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## Semiparametric interval estimation of $\Pr\{Y > X\}$

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**Keywords:** Confidence interval; Empirical likelihood; Receiver operating characteristic (ROC) curve; Area under the ROC curve; Stress-strength problem.

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## 1 Introduction and motivation

Let  $X$  and  $Y$  be two independent random variables (rv's) with continuous cumulative distribution functions (cdf's)  $G$  and  $F$ , respectively. A wide range of problems, especially in engineering and medical research, involves making inference about the quantity  $\rho = \Pr\{Y > X\}$ .

In reliability contexts, evaluation of, and inference on,  $\rho$  is known as the stress-strength problem (see Kotz *et al.*, 2003, as a general reference). Take  $X$  to be the stress potentially affecting a component, and take  $Y$  to be the strength at failure of the component, i.e. the stress at which the component will fail. In this setting,  $\rho$  represents the probability that the component will not fail, i.e. its reliability. The stress-strength problem involves typically two aspects: (i) deriving theoretical expressions for  $\rho$  under distributional assumptions about  $X$  and  $Y$ ; (ii) making inference about  $\rho$  in light of sample data. In applications, the data for the strength could be actual data indicative of the strength of the material, i.e. maximum applied stress to cause failure, and the stress data could be actual stress data of the material under usual operating conditions.

The quantity  $\rho$  also equals the area under the receiver operating characteristic

(ROC) curve for diagnostic tests or bio-markers with continuous outcome (see Bamber, 1975). The ROC curve is widely used, in biological, medical and health service research, to evaluate the ability of diagnostic tests or bio-markers to distinguish between two groups of subjects, usually non-diseased and diseased subjects. Let  $X$  and  $Y$  denote the diagnostic variable conditional on non-disease and disease, respectively, and assume that, for a generic subject, the disease is diagnosed, i.e. the test is positive, if the diagnostic variable is greater than a suitable threshold  $c$ . Then, the ROC curve is a plot of  $1 - F(c)$ , i.e. the true-positive rate, versus  $1 - G(c)$ , i.e. the false-positive rate, across all possible threshold values  $c$ . Alternatively, the ROC curve can be defined as  $R(u) = 1 - F(G^{-1}(1 - u))$ , for  $0 \leq u \leq 1$ . See, e.g., Lloyd (1998). The accuracy of a test depends on how well it separates the subjects being tested into those with and without the disease in question. The area under the ROC curve represents the most commonly used global index of diagnostic accuracy. In this context, therefore,  $\rho$  measures the inherent capacity of a test or bio-marker for discriminating a diseased from a non-diseased subject across all possible levels of positivity. Values of  $\rho$  close to 1 indicate that the test has high diagnostic accuracy.

Other interpretations of  $\rho$  arise, however, in other situations. In fact,  $\rho$  may be considered as a general measure for the difference between two distributions (see e.g. Wolfe and Hogg, 1971) and, as such, is related to the classical two-sample problem.

Since the mid 50's, the problem of making inference on  $\rho$  has been extensively discussed, with emphasis oriented to the specific application at hand. It is practically impossible to mention all the contributors to the topic; we cite, among others, the papers by Ury (1972), Hanley and McNeil (1982), Hsieh and Turnbull (1996), Gupta *et al.* (1999), Surlles and Padgett (2001), Faraggi and Reiser (2002) and the monograph by Kotz *et al.* (2003), referring the reader to references therein. Most contributions addressing inference about  $\rho$  take a parametric point of view, i.e. assuming parametric models for both  $X$  and  $Y$ , although some work has been developed also in nonparametric settings.

In this paper, we shall discuss procedures to handle problems in which distributional assumptions can be reasonably formulated for one of the two rv's, whereas no safe probabilistic assertions can be expressed for the second rv. In reliability studies, this is justified by the fact that the stress variable is usually difficult to model accurately, due to the lack of sufficient knowledge about the stress in use of a component, whereas the strength variable might be more easily elicited via expert opinion. In biomedical research, a diagnostic test, whose accuracy has to be assessed, often shows marked differences in terms of the distribution of the associate diagnostic variable conditional on non-disease and disease, respectively. In this case, it may be unsafe to confine these differences to differences in the parameters of some statistical model, or it may be hard to adopt two reasonable different parametric models. A similar situation arises in comparing new to existing treatments, where the distribution of the response may be largely known for standard treatments, whereas little or no information may be available on the response to new treatments. In all these situations, a semiparametric approach appears to be more desirable than a parametric one and it is expected to be more efficient than the fully nonparametric approach.

In the semiparametric framework that we consider, we shall review, in particu-

lar, three techniques to obtain confidence intervals for  $\rho$ . These lead to confidence intervals with different theoretical properties. The first method basically relies on the asymptotic normality of an estimator for  $\rho$ ; the remaining methods involve the empirical likelihood (see Owen, 2001, as a general reference) and combine it with maximum likelihood estimation and with full parametric likelihood, respectively. Finite-sample accuracy of the resulting confidence intervals is assessed through a simulation study. An application to a dataset on the detection of carriers of Duchenne Muscular Dystrophy is also presented, which demonstrates usefulness of the semi-parametric approach and allows to contrast the methods.

The paper is organized as follows. Section 2 describes the methods giving theoretical justification. Section 3 presents some simulation results, and the application is discussed in Section 4. Section 5 contains some final remarks. Some technical details are given in the Appendix.

## 2 Methodologies

Consider a general parametric model  $\{F(y; \theta); \theta \in \Theta\}$  for the variable  $Y$ . Here,  $F(y; \theta) = \Pr\{Y \leq y; \theta\}$  denotes the cdf, which depends on an unknown parameter  $\theta$  belonging to some set  $\Theta \subseteq \mathbb{R}^q$ ,  $q \geq 1$ . Let  $S(y; \theta) = 1 - F(y; \theta)$  denote the survival function corresponding to  $F(y; \theta)$ . We do not make any parametric assumption about the distribution of the variable  $X$ . We only assume that  $X$  is independent of  $Y$ . In this setting,  $\rho = \Pr\{Y > X; \theta\}$ .

Let  $X_1, X_2, \dots, X_n$  be a random sample of size  $n$  from  $X$  and  $Y_1, Y_2, \dots, Y_m$  a random sample of size  $m$  from  $Y$ . In the following, we assume that the ratio  $n/m$  converges to some positive and finite constant  $\kappa$ , as  $n$  and  $m$  increase to  $+\infty$ . Let  $\theta_0$  and  $\rho_0$  indicate the true values of  $\theta$  and  $\rho$ , respectively. Since

$$\rho_0 = \Pr\{Y > X; \theta_0\} = E[\Pr\{Y > X | X; \theta_0\}] = E\{S(X; \theta_0)\},$$

an obvious estimator for  $\rho_0$  is given by

$$\hat{\rho} = \frac{1}{n} \sum_{i=1}^n S(X_i; \hat{\theta}), \quad (1)$$

where  $\hat{\theta}$  denotes the maximum likelihood estimator (mle) of  $\theta_0$  based on the sample  $Y_1, Y_2, \dots, Y_m$ . Throughout the paper, we assume standard regularity conditions, which ensure the consistency and the asymptotic normality of the mle  $\hat{\theta}$  and legitimize some Taylor expansion. Under these conditions, we can write

$$\frac{1}{n} \sum_{i=1}^n S(X_i; \hat{\theta}) = \frac{1}{n} \sum_{i=1}^n S(X_i; \theta_0) + \left\{ \frac{1}{n} \sum_{i=1}^n \dot{S}(X_i; \theta_0) \right\}^\top (\hat{\theta} - \theta_0) + o_p(n^{-1/2}),$$

where  $\dot{S}(\cdot; \cdot)$  denotes the derivative of  $S(y; \theta)$  with respect to  $\theta$ . Then

$$\sqrt{n}(\hat{\rho} - \rho_0) = \sqrt{n} \left\{ \frac{1}{n} \sum_{i=1}^n S(X_i; \theta_0) - \rho_0 \right\} + \sqrt{\kappa m} \beta^\top (\hat{\theta} - \theta_0) + o_p(1),$$

being  $\beta = E\{\dot{S}(X; \theta_0)\}$ . It follows that  $\sqrt{n}(\hat{\rho} - \rho_0)$  is asymptotically normal with mean zero and variance

$$\omega^2 = \omega_S^2 + \kappa\beta^\top \Omega\beta,$$

where  $\omega_S^2$  is the variance of  $S(X; \theta_0)$  and  $\Omega$  denotes the asymptotic covariance matrix of  $\sqrt{m}(\hat{\theta} - \theta_0)$ . This suggests that confidence intervals for  $\rho_0$  may be obtained by the classical normal approximation approach. Clearly, we need to estimate the asymptotic variance  $\omega^2$ . Let  $\hat{\Omega}$  denote a consistent estimator of  $\Omega$ . Then, a consistent estimator of  $\omega^2$  is

$$\hat{\omega}^2 = \hat{\omega}_S^2 + (n/m)\hat{\beta}^\top \hat{\Omega}\hat{\beta},$$

where  $\hat{\omega}_S^2 = n^{-1} \sum_{i=1}^n \{S(X_i; \hat{\theta}) - \hat{\rho}\}^2$  is a consistent estimator of  $\omega_S^2$  (see the Appendix) and  $\hat{\beta} = n^{-1} \sum_{i=1}^n \dot{S}(X_i; \hat{\theta})$ .

Despite its usefulness, there are some drawbacks associated with the crude normal approximation approach. Firstly, this method does not always work well for small samples, yielding confidence intervals with poor accuracy. Secondly, the method is not range-preserving, so that confidence intervals for  $\rho_0$  could contain values outside its range. Finally, the method artificially imposes a predetermined symmetry constraint on the shape of the confidence intervals.

To overcome the drawbacks encountered by the crude normal approximation approach, three routes can be considered, which we describe in what follows.

**Reparameterization.** Let  $t(\cdot)$  be an invertible function with continuous derivative  $\dot{t}(\cdot)$ , mapping the interval  $(0,1)$  to the real line, and consider the new parameter  $\tau = t(\rho)$ . Let  $\tau_0 = t(\rho_0)$  and  $\hat{\tau} = t(\hat{\rho})$ . Then,  $\sqrt{n}(\hat{\tau} - \tau_0)$  is asymptotically normally distributed with mean zero and variance  $\dot{t}^2(\rho_0)\omega^2$ . This asymptotic distribution can be used to construct confidence intervals on the  $\tau$  scale, and then to convert them back to the  $\rho$  scale by the inverse transformation  $t^{-1}$ . Equivalently, the intervals can be obtained by approximating the distribution of the pivot

$$w_t(\rho) = \frac{n\{t(\hat{\rho}) - t(\rho)\}^2}{\dot{t}^2(\hat{\rho})\hat{\omega}^2} \quad (2)$$

by a chi-square distribution with one degree of freedom ( $\chi_1^2$ ). Therefore, an approximate confidence interval for  $\rho_0$ , with nominal coverage  $1 - \gamma$ , is the set  $\{\rho : w_t(\rho) \leq c_\gamma\}$ , where  $c_\gamma$  is such that  $\Pr\{\chi_1^2 \leq c_\gamma\} = 1 - \gamma$ .

The reason for the transformation is two-fold: it provides range-respecting confidence intervals, and it generally improves their accuracy, since the normal approximation works better in an unrestricted space for a distribution with less skewness.

Suitable transformations, which turn out to be useful in this setting are, for instance, the logit and the probit transformation. In particular, for the logit transformation,  $t(\rho) = \text{logit}(\rho) = \log\{\rho/(1 - \rho)\}$  and  $\dot{t}(\rho) = 1/\{\rho(1 - \rho)\}$ .

**Estimated empirical likelihood.** If  $\theta_0$  were known, one could construct confidence intervals for  $\rho_0$ , the mean of  $S(X; \theta_0)$ , using the empirical likelihood method (Owen, 1988, 1990). The empirical log likelihood ratio function for the mean of

$S(X; \theta_0)$ , evaluated at some possible candidate  $\rho$ , is defined as

$$l(\rho) = -2 \sup_{p_1, p_2, \dots, p_n} \sum_{i=1}^n \log(np_i),$$

where the supremum is taken subject to the constraints

$$p_i \geq 0 \quad \text{for all } i, \quad \sum_{i=1}^n p_i = 1 \quad \text{and} \quad \sum_{i=1}^n S(X_i; \theta_0)p_i = \rho. \quad (3)$$

It follows from Owen (1988) that, when evaluated at the true value  $\rho_0$ , the empirical log likelihood ratio has an asymptotic  $\chi_1^2$  distribution; that is  $l(\rho_0) \xrightarrow{d} \chi_1^2$ .

Of course,  $l(\rho)$  cannot be computed since it depends on  $\theta_0$  which is unknown. A natural solution is then to replace  $\theta_0$  in (3) by its mle  $\hat{\theta}$ . This leads to an estimated empirical log likelihood ratio defined as

$$\hat{l}(\rho) = -2 \sup \left\{ \sum_{i=1}^n \log(np_i) : p_i \geq 0 \forall i, \sum_{i=1}^n p_i = 1, \sum_{i=1}^n S(X_i; \hat{\theta})p_i = \rho \right\}.$$

A Lagrangian argument gives an explicit expression for  $\hat{l}(\rho)$ . Let  $X_{(1)}$  and  $X_{(n)}$  be the minimum and the maximum of the  $X$  values. When  $S(X_{(n)}; \hat{\theta}) < \rho < S(X_{(1)}; \hat{\theta})$ , we have

$$\hat{l}(\rho) = 2 \sum_{i=1}^n \log[1 + \lambda\{S(X_i; \hat{\theta}) - \rho\}], \quad (4)$$

where  $\lambda = \lambda(\rho)$  is the solution of the equation

$$\frac{1}{n} \sum_{i=1}^n \frac{S(X_i; \hat{\theta}) - \rho}{1 + \lambda\{S(X_i; \hat{\theta}) - \rho\}} = 0. \quad (5)$$

Outside the interval bounded by  $S(X_{(n)}; \hat{\theta})$  and  $S(X_{(1)}; \hat{\theta})$ , it is necessary to set  $\hat{l}(\rho) = +\infty$ . The function  $\hat{l}(\rho)$  attains its minimum value at  $\rho = \hat{\rho}$ .

Due to the substitution of  $\theta_0$  with  $\hat{\theta}$  in (3),  $\hat{l}(\rho_0)$  no longer has the usual asymptotic chi-square distribution. However, it can be shown (see the Appendix) that

$$\hat{l}(\rho_0) = n \frac{(\hat{\rho} - \rho_0)^2}{\hat{\omega}_S^2} + o_p(1) \quad \text{as } n, m \rightarrow +\infty. \quad (6)$$

It follows that

$$\tilde{l}(\rho_0) = \frac{\hat{\omega}_S^2}{\hat{\omega}^2} \hat{l}(\rho_0) \xrightarrow{d} \chi_1^2.$$

The function  $\tilde{l}(\rho) = (\hat{\omega}_S^2/\hat{\omega}^2) \hat{l}(\rho)$  represents an adjusted empirical log likelihood ratio function, with a standard asymptotic behaviour. Then, the set  $\{\rho : \tilde{l}(\rho) \leq c_\gamma\}$  is an approximate confidence interval for  $\rho_0$ , with nominal coverage  $1 - \gamma$ . Confidence intervals obtained by  $\tilde{l}(\rho)$  are indeed intervals, are range-respecting and are not subject to symmetry constraints, having shape which is determined automatically by the data. Moreover, they are equivariant under one-to-one transformations of

the parameter  $\rho$ . Given a transformation, confidence intervals for the transformed parameter can be obtained by applying such transformation to each point of the original confidence intervals for  $\rho_0$ .

**Combined likelihood.** The approach based on  $\tilde{l}(\rho)$  combines mle and empirical likelihood. A more sophisticated approach, which fully combines parametric and empirical likelihoods, is also possible. This approach is developed in Qin (1997).

Let  $f(y; \theta)$  denote the density function corresponding to  $F(y; \theta)$ . The combined log likelihood function for  $(\theta, \rho)$  can be defined as

$$\ell(\theta, \rho) = \sum_{j=1}^m \log\{f(Y_j; \theta)\} + \sup_{p_1, p_2, \dots, p_n} \sum_{i=1}^n \log(p_i),$$

where the supremum is taken subject to the constraints

$$p_i \geq 0, \quad \sum_{i=1}^n p_i = 1 \quad \text{and} \quad \sum_{i=1}^n S(X_i; \theta)p_i = \rho.$$

This function attains its maximum value at  $(\hat{\theta}, \hat{\rho})$ . Using Lagrange multipliers leads to

$$\ell(\theta, \rho) = \sum_{j=1}^m \log\{f(Y_j; \theta)\} - \sum_{i=1}^n \log[1 + \lambda\{S(X_i; \theta) - \rho\}] - n \log(n), \quad (7)$$

where  $\lambda = \lambda(\theta, \rho)$  is the solution of

$$\frac{1}{n} \sum_{i=1}^n \frac{S(X_i; \theta) - \rho}{1 + \lambda\{S(X_i; \theta) - \rho\}} = 0.$$

Expression (7) for  $\ell(\theta, \rho)$  is correct if the couple  $(\theta, \rho)$  is such that  $S(X_{(n)}; \theta) < \rho < S(X_{(1)}; \theta)$ . Otherwise, it is necessary to set  $\ell(\theta, \rho) = -\infty$ . A profile combined log likelihood for  $\rho$  is then obtained as

$$\ell_P(\rho) = \sup_{\theta} \ell(\theta, \rho),$$

so that the profile combined log likelihood ratio function for  $\rho$  is

$$l_P(\rho) = 2\{\ell_P(\hat{\rho}) - \ell_P(\rho)\}.$$

Of course,  $\ell_P(\hat{\rho}) = \ell(\hat{\theta}, \hat{\rho})$ .

By results in Qin (1997) (see also Theorem 2 of Qin, 2000), it follows that, under standard regularity conditions,

$$l_P(\rho_0) \xrightarrow{d} \chi_1^2, \quad \text{as } n, m \rightarrow +\infty.$$

Therefore, the set  $\{\rho : l_P(\rho) \leq c_\gamma\}$  constitutes an approximate confidence interval for  $\rho_0$ , with nominal coverage  $1 - \gamma$ . Confidence intervals obtained by  $l_P(\rho)$  have the same good properties of those obtained by  $\tilde{l}(\rho)$ . Moreover, they are also invariant



with respect to invertible transformations of the nuisance parameter  $\theta$ , so that the family of distributions for  $Y$  can be reparameterized without affecting confidence intervals for  $\rho_0$ . Finally, it is worth noting that the combined likelihood approach does not require the estimation of the asymptotic variance of any statistic.

The described techniques give rise to confidence intervals with different theoretical properties. However, the techniques are asymptotically equivalent, in that functions  $w_t(\rho)$ ,  $\tilde{l}(\rho)$  and  $l_P(\rho)$  are identical to first order of approximation. Therefore, the resulting confidence intervals tend to be identical as the sample sizes increase.

Estimator  $\hat{\rho}$ , from which we started, can be viewed as a semiparametric analogue of the well known Mann-Whitney statistic. The latter is obtainable by estimating the survival function  $S$  in (1) by its empirical counterpart. Moreover,  $\hat{\rho}$  represents also the maximum adjusted empirical likelihood estimator and the maximum combined likelihood estimator of  $\rho$ . Another semiparametric estimator of  $\rho$ , obtained by integrating an estimator of the ROC curve, is derived in Li *et al* (1999). Asymptotic normality of such an estimator could be used to obtain confidence intervals for  $\rho$ , although the variance of the asymptotic distribution appears to be more involved to estimate.

We conclude this section with two remarks.

REMARK 1. Suppose that interest lies in  $\rho^* = \Pr\{Y \leq X; \theta\} = 1 - \rho$ . Then the adjusted empirical log likelihood ratio for  $\rho^*$ , say  $\tilde{l}(\cdot)$ , is immediately derived by  $\tilde{l}(\cdot)$ , being  $\tilde{l}(\rho^*) = \tilde{l}(1 - \rho^*)$ . The same holds for the combined likelihood approach, where  $l_P(\rho^*) = l_P(1 - \rho^*)$ .

REMARK 2. The techniques based on the normal approximation with reparameterization and on the adjusted empirical log likelihood ratio use the mle  $\hat{\theta}$ . However, any  $\sqrt{m}$ -consistent estimator of  $\theta$  could be employed. For instance, one may want to use robust estimators to protect inference from effects of outliers or (small) departures of the data distribution from the specified parametric model.

### 3 Some simulation results

In this section, we report the results of a simulation study carried out to assess the finite-sample accuracy of the confidence intervals obtained by using the techniques discussed in Section 2.

For three levels of nominal coverage  $1 - \gamma$ , Tables 1, 2, 3 give the estimated coverage probabilities of the confidence intervals based on the profile combined log likelihood ratio  $l_P(\rho)$  (CL), the adjusted empirical log likelihood ratio  $\tilde{l}(\rho)$  (AEL), and the asymptotic normality of  $t(\hat{\rho})$ , with  $t(\cdot)$  being the logit transformation (NAL). Each table refers to a particular value fixed for the true  $\rho_0$ , i.e. 0.50, 0.75 and 0.95, respectively.

In the simulation work, we have considered three different parametric models for  $Y$ : (i) a Gaussian model ( $N(\alpha, \sigma)$ ), (ii) a Gamma model ( $\text{Ga}(\alpha, \sigma)$ ), and (iii) a scaled Burr type X model ( $\text{BurrX}(\alpha, \sigma)$ ). The first two are well-known and largely

used parametric models. We recall that the  $\text{Ga}(\alpha, \sigma)$  distribution has cdf

$$F(y; \alpha, \sigma) = \frac{1}{\Gamma(\alpha)} \int_0^{y/\sigma} z^{\alpha-1} e^{-z} dz, \quad y > 0, \quad \alpha > 0, \quad \sigma > 0,$$

where  $\Gamma(\cdot)$  is the gamma function. The scaled Burr type X model has been recently introduced for applications in reliability studies. We refer the interested reader to Surles and Padgett (2001) for results about likelihood-based inference for this model and inference on  $\rho$  when  $X$  and  $Y$  are independently distributed as scaled Burr type X rv's. Here, we recall only that the  $\text{BurrX}(\alpha, \sigma)$  distribution has cdf

$$F(y; \alpha, \sigma) = \left\{ 1 - e^{-(y/\sigma)^2} \right\}^\alpha, \quad y > 0, \quad \alpha > 0, \quad \sigma > 0.$$

Evidently, in this setting  $\theta = (\alpha, \sigma)$ . To perform the simulation experiments, random samples for the  $Y$  and the  $X$  values have been generated, respectively, from a  $\text{N}(\alpha, \sigma)$  and a  $\text{N}(0, \sigma_X)$  in case (i), from a  $\text{Ga}(\alpha, \sigma)$  and a  $\text{Ga}(\alpha_X, 1)$  in case (ii) and from a  $\text{BurrX}(\alpha, \sigma)$  and a  $\text{BurrX}(\alpha_X, 1)$  in case (iii), for various combinations of the parameters  $\alpha$ ,  $\sigma$ ,  $\alpha_X$  and  $\sigma_X$ . Of course, the values for  $\alpha$ ,  $\sigma$  and  $\sigma_X$ , in case (i), and  $\alpha$ ,  $\sigma$  and  $\alpha_X$ , in cases (ii) and (iii), have been chosen in a way such that the true  $\rho_0$  were always equal to the chosen reference value.

As for the sample sizes, for each value of  $\rho_0$  we have chosen two different settings. In detail, for  $\rho_0 = 0.50$  we have set  $m = 10$ ,  $n = 20$  and  $m = 20$ ,  $n = 40$ ; for  $\rho_0 = 0.75$  we have set  $m = 12$ ,  $n = 25$  and  $m = 25$ ,  $n = 50$ ; finally, for  $\rho_0 = 0.95$  we have set  $m = 25$ ,  $n = 50$  and  $m = 50$ ,  $n = 100$ . Each simulation experiment is based on 5000 replications.

[Insert Table 1, 2, 3 around here]

Simulation results show that confidence intervals based on the three techniques are accurate in almost all considered cases, even for the smallest sample sizes. In particular, we underline the good performance of the NAL approach, which results in surprisingly accurate confidence intervals. We have tested other transformations (such as the probit), obtaining results worse than those given by the logit transformation.

Although competitive with the CL and NAL approaches, the AEL approach shows the least satisfactory results. In particular, accuracy tends to slightly diminish for extreme values of  $\rho_0$  and small sample sizes. Moreover, the poor performance for the Gaussian case with  $\sigma_X = 1$  and  $\sigma = 4$  may be explained by the fact that  $1 - \Pr\{S(X_{(n)}; \hat{\theta}) < \rho_0 < S(X_{(1)}; \hat{\theta})\}$  becomes, in small samples, relatively high, so that  $\tilde{l}(\rho_0)$  attains  $+\infty$  too many times. However, accuracy increases with sample size and, generally, this approach still greatly outperforms the crude normal approximation approach (results not reported here).

It is worth noting that the smallest sample sizes used in the simulations are indicative of the effective sizes needed to guarantee sufficiently accurate coverages. Clearly, the closer the value of  $\rho_0$  to the boundary, the larger the sample sizes necessary.

Some simulations have also been performed for small values of  $\rho_0$  (0.05 and 0.25), leading to similar conclusions.

## 4 An example

Duchenne muscular dystrophy is one of the most prevalent types of muscular dystrophy and is characterized by rapid progression of muscle degeneration that occurs early in life. It is a genetically transmitted disease, which is passed from a mother to her children. Unfortunately, no cure has yet been discovered, so that the screening of females who could be potential carriers is of great importance.

Andrews and Herzberg (1985) report some data collected during a program run at the Hospital for Sick Children of Toronto. Knowing that carriers tend to exhibit elevated levels of some serum enzymes, values of four blood serum markers were measured in known carriers and in non-carriers, i.e. healthy females, with the aim of evaluating their performance as diagnostic tests. Complete data are available on 127 healthy females and 67 carriers.

To illustrate usefulness of the semiparametric approach adopted in this paper, we shall consider one of the four markers, i.e. pyruvate kinase (PK), and calculate confidence intervals for the probability that PK levels in carriers are greater than in healthy females.

Inspection of the data reveals non-normality of both samples, i.e. carriers and healthy females. A standard parametric approach relies on a single transformation of the data which brings both the samples back to normality (see, for instance, Faraggi and Reiser, 2002, which analyze for the same subjects blood serum creatine kinase levels). However, for PK measurements it is not possible to find such a transformation, although it is possible to find two different transformations, which separately map the two samples to normality. The semiparametric approach appears therefore to be useful in this case.

We transform the carriers' measurements by taking the power of  $-0.56$ , as suggested by the Box-Cox method, and assume a  $N(\alpha, \sigma)$  distribution for the transformed values. The same transformation is applied to the healthy females measurements, for which we do not make any parametric assumption. Figure 1 shows the normal quantile-quantile plots for the transformed data. Note that we assume the parametric model for the smallest sample.

[Insert Figure 1 around here]

Let  $X^*$  and  $Y^*$  denote the PK levels for a healthy and a carrier female, respectively, and let  $X$  and  $Y$  denote the transformed PK levels. Our interest lies in computing confidence intervals for

$$\rho^* = \Pr\{Y^* > X^*\} = 1 - \Pr\{Y > X; \theta\}, \quad \theta = (\alpha, \sigma),$$

which can be derived by applying the techniques described in Section 2. Figure 2 shows the profile combined log likelihood ratio for  $\rho^*$ ,  $l_P(\rho^*)$ , the adjusted empirical log likelihood ratio  $\hat{l}(\rho^*)$  (see Remark 1), and the function  $w_t(\rho^*)$  derived from (2) on letting  $t(\cdot)$  be the logit transformation. The horizontal dotted line is at the asymptotically justified 95% coverage level.

As may be seen, the three functions are very close. This result might be expected, in view of the sample sizes with which we deal. In particular, the profile

combined log likelihood ratio  $l_P(\rho^*)$  and the adjusted empirical log likelihood ratio  $\tilde{l}(\rho^*)$  are practically indistinguishable, leading to the same 0.95-level confidence interval (0.742, 0.868). The point estimate is  $\hat{\rho}^* = 1 - \hat{\rho} = 0.812$ , which is the value that minimizes the three curves.

[Insert Figure 2 around here]

## 5 Conclusions

In this paper, we have considered the problem of making inference on  $\rho$  in a semi-parametric framework. In particular, we have discussed three techniques to obtain confidence intervals. Simulation results have shown a substantial comparability of the three procedures, at least so far as accuracy of the corresponding confidence intervals is concerned. Overall, we have observed a good agreement between nominal and actual coverages.

However, the techniques lead to confidence intervals with different theoretical properties and present also different degrees of computational complexity. From a theoretical point of view, the most appealing technique is the one based on the combined likelihood. Nevertheless, its practical use is, computationally, the most demanding. In fact, for each fixed value of  $\rho$ , the computation of the profile combined log likelihood ratio  $l_P(\rho)$  requires maximization with respect to  $\theta$  of the function  $\ell(\theta, \rho)$ , whose evaluation involves solving a nonlinear equation (see also Qin, 1997). In contrast, the computation of the adjusted empirical log likelihood ratio  $\tilde{l}(\rho)$  requires solving only one such equation. Naturally, all techniques rely on the computation of the mle  $\hat{\theta}$ , for which a closed expression might not exist. The technique based on the normal approximation with reparameterization is the least attractive from a theoretical perspective, but it could be recommended due to its simplicity. In particular, we strongly advise the use of the logit transformation, which has shown unexpected good performance in our simulation study.

## Acknowledgements

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## Appendix

In this appendix we sketch a proof of (6). Let  $\xi_L = \inf\{x : G(x) > 0\}$  and  $\xi_U = \sup\{x : G(x) < 1\}$ , where it may be  $\xi_L = -\infty$  and  $\xi_U = +\infty$ . Moreover, let  $\rho_L = S(\xi_U; \theta_0)$ ,  $\rho_U = S(\xi_L; \theta_0)$  and assume that  $\rho_L < \rho_U$ . Thus,  $\rho_L < \rho_0 < \rho_U$ .

As  $n$  and  $m$  increase to  $+\infty$ ,  $X_{(1)}$ ,  $X_{(n)}$  and  $\hat{\theta}$  converge in probability to  $\xi_L$ ,  $\xi_U$  and  $\theta_0$ , respectively. Then,  $S(X_{(1)}; \hat{\theta})$  and  $S(X_{(n)}; \hat{\theta})$  converge to  $\rho_U$  and  $\rho_L$ , respectively, so that  $\Pr\{S(X_{(n)}; \hat{\theta}) < \rho_0 < S(X_{(1)}; \hat{\theta})\} \rightarrow 1$  as  $n, m \rightarrow +\infty$ . This means that  $\hat{l}(\rho_0)$  exists (finite) with probability tending to 1.

By Dini's Theorem, the function  $\lambda(\rho)$  defined by equation (5) is continuous in a neighbourhood of  $\hat{\rho}$ , resulting in

$$\dot{\lambda}(\hat{\rho}) = \left. \frac{d\lambda(\rho)}{d\rho} \right|_{\rho=\hat{\rho}} = -\frac{1}{\hat{\omega}_S^2}, \quad \text{with} \quad \hat{\omega}_S^2 = n^{-1} \sum_{i=1}^n \{S(X_i; \hat{\theta}) - \hat{\rho}\}^2.$$

Since

$$\hat{\omega}_S^2 = \frac{1}{n} \sum_{i=1}^n \{S(X_i; \hat{\theta}) - \rho_0\}^2 + O_p(n^{-1}), \quad (8)$$

and

$$\frac{1}{n} \sum_{i=1}^n \{S(X_i; \hat{\theta}) - \rho_0\}^2 = \omega_S^2 + o_p(1),$$

we have  $\hat{\omega}_S^2 = \omega_S^2 + o_p(1)$ . Then we consider the Taylor series expansion of  $\lambda(\rho)$  around  $\hat{\rho}$ ,

$$\lambda(\rho) = \lambda(\hat{\rho}) + \dot{\lambda}(\hat{\rho})(\rho - \hat{\rho}) + o(|\rho - \hat{\rho}|).$$

Let  $\lambda_0 = \lambda(\rho_0)$ . Since  $\lambda(\hat{\rho}) = 0$ , at  $\rho = \rho_0$  the above expression becomes

$$\lambda_0 = \frac{\hat{\rho} - \rho_0}{\hat{\omega}_S^2} + o_p(n^{-1/2}). \quad (9)$$

Thus  $\lambda_0 = O_p(n^{-1/2})$  and  $|\lambda_0| \max_{1 \leq i \leq n} |S(X_i; \hat{\theta}) - \rho_0| = O_p(n^{-1/2})$ ; then, using the McLaurin series expansion

$$\log(1+z) = z - \frac{1}{2}z^2 + \frac{z^3}{3(1+z)^3}, \quad |\bar{z}| \leq |z|,$$

in the expression of  $\hat{l}(\rho_0)$ , i.e. in (4) evaluated at  $\rho = \rho_0$ , we obtain

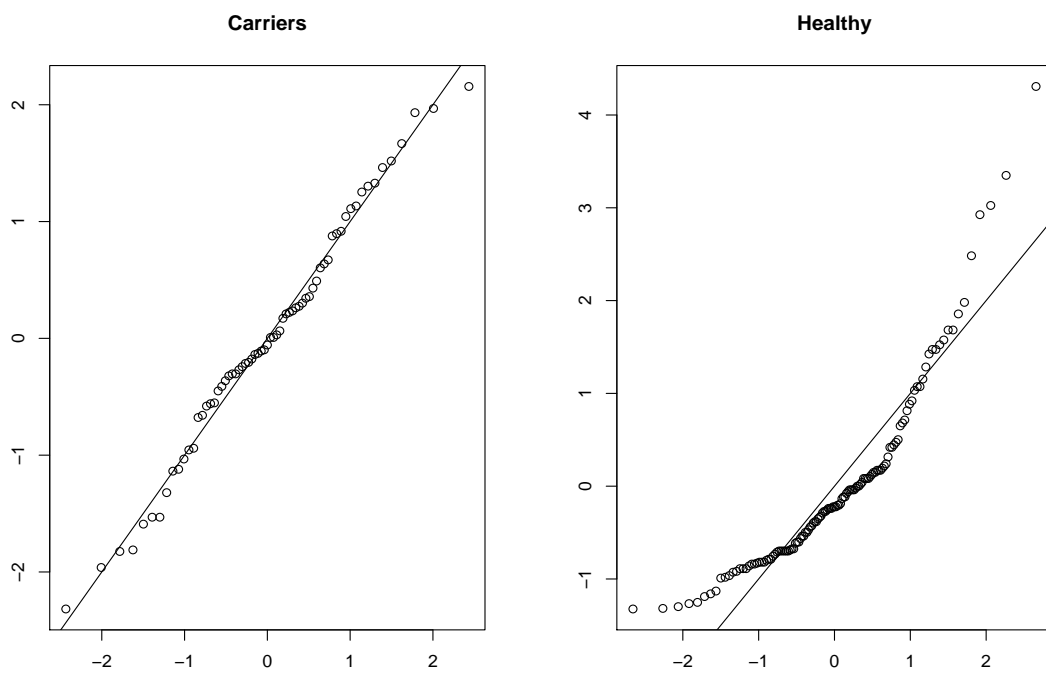
$$\hat{l}(\rho_0) = 2\lambda_0 \sum_{i=1}^n \{S(X_i; \hat{\theta}) - \rho_0\} - \lambda_0^2 \sum_{i=1}^n \{S(X_i; \hat{\theta}) - \rho_0\}^2 + o_p(1). \quad (10)$$

Equation (6) follows from (10), using also (8) and (9).

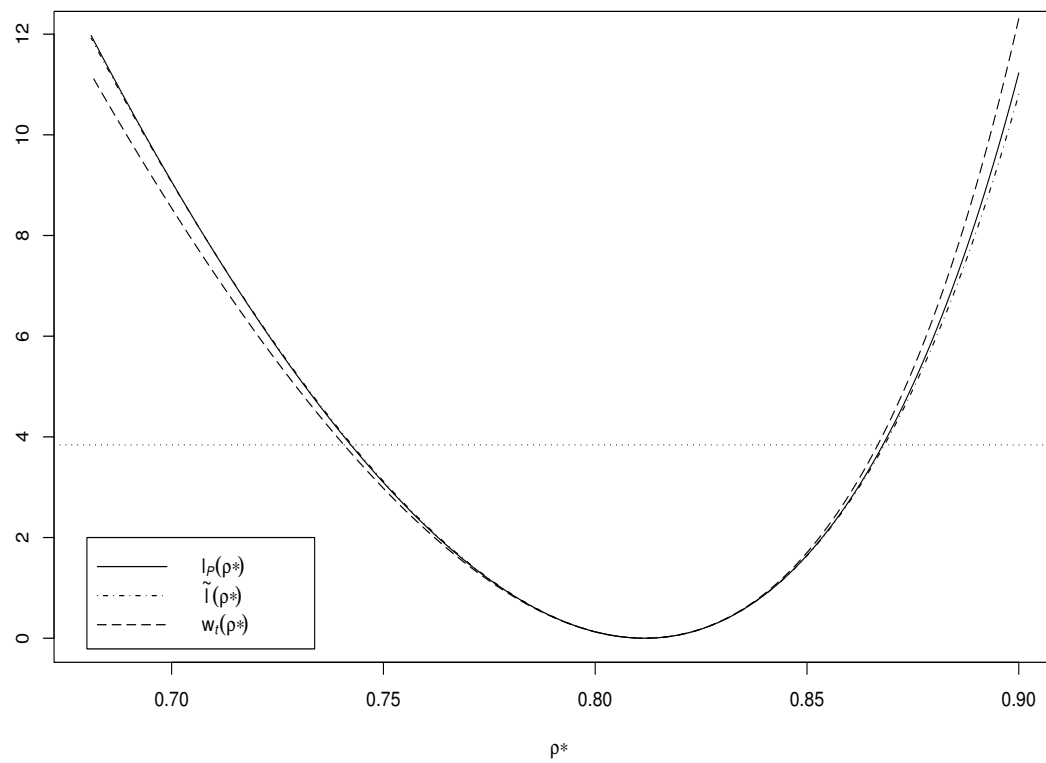
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**Figure 1:** Normal quantile-quantile plots of the transformed PK levels.



**Figure 2:** Profile combined log likelihood ratio function,  $l_P(\cdot)$ , adjusted empirical log likelihood ratio function  $\tilde{I}(\cdot)$  and function  $w_t(\cdot)$  for the probability  $\rho^*$  that PK levels in carriers are greater than in healthy females. The function  $w_t(\cdot)$  is derived from (2) on considering the logit transformation.



			$m = 10, n = 20$			$m = 20, n = 40$			
			$1 - \gamma$			$1 - \gamma$			
			0.99	0.95	0.90	0.99	0.95	0.90	
$\alpha$	$\sigma_X$	$\sigma$	Gaussian						
0	1	1	CL	0.985	0.940	0.879	0.990	0.948	0.890
			AEL	0.986	0.943	0.884	0.992	0.953	0.894
			NAL	0.989	0.947	0.888	0.991	0.950	0.893
0	1	4	CL	0.982	0.932	0.872	0.985	0.939	0.880
			AEL	0.819	0.802	0.779	0.957	0.931	0.896
			NAL	0.989	0.941	0.879	0.987	0.943	0.883
0	1	2	CL	0.984	0.928	0.876	0.989	0.945	0.889
			AEL	0.963	0.922	0.873	0.992	0.963	0.913
			NAL	0.987	0.932	0.879	0.990	0.947	0.892
0	2	1	CL	0.988	0.947	0.892	0.988	0.946	0.898
			AEL	0.991	0.951	0.895	0.989	0.950	0.900
			NAL	0.995	0.960	0.908	0.990	0.954	0.905
0	1	0.5	CL	0.991	0.947	0.889	0.990	0.947	0.896
			AEL	0.993	0.949	0.893	0.991	0.949	0.897
			NAL	0.996	0.956	0.905	0.993	0.952	0.901
0	1	0.25	CL	0.990	0.949	0.893	0.989	0.946	0.891
			AEL	0.991	0.951	0.894	0.990	0.947	0.892
			NAL	0.996	0.964	0.910	0.993	0.954	0.898
$\alpha$	$\alpha_X$	$\sigma$	Gamma						
1	1	1	CL	0.985	0.940	0.890	0.988	0.941	0.890
			AEL	0.983	0.941	0.893	0.990	0.945	0.893
			NAL	0.989	0.947	0.899	0.990	0.944	0.894
1.71	1	0.5	CL	0.988	0.944	0.893	0.991	0.951	0.897
			AEL	0.989	0.949	0.895	0.993	0.954	0.899
			NAL	0.992	0.953	0.908	0.994	0.956	0.901
0.631	1	2	CL	0.985	0.937	0.879	0.989	0.941	0.887
			AEL	0.978	0.931	0.882	0.992	0.950	0.894
			NAL	0.989	0.942	0.886	0.990	0.944	0.890
3.69	2	0.5	CL	0.989	0.940	0.885	0.984	0.946	0.892
			AEL	0.989	0.946	0.890	0.986	0.947	0.894
			NAL	0.993	0.952	0.897	0.987	0.949	0.899
2	2	1	CL	0.987	0.937	0.887	0.990	0.950	0.904
			AEL	0.989	0.941	0.890	0.993	0.954	0.909
			NAL	0.992	0.948	0.895	0.992	0.952	0.907
1.149	2	2	CL	0.986	0.943	0.881	0.987	0.945	0.888
			AEL	0.984	0.942	0.885	0.992	0.953	0.897
			NAL	0.991	0.948	0.887	0.989	0.948	0.890
$\alpha$	$\alpha_X$	$\sigma$	scaled Burr type X						
1	1	1	CL	0.983	0.939	0.885	0.989	0.947	0.902
			AEL	0.982	0.941	0.889	0.991	0.949	0.905
			NAL	0.988	0.947	0.894	0.989	0.948	0.905
10	10	1	CL	0.986	0.933	0.880	0.988	0.947	0.885
			AEL	0.987	0.937	0.886	0.990	0.952	0.892
			NAL	0.991	0.944	0.888	0.989	0.951	0.891
10	30	1.187	CL	0.986	0.937	0.885	0.986	0.940	0.899
			AEL	0.980	0.937	0.885	0.991	0.951	0.898
			NAL	0.989	0.944	0.890	0.988	0.942	0.892
30	10	0.843	CL	0.991	0.947	0.889	0.989	0.947	0.894
			AEL	0.992	0.951	0.895	0.992	0.949	0.898
			NAL	0.994	0.957	0.903	0.992	0.950	0.899
50	50	1	CL	0.986	0.940	0.890	0.991	0.947	0.892
			AEL	0.987	0.948	0.893	0.992	0.952	0.901
			NAL	0.992	0.952	0.898	0.993	0.951	0.898

**Table 1:** *Estimated coverage probabilities of the confidence intervals for  $\rho_0 = 0.50$ .*

			$m = 12, n = 25$			$m = 25, n = 50$			
			$1 - \gamma$			$1 - \gamma$			
			0.99	0.95	0.90	0.99	0.95	0.90	
$\alpha$	$\alpha_X$	$\sigma$	Gaussian						
0.954	1	1	CL	0.987	0.939	0.884	0.988	0.945	0.897
			AEL	0.983	0.940	0.888	0.992	0.951	0.901
			NAL	0.991	0.947	0.895	0.990	0.948	0.898
2.781	1	4	CL	0.983	0.933	0.878	0.988	0.943	0.895
			AEL	0.837	0.823	0.802	0.968	0.949	0.919
			NAL	0.992	0.944	0.891	0.991	0.948	0.898
1.509	1	2	CL	0.983	0.938	0.888	0.988	0.937	0.880
			AEL	0.963	0.924	0.882	0.992	0.954	0.903
			NAL	0.987	0.944	0.894	0.990	0.941	0.881
1.509	2	1	CL	0.988	0.948	0.894	0.990	0.948	0.900
			AEL	0.989	0.950	0.895	0.992	0.953	0.902
			NAL	0.995	0.957	0.907	0.992	0.955	0.906
0.754	1	0.5	CL	0.989	0.948	0.894	0.990	0.950	0.899
			AEL	0.989	0.952	0.900	0.990	0.951	0.902
			NAL	0.994	0.958	0.910	0.990	0.953	0.908
0.695	1	0.25	CL	0.992	0.947	0.900	0.992	0.954	0.905
			AEL	0.993	0.949	0.901	0.992	0.955	0.906
			NAL	0.995	0.960	0.917	0.993	0.962	0.917
$\alpha$	$\alpha_X$	$\sigma$	Gamma						
1	1	3	CL	0.985	0.939	0.884	0.987	0.940	0.886
			AEL	0.979	0.937	0.886	0.990	0.948	0.894
			NAL	0.991	0.947	0.896	0.988	0.943	0.889
3.42	1	0.5	CL	0.990	0.948	0.895	0.989	0.944	0.892
			AEL	0.990	0.949	0.897	0.992	0.949	0.894
			NAL	0.993	0.959	0.906	0.991	0.950	0.898
2	1	1	CL	0.986	0.941	0.890	0.991	0.949	0.898
			AEL	0.984	0.942	0.892	0.993	0.953	0.902
			NAL	0.990	0.953	0.899	0.993	0.953	0.903
1.262	1	2	CL	0.985	0.938	0.884	0.988	0.939	0.887
			AEL	0.981	0.940	0.889	0.989	0.947	0.892
			NAL	0.990	0.946	0.896	0.989	0.944	0.891
6.177	2	0.5	CL	0.990	0.950	0.892	0.989	0.948	0.899
			AEL	0.988	0.950	0.896	0.991	0.952	0.901
			NAL	0.992	0.957	0.907	0.991	0.952	0.902
3.445	2	1	CL	0.989	0.944	0.891	0.989	0.945	0.897
			AEL	0.985	0.943	0.892	0.991	0.951	0.902
			NAL	0.994	0.953	0.901	0.990	0.950	0.902
2.045	2	2	CL	0.986	0.935	0.881	0.989	0.937	0.891
			AEL	0.979	0.933	0.881	0.992	0.947	0.896
			NAL	0.989	0.943	0.888	0.991	0.941	0.891
$\alpha$	$\alpha_X$	$\sigma$	scaled Burr type X						
1	1	1.733	CL	0.983	0.942	0.889	0.988	0.947	0.896
			AEL	0.988	0.936	0.888	0.990	0.955	0.904
			NAL	0.989	0.947	0.894	0.990	0.948	0.901
10	10	1.218	CL	0.988	0.937	0.882	0.989	0.946	0.898
			AEL	0.984	0.933	0.882	0.990	0.949	0.902
			NAL	0.993	0.945	0.891	0.990	0.950	0.902
10	30	1.412	CL	0.987	0.937	0.888	0.984	0.940	0.889
			AEL	0.978	0.931	0.885	0.986	0.945	0.893
			NAL	0.990	0.943	0.895	0.985	0.942	0.891
30	10	1	CL	0.989	0.944	0.895	0.988	0.945	0.894
			AEL	0.987	0.944	0.897	0.990	0.947	0.898
			NAL	0.993	0.951	0.904	0.989	0.951	0.900
50	50	1.136	CL	0.988	0.939	0.884	0.989	0.938	0.892
			AEL	0.984	0.937	0.882	0.990	0.946	0.896
			NAL	0.991	0.946	0.893	0.991	0.943	0.895

**Table 2:** Estimated coverage probabilities of the confidence intervals for  $\rho_0 = 0.75$ .

				$m = 25, n = 50$			$m = 50, n = 100$		
				$1 - \gamma$			$1 - \gamma$		
				0.99	0.95	0.90	0.99	0.95	0.90
$\alpha$	$\sigma_X$	$\sigma$		Gaussian					
2.327	1	1	CL	0.986	0.937	0.891	0.989	0.948	0.897
			AEL	0.978	0.926	0.881	0.987	0.950	0.902
			NAL	0.990	0.946	0.894	0.989	0.950	0.902
6.782	1	4	CL	0.987	0.938	0.878	0.990	0.945	0.895
			AEL	0.884	0.868	0.844	0.983	0.963	0.932
			NAL	0.991	0.949	0.890	0.989	0.951	0.898
3.68	1	2	CL	0.988	0.946	0.894	0.988	0.943	0.891
			AEL	0.974	0.935	0.892	0.990	0.954	0.904
			NAL	0.990	0.950	0.901	0.990	0.947	0.894
3.68	2	1	CL	0.974	0.923	0.872	0.982	0.940	0.886
			AEL	0.969	0.920	0.868	0.984	0.941	0.888
			NAL	0.986	0.938	0.883	0.985	0.942	0.890
1.839	1	0.5	CL	0.974	0.918	0.868	0.986	0.947	0.894
			AEL	0.967	0.913	0.864	0.987	0.948	0.896
			NAL	0.985	0.930	0.879	0.988	0.950	0.898
1.696	1	0.25	CL	0.948	0.898	0.851	0.980	0.941	0.888
			AEL	0.943	0.896	0.851	0.979	0.941	0.890
			NAL	0.965	0.909	0.862	0.982	0.946	0.893
$\alpha$	$\alpha_X$	$\sigma$		Gamma					
1	1	19	CL	0.987	0.940	0.886	0.986	0.942	0.884
			AEL	0.971	0.935	0.893	0.992	0.957	0.906
			NAL	0.992	0.952	0.899	0.989	0.946	0.888
7.39	1	0.5	CL	0.981	0.931	0.884	0.984	0.946	0.897
			AEL	0.973	0.925	0.877	0.984	0.947	0.896
			NAL	0.987	0.940	0.890	0.985	0.950	0.898
4.322	1	1	CL	0.984	0.953	0.881	0.989	0.947	0.896
			AEL	0.976	0.929	0.877	0.988	0.949	0.897
			NAL	0.990	0.944	0.893	0.991	0.952	0.899
2.727	1	2	CL	0.983	0.941	0.888	0.991	0.946	0.894
			AEL	0.975	0.933	0.882	0.992	0.950	0.901
			NAL	0.989	0.949	0.900	0.993	0.951	0.897
11.228	2	0.5	CL	0.979	0.933	0.884	0.986	0.941	0.889
			AEL	0.969	0.923	0.870	0.985	0.939	0.886
			NAL	0.979	0.935	0.885	0.987	0.940	0.889
6.391	2	1	CL	0.985	0.939	0.884	0.987	0.948	0.896
			AEL	0.975	0.928	0.878	0.988	0.951	0.901
			NAL	0.986	0.946	0.891	0.989	0.952	0.902
3.892	2	2	CL	0.987	0.944	0.888	0.989	0.949	0.893
			AEL	0.979	0.936	0.880	0.988	0.955	0.898
			NAL	0.991	0.953	0.898	0.990	0.954	0.898
$\alpha$	$\alpha_X$	$\sigma$		scaled Burr type X					
1	1	4.36	CL	0.987	0.943	0.890	0.987	0.947	0.894
			AEL	0.972	0.937	0.897	0.991	0.960	0.917
			NAL	0.991	0.955	0.901	0.989	0.955	0.901
10	10	1.62	CL	0.988	0.945	0.888	0.992	0.953	0.899
			AEL	0.978	0.929	0.873	0.990	0.953	0.904
			NAL	0.992	0.951	0.896	0.993	0.955	0.906
10	30	1.825	CL	0.990	0.944	0.890	0.986	0.944	0.893
			AEL	0.972	0.929	0.878	0.984	0.944	0.894
			NAL	0.993	0.953	0.899	0.988	0.947	0.898
30	10	1.275	CL	0.983	0.930	0.878	0.988	0.943	0.892
			AEL	0.973	0.922	0.870	0.986	0.944	0.896
			NAL	0.987	0.943	0.889	0.988	0.947	0.896
50	50	1.368	CL	0.989	0.946	0.897	0.988	0.947	0.899
			AEL	0.980	0.937	0.885	0.988	0.948	0.901
			NAL	0.989	0.953	0.904	0.991	0.950	0.903

**Table 3:** Estimated coverage probabilities of the confidence intervals for  $\rho_0 = 0.95$ .



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