055
0.04006	0.94960	0.94745	1.00000	0.50180
0.06681	0.94965	0.94850	1.00000	0.73925
0.10565	0.95075	0.95000	0.99985	0.87680
0.15866	0.94980	0.94955	0.99850	0.93240
0.22633	0.95215	0.95215	0.99355	0.95030
0.30854	0.94880	0.94880	0.98155	0.94845
0.40129	0.95065	0.95070	0.97485	0.94560
0.50000	0.94780	0.94830	0.99150	0.94245
0.59871	0.94860	0.94975	0.99915	0.95055
0.69146	0.94930	0.95105	0.99990	0.96835
0.77337	0.94970	0.95295	0.99995	0.98215
0.84134	0.95440	0.95790	1.00000	0.99540
0.89435	0.94920	0.95375	1.00000	0.99820
0.93319	0.95005	0.95485	1.00000	0.99970
0.95994	0.95435	0.95980	1.00000	0.99995
0.97725	0.94885	0.95685	1.00000	1.00000
0.98778	0.94880	0.95625	1.00000	1.00000
0.99379	0.94630	0.95285	1.00000	1.00000

Table 3. Simulation Results for Bivariate Normal with n=15

True Probability	Estimators	Bias	St. Dev	Root MSE
0.0520	M	-0.0026	0.0353	0.0354
	U	-0.0002	0.0376	0.0376
0.1024	M	0.0002	0.0446	0.0446
	U	0.0002	0.0433	0.0433
0.1586	M	-0.0069	0.0748	0.0751
	U	0.0002	0.0776	0.0776
0.2015	M	0.0003	0.0769	0.0769
	U	0.0002	0.0743	0.0743
0.2500	M	-0.0008	0.0893	0.0893
	U	-0.0008	0.0861	0.0861
0.3500	M	0.0071	0.0969	0.0972
	U	-0.0006	0.0930	0.0930
0.4421	M	0.0116	0.1003	0.1010
	U	-0.0013	0.0974	0.0974
0.5075	M	0.0123	0.1053	0.1060
	U	-0.0003	0.1027	0.1027
0.5442	M	0.0126	0.1061	0.1068
	U	0.0010	0.1033	0.1033
0.6603	M	0.0075	0.1004	0.1007
	U	-0.0011	0.0988	0.0988
0.7079	M	0.0138	0.0904	0.0915
	U	0.0001	0.0933	0.0933
0.7525	M	0.0121	0.0849	0.0857
	U	0.0003	0.0887	0.0887
0.8105	M	0.0085	0.0797	0.0802
	U	-0.0001	0.0829	0.0829
0.8674	M	0.0039	0.0609	0.0610
	U	-0.0003	0.0662	0.0662
0.9048	M	0.0016	0.0512	0.0513
	U	0.0001	0.0559	0.0560

Table 4. Data from Jordan and Garrett (1992)

Patient	Variable	Time	With NSI	Without NSI
1	Heart rate	Pre	120	122
		Post	119	126
	Vent. rate	Pre	38	42
		Post	44	50
	Secretions	Post	5	0.5
2	Heart rate	Pre	81	92
		Post	111	121
	Vent. rate	Pre	18	14
		Post	20	20
	Secretions	Post	5.0	1.0
3	Heart rate	Pre	120	120
		Post	125	122
	Vent. rate	Pre	45	50
		Post	52	60
	Secretions	Post	3.5	2.0
4	Heart rate	Pre	84	78
		Post	89	92
	Vent. rate	Pre	6	8
		Post	14	12
	Secretions	Post	3.0	1.5
5	Heart rate	Pre	132	127
		Post	144	135
	Vent. rate	Pre	43	42
		Post	64	56
	Secretions	Post	4.0	2.0
6	Heart rate	Pre	121	118
		Post	140	126
	Vent. rate	Pre	7	8
		Post	14	9
	Secretions	Post	6	4.0
7	Heart rate	Pre	135	126
		Post	146	130
	Vent. rate	Pre	43	42
		Post	64	56
	Secretions	Post	3.5	1.0
8	Heart rate	Pre	97	95
		Post	103	102
	Vent. rate	Pre	10	14
		Post	19	18
	Secretions	Post	5.0	1.5
9	Heart rate	Pre	85	82
		Post	99	94
	Vent. rate	Pre	24	21
		Post	42	33
	Secretions	Post	4.0	0.5
10	Heart rate	Pre	113	116
		Post	129	125
	Vent. rate	Pre	14	16
		Post	25	22
	Secretions	Post	3.5	1.0

Table 5. Estimates and lower bounds for the data.

Variable	MLE	UMVUE	L-Using (6)	L_{A_1}	L_{A_2}	L_{A_3}
Secretions	0.99686	0.99988	1.43813	1.40315	0.37364	0.96930
Heart Rate	0.62184	0.61194	-0.24557	-0.24582	-0.33987	-0.23241
Vent. Rate	0.57866	0.57204	-0.34189	-0.34197	-0.46876	-0.33368