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Interval Estimation of the Intraclass Correlation in a Nonlinear Mixed Effects Model

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Abstract

The computation of confidence intervals for the intra-class correlation coefficient (ICC) is addressed under a nonlinear dose–response model that includes a single random effect. Likelihood based higher order asymptotic procedures are employed for the interval estimation of the ICC, and are noted to perform well in terms of maintaining the coverage probability. The results are applied to a case study taken from the literature dealing with a meta-analysis of the individual participant data used to investigate the association between various dose levels of antipsychotic medications and the corresponding responses. The ICC is used in the case study in order to assess the possible heterogeneity across the different studies.

Keywords: Beta Approach; Dose-response Model; Heterogeneity; Meta-Analysis; Higher Order Asymptotics.

AMS Subject Classification: 62F25.

0. Professors Bimal Sinha and Bikas Sinha: A personal tribute

Professors Bimal Sinha and Bikas Sinha have been my teachers, collaborators, friends and mentors. In particular, Professor Bimal Sinha has been my senior colleague at the University of Maryland Baltimore County (UMBC) since 1985. His leadership was crucial in building up a top-rated statistics program at UMBC, starting from scratch. Some of my best collaborative research was carried out under his inspiration. While his outstanding research accomplishments are well-known, what I have found very touching is the way he has passionately looked out

for junior colleagues and students. If I was deserving of an academic opportunity or recognition, he took it up and pursued it even before I thought about it. Suffice to say words fail if I try to express my gratitude. Professor Bikas Sinha's frequent visits to our campus granted me the privilege to collaborate with him on a few research projects. I have always found his energy and excitement infectious. Thus it is a great privilege and honor to be contributing to this special issue of the *International Journal of Statistical Sciences.*

1. Introduction and Background

The intraclass correlation, or the intraclass correlation coefficient (ICC), is the correlation between a pair of repeated measurements on the same subject. It is also the proportion of the total variance that is not explained by the within-subject errors. The ICC is often used as a measure of the reliability of a measurement method, or an experimental method. The article by Liljequist, Elfving and Roaldsen (2019) provides a detailed discussion of the ICC. In the context of linear mixed and random effects models, inference concerning the ICC has been well-investigated in the literature; we refer to the work by Demetrashvili, Wit and Van den Heuvel (2016), and the recent article by Feng, Mathew and Adragni (2021) where accurate confidence intervals are developed for the ICC under linear mixed and random effects models.

The present work takes up the interval estimation of the ICC in a specific non-linear mixed effects model considered by Demetrashvili and Van den Heuvel (2015). The model was used in a meta-analysis application investigating the dose-response relationship between different doses of several antipsychotic drugs and the dopamine D_2 receptor occupancy. For eight antipsychotic medications, the meta-analysis was carried out by Lako et al. (2013). In order to briefly describe the scenario, let m denote the number of studies in the meta-analysis, with n_i patients in the ith study, and suppose O_{ij} denotes the dopamine D_2 receptor occupancy on the jth patient in the ith study. In their work, Lako et al. (2013) modeled the quantity $y_{ij} = \ln(1 - O_{ij})$ as a non-linear mixed effects model where the mean is a non-linear function of the administered dose; however, an additive random effect was included in the model in order to account for possible between study heterogeneity. If x denotes the administered dose, the non-linear function that was used to model the mean, say $\mu(x, \beta)$ was the following form of the Michaelis-Menten curve:

$$\mu(x, \beta) = \ln\left(\frac{\beta_2 + (1-\beta_1)x}{\beta_2 + x}\right),$$

where $\beta = (\beta_1, \beta_2)$ is an unknown parameter vector. The parameter β_1 has the range (0, 1]; it represents the maximum response of the drug in the population. In the literature, the notation E_{max} is also used instead of β_1. The parameter β_2 is assumed to be greater than 0, and it represents the dose associated with a 50% of response value, it is also denoted as EC_{50}.

Suppose there are m studies, and let x_{ij} denote the jth dose level used in the ith study, with y_{ij} denoting the corresponding response; j = 1, 2, ..., n_i, i = 1, 2, ..., m . An additive random effect τ_i is assumed for the unexplained among-study variation, and an error term ϵ_{ij} will take care of the within-study variability. Thus the assumed nonlinear mixed effects model is given by

$$y_{ij} = \mu(x_{ij}; \beta) + \tau_i + \epsilon_{ij}, \tag{1.1}$$

where τ_i and ϵ_{ij} are a independent random variables having the distributions $\tau_i \sim N(0, \sigma_\tau^2)$ and $\epsilon_{ij} \sim N(0, \sigma_\epsilon^2)$. Here we want to point out that even though the parameters β_1 and β_2 enter non-linearly in the model, the random effect τ_i is an additive term.

Based on the proposed nonlinear mixed effect model, the ICC is defined as the correlation coefficient on repeated measurements on the same patient in the same study, i.e., ICC = $\text{corr}(Y_{ij}, Y_{ij'})$, $j \neq j'$. Under the assumptions on the random variables τ_i and ϵ_{ij} appearing in the model (1.1), we see that the ICC, to be denoted by ρ, has the expression

$$\rho = \frac{\sigma_\tau^2}{\sigma_\tau^2 + \sigma_\epsilon^2}, \tag{1.2}$$

where σ_τ^2 and σ_ϵ^2 are the variances of τ_i and ϵ_{ij}, respectively. From the expression in (1.2), we see that we can interpret the ICC as the proportion of variation unrelated to individuals in the total variation.

It is the above set up that is considered in Lako et al. (2013), and taken up by Demetrashvili and Van den Heuvel (2015). The latter authors investigated the extent to which the between-study variability could be dominating, assessed using the ICC. In their work, Demetrashvili and Van den Heuvel (2015) have derived confidence limits for the ICC by the delta method, percentile bootstrap and an

approach referred to as the *beta-approach*, and have compared them based on estimated coverage probabilities. The authors conclude that in terms of maintaining the coverage probability, the beta-approach is to be preferred over the solutions obtained using the delta method and the percentile bootstrap.

In the present work, we shall investigate the interval estimation of the ICC by applying some likelihood based higher order asymptotic procedures due to DiCiccio, Martin and Stern (2001). We shall also compare our solution with that obtained using the beta-approach in terms of coverage probabilities and expected widths of the confidence intervals. The results will be illustrated using the example considered in Demetrashvili and van den Heuvel (2015).

2. Confidence intervals for the ICC

We shall now discuss different methods for the interval estimation of the ICC parameter under the model (1.1). We shall propose and compare them based on their estimated coverage probabilities and expected widths.

Let $y_i = (y_{i1}, \ldots, y_{in_i})'$ be the $n_i \times 1$ response vector from the ith study, and let $\boldsymbol{\mu}_i(\boldsymbol{x}_i; \beta) = \mu_i = (\mu(x_{i1}; \beta), \mu(x_{i2}; \beta), \ldots, \mu(x_{in_i}; \beta))'$ be the corresponding $n_i \times 1$ mean vector, where $\boldsymbol{x}_i = (x_{i1}, x_{i2}, \ldots, x_{in_i})'$. Note that $\boldsymbol{x}_i$ is the vector consisting of the dose levels used in the ith study. Under the model (1.1), we have the multivariate normal distribution

$$y_i \sim N[\boldsymbol{\mu}_i(\boldsymbol{x}_i; \beta), \Sigma_i], \quad where \quad \Sigma_i = \sigma_\tau^2 I_{ni} + \sigma_\epsilon^2 J_{n_i}, \tag{2.1}$$

J_{n_i} being an $n_i \times n_i$ matrix of ones. Let θ be the 4×1 vector of unknown parameters:

$$\theta = (\beta_1, \beta_2, \sigma_\tau^2, \sigma_\epsilon^2)'. \tag{2.2}$$

As a function of the parameter vector θ, the log-likelihood function, say $l(\theta)$, is given by

$$l(\theta) = -\frac{N}{2}\ln(2\pi) - \frac{1}{2}\sum_{i=1}^{m} \ln|\Sigma_i| - \frac{1}{2}\sum_{i=1}^{m} [(y_i - \boldsymbol{\mu}_i)'\Sigma_i^{-1}(y_i - \boldsymbol{\mu}_i)], \tag{2.3}$$

where we use the notations $\boldsymbol{\mu}_i = \boldsymbol{\mu}_i(\boldsymbol{x}_i; \beta)$, $\Sigma_i = \sigma_\tau^2 I_{ni} + \sigma_\epsilon^2 J_{n_i}$, i = 1, 2, ..., m, and $N = \sum_{i=1}^{m} n_i$. The maximum likelihood estimators of the parameters can be numerically obtained by maximizing the log-likelihood function (2.3); clearly,

closed-form solutions can't be found. A quasi-Newton optimization algorithm can be used to obtain the MLEs.

With the parameters as defined in (2.2), let $\hat{\theta}$ denote the MLE of θ, and $\hat{\theta}_\rho$ denote the constrained MLE of θ for a fixed value of the ICC ρ. The signed log-likelihood root $r(\rho)$ is given below, and its asymptotic normality, can be used for large sample inference concerning ρ:

$$r(\rho) = sign\,(\hat{\rho} - \rho)[2\{\ell(\hat{\theta}) - \ell(\hat{\theta}_\rho)\}]^{1/2}, \tag{2.4}$$

where $\text{sign}(x)$ is $+1$ if $x > 0$ and -1 if $x < 0$. Confidence limits for ρ can be obtained by equating $r(\rho)$ to standard normal percentiles, and solving for ρ. For example, a $100(1-\alpha)\%$ upper confidence limit for ρ is the solution of ρ to the equation $r(\rho) = -z_\alpha$, where z_α is the $100(1-\alpha)$th percentile of the standard normal distribution. Once the data are available, the required solution can be numerically obtained.

2.1. Two Higher Order Procedures

Higher order asymptotics consist of modifying the signed log-likelihood ratio test statistic $r(\rho)$ so that accurate small sample performance can be achieved. Here we shall not provide any technical details, and the necessary regularity conditions. In fact the necessary technical conditions are not entirely clear, since we are not in an iid set up. Nevertheless, we shall apply the higher order modifications, and then verify their accuracy based on simulations. The higher order modifications of $r(\rho)$ that we are proposing are based on the methodology developed in DiCiccio, Martin and Stern (2001). We shall refer to these as Modification 1 (M1) and Modification 2 (M2).

2.1.1. Modification 1

In order to present the first modification, let the mean and variance of $r(\rho)$ be denoted by $E(r(\rho)) = m(\theta)$ and $Var(r(\rho)) = 1 + v(\theta)$, where we recall that θ is the parameter vector defined in (2.2). The modified quantity, to be denoted by $r_1(\rho)$, is a standardization of $r(\rho)$ using the mean $m(\hat{\theta}_\rho)$ and variance $1 + v(\hat{\theta}_\rho)$, where $\hat{\theta}_\rho$ is the MLE of θ for a fixed value of ρ. Thus

$$r_1(\rho) = \frac{r(\rho) - m(\hat{\theta}_\rho)}{\{1 + v(\hat{\theta}_\rho)\}^{1/2}}. \tag{2.5}$$

We note that the only unknown parameter involved in $r_1(\rho)$ is the ICC ρ. A normal approximation for the distribution of $r_1(\rho)$ is known to be significantly more accurate compared to that for $r(\rho)$. Thus confidence limits for ρ obtained using $r_1(\rho)$ as a pivot is expected to be more accurate in terms of maintaining the coverage probability.

It should however be noted that analytic expressions for $m(\theta)$ and $v(\theta)$ are not available, and the computation of $m(\hat{\theta}_\rho)$ and $1 + v(\hat{\theta}_\rho)$ is an issue that needs to be addressed. As suggested in DiCiccio, Martin and Stern (2001), these quantities can be numerically obtained by proceeding as follows. For a fixed value of ρ, generate observation vectors, say y_i^*, i = 1, 2, ..., m, under the model (2.1) with the parameter θ replaced by $\hat{\theta}_\rho$. Compute the value of $r(\rho)$ given in (2.4), using y_i^* in the place of y_i, i = 1, 2, ..., m; let $r^*(\rho)$ denote the value of $r(\rho)$ so obtained. For the same fixed value of ρ, repeat this several times, say M times, resulting in M values of $r^*(\rho)$, say $r_j^*(\rho)$, j = 1, 2, ..., M. The mean and variance of these M values give estimates of $m(\hat{\theta}_\rho)$ and $1 + v(\hat{\theta}_\rho)$, respectively. Once $m(\hat{\theta}_\rho)$ and $1 + v(\hat{\theta}_\rho)$ are thus obtained, the statistic $r_1(\rho)$ given in (2.5) can be evaluated at the fixed value of ρ. Equating $r_1(\rho)$ to appropriate standard normal percentiles, confidence limits for ρ can be obtained. In order to implement such a methodology, it is necessary to repeat the procedure just outlined for a grid of values of ρ, until a value of ρ is found so that $r_1(\rho)$ is equal to the appropriate percentile of the standard normal distribution. We note that a $100(1-\alpha)$% upper confidence limit for ρ is obtained as the solution to $r_1(\rho) = -z_\alpha$, where z_α is the $100(1-\alpha)$th percentile of the standard normal distribution. Similarly, two-sided confidence limits are obtained by solving $r_1(\rho) = z_{\alpha/2}$ and $r_1(\rho) = -z_{\alpha/2}$. The algorithm given below gives the steps necessary to compute the confidence limits for ρ using the procedure just outlined; the algorithm is presented for the computation of a $100(1-\alpha)$% upper confidence limit for ρ.

Algorithm 1: Steps for computing a $100(1-\alpha)$% upper confidence limit for ρ using the normal approximation for the statistic $r_1(\rho)$ given in (2.5)

1. Compute the MLE $\hat{\theta}$ of the parameter vector θ by maximizing the log-likelihood function $l(\theta)$ in (2.3).

2. Fix a value for ρ, say $\tilde{\rho}$, and maximize $l(\theta)$ subject to the constraint that $\rho = \tilde{\rho}$. Let the corresponding estimate of θ be denoted as $\hat{\theta}_{\tilde{\rho}}$.

3. Compute $r(\tilde{\rho})$ using the expression given in (2.4).

4. Generate an observation vector y_i^* under the model (2.1) with the parameters replaced by $\hat{\theta}_{\tilde{\rho}}$, i = 1, 2, ..., m. Compute the value of $r(\tilde{\rho})$ in (2.4) using y_i^* in the place of y_i, i = 1, 2, ..., m. Let $r^*(\tilde{\rho})$ denote the value of $r(\tilde{\rho})$ so obtained.

5. Repeat the above step several times, say M times, resulting in M values of $r^*(\tilde{\rho})$, say $r_j^*(\tilde{\rho})$, j = 1, 2, ..., M. Compute the mean and variance of these M values, to be denoted by $m(\hat{\theta}_{\tilde{\rho}})$ and $1 + v(\hat{\theta}_{\tilde{\rho}})$, respectively.

6. Using the values of $m(\hat{\theta}_{\tilde{\rho}})$ and $1 + v(\hat{\theta}_{\tilde{\rho}})$ so obtained, compute the statistic $r_1(\tilde{\rho})$ in (2.5).

7. If $r_1(\tilde{\rho}) = -z_\alpha$, then $\tilde{\rho}$ is the $100(1-\alpha)\%$ upper confidence limit for ρ. If $r_1(\tilde{\rho}) \neq -z_\alpha$, adjust the value of $\tilde{\rho}$ in Step 2, and repeat steps 2-6, until a value is found for which $r_1(\rho_0) = -z_\alpha$.

2.1.2. Modification 2

A second higher order procedure given in DiCiccio, Martin and Stern (2001) starts with a hypothesis testing scenario:

$$H_0: \rho = \rho_0,\ H_a: \rho > \rho_0,$$

for a specified ρ_0. The proposed method consists of computing the p-value as

$$P_{\hat{\theta}_{\rho_0}}(r(\rho) \leq r_{obs}),$$

where $r(\rho_0)$ is defined in (2.4), and r_{obs} denotes its observed value. Note that the p-value given above is not computed using an asymptotic normal distribution of $r(\rho)$; rather, it is computed by Monte carlo simulation when the parameter θ takes the value $\hat{\theta}_{\rho_0}$. In order to compute confidence limits for ρ, we proceed as follows. Generate M parametric bootstrap samples when ρ takes the value ρ_0 and the parameter θ takes the value $\hat{\theta}_{\rho_0}$. Now compute M values of $r(\rho_0)$, say $r_j^*(\rho_0)$, j = 1, 2, ..., M, based on the M generated samples, and compute the proportion of the $r_j^*(\rho_0)$ values that are less than r_{obs}. If the value ρ_0 is such that this proportion is equal to $(1-\alpha)$, then such a value ρ_0 is a $100(1-\alpha)\%$ upper confidence limit for ρ. For obtaining a lower confidence limit for ρ, we want ρ_0 such that the proportion of the $r_j^*(\rho_0)$ values that are less than r_{obs} is equal to α.

2.2. Other Methods

2.2.1. Beta-approach (Demetrashvili and Van den Heuvel (2015))

The beta-approach proposed in Demetrashvili and Van den Heuvel (2015), consists of approximating the distribution of the MLE $\hat{\rho}$ of ρ by a beta distribution: $\hat{\rho} \sim \mathrm{B}eta(a, b)$, where $a > 0$ and $b > 0$. Let $\hat{\sigma}^2_{\hat{\rho}}$ be the estimated variance of $\hat{\rho}$ (see below). Equating the mean and variance of $\mathrm{B}eta(a, b)$ to $\hat{\rho}$ and $\hat{\sigma}^2_{\hat{\rho}}$, respectively, we can solve for a and b. The solutions will be denoted by $\hat{a}$ and $\hat{b}$, respectively, and are given by

$$\hat{a} = \frac{\hat{\rho}[\hat{\rho}(1-\hat{\rho})-\hat{\sigma}^2_{\hat{\rho}}]}{\hat{\sigma}^2_{\hat{\rho}}}$$

$$\hat{b} = \frac{(1-\hat{\rho})[\hat{\rho}(1-\hat{\rho})-\hat{\sigma}^2_{\hat{\rho}}]}{\hat{\sigma}^2_{\hat{\rho}}}$$

A first-order Taylor expansion is used in Demetrashvili and Van den Heuvel (2015) in order to estimate the variance of $\hat{\rho}$, and the estimated variance is given by

$$\hat{\sigma}^2_{\hat{\rho}} = \frac{\hat{\sigma}^4_{\epsilon}}{(\hat{\sigma}^2_{\tau}+\hat{\sigma}^2_{\epsilon})^4}\hat{V}_{\hat{\sigma}^2_{\tau}} + \frac{\hat{\sigma}^4_{\tau}}{(\hat{\sigma}^2_{\tau}+\hat{\sigma}^2_{\epsilon})^4}\hat{V}_{\hat{\sigma}^2_{\epsilon}} - \frac{2\hat{\sigma}^2_{\tau}\hat{\sigma}^2_{\epsilon}}{(\hat{\sigma}^2_{\tau}+\hat{\sigma}^2_{\epsilon})^4}\hat{C}_{\hat{\sigma}^2_{\tau}\hat{\sigma}^2_{\epsilon}}$$

where, $\hat{V}_{\hat{\sigma}^2_{\tau}}$ and $\hat{V}_{\hat{\sigma}^2_{\epsilon}}$ are the estimated variance of estimators (MLEs) $\hat{\sigma}^2_{\tau}$ and $\hat{\sigma}^2_{\epsilon}$, and $\hat{C}_{\hat{\sigma}^2_{\tau}\hat{\sigma}^2_{\epsilon}}$ is the estimated covariance between $\hat{\sigma}^2_{\tau}$ and $\hat{\sigma}^2_{\epsilon}$. Then by using the $\mathrm{B}eta(\hat{a}, \hat{b})$ approximation, $100(1-\alpha)\%$ confidence limits for ρ can be obtained. The lower and upper limits of the $100(1-\alpha)\%$ two-sided confidence interval are thus obtained as $\mathrm{B}eta_{\frac{\alpha}{2}}(\hat{a}, \hat{b})$ and $\mathrm{B}eta_{1-\frac{\alpha}{2}}(\hat{a}, \hat{b})$, respectively. Here $\mathrm{B}eta_{\gamma}(\hat{a}, \hat{b})$ stands for the 100γth percentile of $\mathrm{B}eta(\hat{a}, \hat{b})$. In the cases where the ICC is estimated to be zero, the expressions for $\hat{a}$ and $\hat{b}$ are different from above; details are given in Demetrashvili and Van den Heuvel (2015).

2.2.2. The Wald statistic: bootstrap and normal approximations

Let

$$W_{\rho} = \frac{(\hat{\rho}-\rho)}{[\hat{V}\hat{\rho})]^{1/2}}$$

where $\hat{\rho}$ is the MLE of ρ and $\hat{V}(\hat{\rho})$ is its estimated asymptotic variance. We shall explore the possibility of computing confidence limits for ρ using the usual normal approximation for W_ρ, and also by approximating its distribution using a parametric bootstrap.

3. Simulation Studies

Having introduced several confidence intervals for ρ under the model (1.1), we shall now carry out simulation results to evaluate and compare their performances in terms of estimated coverage probabilities and expected widths. We have considered only two-sided confidence intervals.

3.1. The simulation settings

We have used the simulation settings used in Demetrashvili and Van den Heuvel (2015). The variance components used in the simulations have the following values: $\sigma_\tau^2 = 0.001$ and σ_ϵ^2 = {0.009, 0.004, 0.0023, 0.0015, 0.001, 0.00067, 0.00043, 0.00025, 0.00011}. These choices give the ICC values 0.1, 0.2, 0.3, ... , 0.9. Now recall our notation that we have m studies with n_i responses in the ith study. We shall assume a balanced design, that is, the n_is are all equal, having common value, denoted by n. We have chosen (m, n) = (5, 5), (5, 8), (5, 20), (5, 30), (8, 5), (10, 5), (10, 10), (20, 10), and (30, 10). The dose levels (i.e., the x_{ij}s) were simulated from a Uniform (1, 21) distribution. The parameters β_1 and β_2 were set equal to 0.8 and 16, respectively.

Even though the assumed non-linear model is (1.1), we shall also use another scenario for the simulations; the model settings used in the simulations are given below:

Simulation setting 1

$$y_{ij} = (\beta_1 x_{ij})/(\beta_2 + x_{ij}) + \sigma_\tau z_i + \sigma_\epsilon z_{ij}$$

where the z_i and z_{ij} are independent standard normal random variables.

Simulation setting 2

$$y_{ij} = ln\left((\beta_2 + (1 - \beta_1)x_{ij})/(\beta_2 + x_{ij})\right) + \sigma_\tau z_i + \sigma_\epsilon z_{ij},$$

where the z_i and z_{ij} are once again independent standard normal random variables. We note that the second simulation setting corresponds to our model (1.1).

Throughout, we have used a 95% nominal level. It should be noted that Demetrashvili and Van den Heuvel (2015) have reported numerical results only for the first simulation setting.

3.2. Results on Coverage Probabilities and Expected Widths

In order to estimate the coverage probabilities and expected widths, we have used 10,000 simulations. The results are presented in Table 1 – Table 4. In the tables, M1 and M2 refer to Modification 1 and Modification 2, respectively, given in Section 2.1.

From the coverage probabilities reported in Table 1 and Table 3, we note that the only approach that gives consistently good coverage probabilities is the Modification 2 (M2), with M1 being a close second, regardless of the simulation scenario. Both $r(\rho)$ and the Wald statistic provide confidence intervals with poor coverage, and these cannot be recommended for practical use. The coverages of the Beta approach, reported in Table 1, are taken from Demetrashvili and Van den Heuvel (2015), and correspond to the implementation of a two-step estimation procedure based on nonlinear least squares and the restricted maximum likelihood. The authors have not reported any coverage probabilities under the second simulation setting, and we also did not carry out any simulations for the Beta approach in the second simulation setting. We conclude from Table 1 that the Beta approach is conservative, overall. In spite of this, the Beta approach does give shorter expected widths in many instances, especially when ρ is small or large (see Table 2). For moderate values of ρ both M1 and M2 provide smaller expected widths, compared to that from the Beta approach. The expected widths reported in Table 2 and Table 4 show that there is not much difference between M1 and M2 in terms of the expected width of the confidence intervals. Table 3 and Table 4 do not include the Beta approach since Demetrashvili and Van den Heuvel (2015) did not consider the simulation setting 2 in their numerical results, and we did not carry out any simulations for the Beta approach under simulation setting 2. Furthermore, in view of the poor coverage probability performance of the confidence intervals based on $r(\rho)$ and the Wald statistic, these were not included while computing the expected width of the confidence intervals.

Table 1: Coverage probabilities of the two-sided 95% confidence intervals under simulation setting 1

			Coverage probability					
m	n	ρ	$r(\rho)$	M1	M2	Beta	Wald normal	Wald bootstrap
5	5	0.1	0.984	0.956	0.948	0.963	0.985	0.834
5	8	0.1	0.989	0.962	0.950	0.972	0.995	0.795
8	5	0.1	0.983	0.960	0.948	0.961	0.988	0.871
10	5	0.1	0.984	0.965	0.948	0.958	0.989	0.829
10	10	0.1	0.950	0.962	0.951	0.994	0.988	0.765
5	5	0.2	0.982	0.965	0.951	0.956	0.979	0.751
5	8	0.2	0.938	0.969	0.949	0.975	0.975	0.735
8	5	0.2	0.952	0.966	0.950	0.959	0.984	0.753
10	5	0.2	0.943	0.963	0.948	0.965	0.985	0.761
10	10	0.2	0.930	0.951	0.952	0.979	0.895	0.817
5	5	0.3	0.929	0.969	0.952	0.950	0.966	0.751
5	8	0.3	0.908	0.945	0.950	0.978	0.874	0.755
8	5	0.3	0.928	0.957	0.952	0.966	0.932	0.777
10	5	0.3	0.932	0.950	0.949	0.977	0.924	0.794
10	10	0.3	0.930	0.950	0.950	0.943	0.866	0.881
5	5	0.4	0.906	0.970	0.954	0.953	0.913	0.769
5	8	0.4	0.907	0.953	0.951	0.976	0.840	0.790
8	5	0.4	0.926	0.952	0.950	0.972	0.891	0.815
10	5	0.4	0.934	0.950	0.949	0.978	0.891	0.845
10	10	0.4	0.930	0.949	0.949	0.932	0.869	0.925
5	5	0.5	0.904	0.958	0.950	0.961	0.876	0.801
5	8	0.5	0.906	0.949	0.949	0.950	0.833	0.830
8	5	0.5	0.926	0.948	0.950	0.975	0.878	0.859
10	5	0.5	0.933	0.952	0.950	0.959	0.886	0.893
10	10	0.5	0.930	0.950	0.950	0.933	0.879	0.952
5	5	0.6	0.905	0.950	0.950	0.964	0.859	0.837
5	8	0.6	0.905	0.949	0.949	0.936	0.838	0.876
8	5	0.6	0.925	0.951	0.951	0.955	0.879	0.904
10	5	0.6	0.932	0.952	0.952	0.950	0.893	0.933
10	10	0.6	0.930	0.950	0.949	0.936	0.889	0.968
5	5	0.7	0.907	0.947	0.951	0.972	0.859	0.878
5	8	0.7	0.907	0.951	0.952	0.933	0.848	0.914
8	5	0.7	0.926	0.950	0.949	0.944	0.888	0.943
10	5	0.7	0.933	0.951	0.950	0.947	0.903	0.959
10	10	0.7	0.934	0.949	0.950	0.937	0.905	0.975
5	5	0.8	0.909	0.948	0.952	0.956	0.869	0.919
5	8	0.8	0.912	0.952	0.953	0.937	0.866	0.947
8	5	0.8	0.926	0.951	0.949	0.946	0.904	0.964
10	5	0.8	0.934	0.952	0.950	0.951	0.917	0.975
10	10	0.8	0.936	0.950	0.951	0.941	0.922	0.978
5	5	0.9	0.912	0.950	0.951	0.957	0.889	0.958
5	8	0.9	0.919	0.953	0.953	0.946	0.901	0.968
8	5	0.9	0.929	0.952	0.950	0.952	0.920	0.976
10	5	0.9	0.937	0.952	0.951	0.950	0.926	0.978
10	10	0.9	0.938	0.952	0.950	0.949	0.933	0.978

Table 2: Expected widths of the 95% confidence intervals under simulation setting 1

m	n	ρ	Expected width		
			M1	M2	Beta
5	5	0.1	0.524	0.521	0.397
5	8	0.1	0.521	0.519	0.394
8	5	0.1	0.528	0.523	0.383
10	5	0.1	0.513	0.515	0.373
10	10	0.1	0.497	0.499	0.370
5	5	0.2	0.681	0.692	0.579
5	8	0.2	0.673	0.680	0.565
8	5	0.2	0.672	0.681	0.569
10	5	0.2	0.661	0.674	0.553
10	10	0.2	0.657	0.660	0.545
5	5	0.3	0.701	0.706	0.709
5	8	0.3	0.697	0.702	0.702
8	5	0.3	0.682	0.685	0.693
10	5	0.3	0.679	0.682	0.672
10	10	0.3	0.645	0.648	0.631
5	5	0.4	0.651	0.664	0.711
5	8	0.4	0.643	0.652	0.697
8	5	0.4	0.647	0.657	0.704
10	5	0.4	0.642	0.654	0.700
10	10	0.4	0.629	0.638	0.687
5	5	0.5	0.671	0.686	0.736
5	8	0.5	0.680	0.690	0.728
8	5	0.5	0.683	0.684	0.732
10	5	0.5	0.668	0.673	0.727
10	10	0.5	0.649	0.657	0.708
5	5	0.6	0.600	0.609	0.604
5	8	0.6	0.591	0.597	0.596
8	5	0.6	0.594	0.601	0.582
10	5	0.6	0.594	0.592	0.580
10	10	0.6	0.583	0.584	0.577
5	5	0.7	0.562	0.589	0.439
5	8	0.7	0.547	0.571	0.421
8	5	0.7	0.551	0.576	0.432
10	5	0.7	0.543	0.568	0.427
10	10	0.7	0.535	0.544	0.418
5	5	0.8	0.473	0.489	0.394
5	8	0.8	0.467	0.484	0.391
8	5	0.8	0.471	0.486	0.388
10	5	0.8	0.463	0.469	0.377
10	10	0.8	0.432	0.438	0.368
5	5	0.9	0.304	0.306	0.313
5	8	0.9	0.289	0.292	0.297
8	5	0.9	0.303	0.310	0.298
10	5	0.9	0.287	0.291	0.283
10	10	0.9	0.257	0.262	0.251

Table 3: Coverage probabilities of the two-sided 95% confidence intervals under simulation setting 2

m	n	ρ	Coverage probability		
			$r(\rho)$	M1	M2
5	5	0.1	0.988	0.958	0.948
5	8	0.1	0.988	0.961	0.951
8	5	0.1	0.935	0.957	0.948
10	5	0.1	0.934	0.958	0.948
10	10	0.1	0.929	0.960	0.951
5	5	0.2	0.984	0.959	0.953
5	8	0.2	0.939	0.961	0.952
8	5	0.2	0.954	0.960	0.952
10	5	0.2	0.941	0.959	0.951
10	10	0.2	0.931	0.952	0.953
5	5	0.8	0.905	0.947	0.952
5	8	0.8	0.920	0.951	0.953
8	5	0.8	0.923	0.953	0.949
10	5	0.8	0.933	0.951	0.950
10	10	0.8	0.931	0.951	0.951
5	5	0.9	0.911	0.952	0.951
5	8	0.9	0.918	0.954	0.953
8	5	0.9	0.930	0.953	0.951
10	5	0.9	0.938	0.952	0.951
10	10	0.9	0.939	0.953	0.952

Table 4: Expected widths of the 95% confidence intervals under simulation setting 2

m	n	ρ	Expected width	
			M1	M2
5	5	0.1	0.542	0.535
5	8	0.1	0.535	0.542
8	5	0.1	0.531	0.533
10	5	0.1	0.513	0.523
10	10	0.1	0.501	0.509
5	5	0.2	0.701	0.705
5	8	0.2	0.696	0.698
8	5	0.2	0.695	0.705
10	5	0.2	0.684	0.697
10	10	0.2	0.682	0.687
5	5	0.8	0.495	0.503
5	8	0.8	0.486	0.506
8	5	0.8	0.499	0.502
10	5	0.8	0.481	0.490
10	10	0.8	0.451	0.459
5	5	0.9	0.326	0.328
5	8	0.9	0.305	0.311
8	5	0.9	0.325	0.328
10	5	0.9	0.304	0.312
10	10	0.9	0.273	0.284

4. An example

We shall now take up the example considered in Demetrashvili and Van den Heuvel (2015). The example is on the relationship between Dopamine D_2 receptor and the psychopathology of diseases such as schizophrenia. For eight antipsychotic medications, an individual participant data meta-analysis is reported in Lako et al. (2013) with the goal of studying the relationship between a prescribed dose and the response. In this meta-analysis, it was also important to assess the magnitude of the variability between studies as a fraction of the total variability. Clearly, this called for inference concerning the ICC.

The data on eight antipsychotic medications consisted of 74 studies with 638 patients in total. The data on each drug was analyzed using the model (1.1). The analysis that follows is based on data for three drugs: Amisulpride (5 studies, with a total of 62 patients), Clozapine (17 studies, with a total of 106 patients, and Halopridol (6 studies, with a total of 90 patients). The following table gives the confidence intervals for the ICC for each drug, computed by the different methods:

Table 5: 95% confidence intervals for the ICC ρ under the model (1.1)

Drug	Method	Lower limit	Upper limit	Width
Haloperidol	M1	0.319	0.870	0.551
	M2	0.307	0.892	0.585
	Beta	0.468	0.875	0.407
Clozapine	M1	0.034	0.516	0.482
	M2	0.031	0.522	0.491
	Beta	0.019	0.407	0.388
Amisulpride	M1	0.151	0.575	0.424
	M2	0.147	0.612	0.465
	Beta	0.094	0.851	0.757

While the confidence intervals based on M1 nd M2 are somewhat similar, we note that the one based on the Beta approach is shorter in the first two cases, but wider in the third case. The maximum likelihood estimates of ρ are 0.682, 0.152 and 0.487, respectively, for Haloperidol, Clozapine and Amisulpride. Thus the estimate is around 0.50 in the third case, and are somewhat towards the extremes in the first and second cases. Thus the widths of the confdence intervals in the example are consistent with what is noted for the expected widths in Table 2.

5. Discussion

The literature on higher order asymptotic procedures has demonstrated the applicability of such procedures for accurate inference in scenarios where the sample sizes may not be large. The book by Brazzale, Davison and Reid (2007) gives a detailed discussion of different likelihood based higher order inference procedures available in the literature. In the present work, we have taken up the

application of two such procedures, due to DiCiccio, Martin and Stern (2001) for the accurate interval estimation of the intraclass correlation coefficient (ICC) in a specific nonlinear mixed effects model that includes a single additive random effect. The ICC is a parameter that has wide applicability for the assessment of the reliability of a measurement method, or of an experimental method. Our work shows that the higher order procedures result in confidence intervals for the ICC that accurately maintain the coverage probability. We have also compared the resulting confidence intervals with another interval proposed in the literature, obtained by approximating the distribution of the estimated ICC with a beta distribution. The latter method is referred to as the beta approach, and it turns out to be somewhat conservative. However, a comparison of the expected widths shows that the beta approach is quite competitive.

In the context of very general linear mixed effects models, accurate inference for the ICC has recently been obtained by Feng, Mathew and Adragni (2021), once again by applying the higher order procedures. An advantage of the higher order procedures is that they can be applied to any parametric function. Furthermore, they are likelihood based, and have rigorous theoretical justifications. We hope that this work will generate further interest in the application of higher order procedures to various parametric inference problems.

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