

Title: Estimation of Coefficients of Individual Agreement (CIAs) for Quantitative and Binary Data using SAS® and R

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Abstract: The coefficients of individual agreement (CIA's), which are based on the ratio of the intra- and inter-observer disagreement, provide a general approach for evaluating agreement between two fixed methods of measurements or human observers. In this paper, a macro is presented for computation of the CIA's between two observers with quantitative or binary measurements. The macro is available in both SAS® and R. A detailed illustration of the computations, macro variable definition, input and output for the SAS and R programs are also included in the text. The macro provides estimation of CIA's, their standard errors as well as confidence intervals, for the cases with or without a reference method. Data from a carotid stenosis screening study is used as an example of continuous measurement. Data from a study involving the evaluation of mammograms by ten radiologists is used to illustrate a binary data example.

Key Words: Agreement, Coefficient of individual agreement, Macro, Mean Squared Difference

1. Introduction

In medical and other related sciences, many statistical approaches have been proposed for assessing agreement among observers or measurement methods. In a recent review paper, Barnhart et al. [1] classified the existing methods for evaluation agreement as follows: (1) descriptive tools, such as descriptive statistics and plots, (2) unscaled agreement indices, such as mean squared deviation, coverage probability (CP) and total deviation index (TDI) [1, 2, 3, 4], and (3) scaled agreement indices.

Among the scaled agreement methods, the intraclass correlation coefficient (ICC) [5, 6] and the concordance correlation coefficient (CCC) [7, 8, 9, 10] are the most popular indices. Under certain conditions, the CCC is equivalent to one version of the ICC. If the ANOVA model assumptions are correct, the CCC reduces to the agreement ICC defined by this ANOVA model [1, 6, 9].

The CCC is based on comparing the mean squared deviation (MSD) [4] to its value under independence. However, independence and disagreement are two different concepts [11]. Furthermore, the CCC depends on the between-subject variability. Atkinson and Nevill [12] pointed out that an increase in the between-subject variability results in a larger value of CCC even if the individual differences between measurements by the two methods remain the same. Barnhart et al. [13] also showed that the CCC depends on the between-subject variability due to the fact that it is scaled relative to the maximum disagreement defined as the expected squared difference under independence. Furthermore, the ICC and the CCC are only defined for quantitative data.

Barnhart and colleagues [14, 15, 16] introduced the coefficients of individual agreement (CIA's), which are scaled relative to an acceptable disagreement, with the goal of establishing interchangeability of observers. An 'acceptable disagreement' requires that the differences between measurements of different observers are similar to the differences between replicated measurements of the same observer. The concept of individual agreement is derived from the idea of individual bioequivalence in bioequivalence studies [15, 17, 18, 19]. Similar agreement indices

have been proposed by Haber et al. [20] and Shao and Zhong [21]. The CIA's compare differences between measurements from different observers to the differences of replicated measurements of the same observer. Therefore, they require replications which allow us to measure the within-observer variability.

In this paper, we present a SAS macro and an R program for the estimation of CIA's with and without a reference. The macros also provide estimates for the standard errors of the estimated CIA's as well as confidence intervals. Computational methods and theory, as well as the estimation of CIA's and the standard errors are introduced in the following section. The details of the SAS and R programs are discussed in section 3. Two examples are included to illustrate the estimation of CIA's in section 4. A brief summary follows in section 5.

2. Method

2.1 General Definition

Haber and Barnhart [14] considered the CIAs for the case of two observers, a continuous measured variable and a general disagreement function. Denote the readings of the two observers by X and Y . A disagreement function $G(X, Y)$ must satisfy (a) $G(X, Y) \geq 0$, and (b) $G(X, Y)$ increases as the disagreement between X and Y increases, according to a specific criterion. The agreement between X and Y is 'acceptable' if the disagreement function does not change when replacing one of the observers by the other, i.e., if $G(X, Y) \approx G(X, X')$ and $G(X, Y) \approx G(Y, Y')$, where $G(X, X')$ is the disagreement between two replicated observations made by observer X and $G(Y, Y')$ is similarly defined for observer Y . Therefore, the estimation of the new coefficients requires replicated observations made by the same observer on the same subject.

When neither X or Y is a 'reference' observer, the (CIA) with a specific disagreement function G is defined as:

$$\psi_G^N = \frac{[G(X, X') + G(Y, Y')]/2}{G(X, Y)}.$$

When X is a 'reference' (gold standard) and Y is a 'new' observer, the CIA is defined as

$$\psi_G^R = \frac{G(X, X')}{G(X, Y)}.$$

When the mean squared difference (MSD) is used as the G function, the coefficient ψ_G^N varies between 0 and 1 [14]; while, ψ_G^R may exceed 1. For both coefficients, a value close to unity or above unity indicates an acceptable agreement. Haber and Barnhart [14] and Haber et al. [16] suggested that $\psi \geq 0.8$ indicates acceptable agreement.

Hereafter, we will use the most common disagreement function,

$G(X, Y) = MSD(X, Y) = E(X - Y)^2$, where MSD is the mean squared deviation. CIA's with continuous observations and different disagreement functions have been discussed in Haber and Barnhart [14].

When the observations are binary, we have:

$G(X, Y) = E(X - Y)^2 = P(X = 0, Y = 1) + P(X = 1, Y = 0) = P(X \neq Y)$. The binary case has been discussed in Haber et al. [16].

Suppose that both observers evaluate the same N study subjects, indexed by $i = 1, \dots, N$. Let X_{ik} denote the k -th replicated observation of X ($k = 1, \dots, K$) and Y_{il} denote the l -th replicated observation of Y ($l = 1, \dots, L$) on subject i .

2.2 Estimation

In this section, the observations may be continuous or binary.

2.2.1 Estimated ψ 's

We first consider the disagreements for a particular subject i . Define:

$$G_i(X, Y) = E[(X_{ik} - Y_{il})^2 | i] ,$$

$$G_i(X, X') = E[(X_{ik} - X_{ik'})^2 | i] \text{ for } k < k' ,$$

$$G_i(Y, Y') = E[(Y_{il} - Y_{il'})^2 | i] \text{ for } l < l' .$$

We then obtain the overall disagreement functions as

$$G(X, Y) = E[G_i(X, Y)], \quad G(X, X') = E[G_i(X, X')], \quad G(Y, Y') = E[G_i(Y, Y')] ,$$

where E stands for the expectation over all study subjects. We first estimate the disagreement functions for each subject:

$$\hat{G}_i(X, Y) = \frac{1}{KL} \sum_{k=1}^K \sum_{l=1}^L (X_{ik} - Y_{il})^2 ,$$

$$\hat{G}_i(X, X') = \frac{2}{K(K-1)} \sum_{k=1}^{K-1} \sum_{k'=k+1}^K (X_{ik} - X_{ik'})^2 ,$$

$$\hat{G}_i(Y, Y') = \frac{2}{L(L-1)} \sum_{l=1}^{L-1} \sum_{l'=l+1}^L (Y_{il} - Y_{il'})^2 .$$

Then, the estimates of the overall disagreement functions are:

$$\hat{G}(X, Y) = \bar{G}(X, Y) = \frac{1}{N} \sum_{i=1}^N \hat{G}_i(X, Y), \quad \hat{G}(X, X') = \bar{G}(X, X') = \frac{1}{N} \sum_{i=1}^N \hat{G}_i(X, X') , \text{ and}$$

$$\hat{G}(Y, Y') = \bar{G}(Y, Y') = \frac{1}{N} \sum_{i=1}^N \hat{G}_i(Y, Y') .$$

Finally, the estimated ψ 's are obtained by substituting the estimated G 's into their definitions in Section 2.1.

2.2.2 Standard Errors of Estimated ψ 's

To simplify the notations, let $G^{(1)} = G(X, X')$, $G^{(2)} = G(Y, Y')$ and $G^{(3)} = G(X, Y)$. Then

$\hat{\psi}^N = A_1 / B$, where $A_1 = (\bar{G}^{(1)} + \bar{G}^{(2)}) / 2$ and $B = \bar{G}^{(3)}$. Similarly, $\hat{\psi}^R = A_2 / B$, where

$A_2 = \bar{G}^{(1)}$. Now, for $p = 1, 2, 3$, denote the sample variances

$S^2(G^{(p)}) = \frac{1}{N-1} \sum_{i=1}^N (\hat{G}_i^{(p)} - \bar{G}^{(p)})^2$, so that $\hat{Var}(\bar{G}^{(p)}) = S^2(G^{(p)}) / N$. In addition, for

$1 \leq p < q \leq 3$, denote the sample covariance of $G^{(p)}$ and $G^{(q)}$ by

$Cov(G^{(p)}, G^{(q)}) = [\sum_{i=1}^N (\hat{G}_i^{(p)} - \bar{G}^{(p)})(\hat{G}_i^{(q)} - \bar{G}^{(q)})] / (N-1)$, so that

$\hat{Cov}(\bar{G}^{(p)}, \bar{G}^{(q)}) = Cov(G^{(p)}, G^{(q)}) / N$.

Using the above notations,

$$\hat{Var}(A_1) = [S^2(G^{(1)}) + S^2(G^{(2)}) + 2Cov(G^{(1)}, G^{(2)})] / 4N,$$

$$\hat{Var}(A_2) = S^2(G^{(1)}) / N,$$

$$\hat{Var}(B) = S^2(G^{(3)}) / N,$$

$$\hat{Cov}(A_1, B) = [Cov(G^{(1)}, G^{(3)}) + Cov(G^{(2)}, G^{(3)})] / 2N,$$

$$\hat{Cov}(A_2, B) = Cov(G^{(1)}, G^{(3)}) / N.$$

Finally, substitute these in the approximation for the variance of a ratio:

$$\hat{Var}(\hat{\psi}^N) = \hat{Var}\left(\frac{A_1}{B}\right) \approx \frac{A_1^2}{B^2} \left[\frac{\hat{Var}(A_1)}{A_1^2} + \frac{\hat{Var}(B)}{B^2} - \frac{2\hat{Cov}(A_1, B)}{A_1 \cdot B} \right].$$

Similarly,

$$\hat{Var}(\hat{\psi}^R) = \hat{Var}\left(\frac{A_2}{B}\right) \approx \frac{A_2^2}{B^2} \left[\frac{\hat{Var}(A_2)}{A_2^2} + \frac{\hat{Var}(B)}{B^2} - \frac{2\hat{Cov}(A_2, B)}{A_2 \cdot B} \right].$$

The standard errors of those two estimators are simply the square roots of the variance estimators.

3. SAS and R Program

The programs in either SAS or R estimate the CIA's and their standard errors for two observers, X and Y . It can be used for quantitative data with the MSD disagreement function or with binary data. As demonstrated before, the estimation of CIA's requires replicated observations by each observer on each subject to estimate the within-observer disagreement. The coefficient ψ^R can be estimated when observer Y does not have replications and observer X has replications and is considered as the reference. The coefficient ψ^N can only be estimated when both X and Y have replications. The program deals separately with the cases where there are replications on Y and when there are no replications on Y . The coefficient ψ^N is not estimated when Y does not have replications.

Furthermore, from the theoretical aspect, ψ^N cannot be greater than 1, but in reality, $\hat{\psi}^N$ can be greater than 1 due to the randomness of the data. Therefore, when the estimated $\hat{\psi}^N$ is greater than 1, the corresponding confidence interval will not show in the results. Furthermore, when $\hat{\psi}^N < 1$ but the upper confidence bound of $\hat{\psi}^N$ exceeds 1, the program sets the upper

bound to 1.

Last but not the least, the complete case scenario is adopted. If one of the replications is missing on a subject, then that subject will be removed from the calculations.

3.1 Input Data

In either the SAS macro or the R function, six parameters, namely, subject identifier, *data_name*, *rep_X*, *rep_Y*, *alpha* and *title* are required for input. Regardless of what the subject identifier is called in the original data, either labeled as *id* or not, the macro variable *id* specifies the subject identifier that is used by the program. *Data_name* specifies the name of the dataset which contains the original data, while *rep_X* and *rep_Y* indicate the numbers of replications of observers *X* and *Y*, respectively. *Rep_X* should be greater than 1, while *rep_Y* can be greater than or equal to 1. *Alpha* is one minus the confidence coefficient. *Title* is designed to help the user identify the current analyses and mark the name of the current comparison if several comparisons are involved.

The dataset is required to have one data line per subject. Furthermore, the original dataset needs to be transformed into an ideal format for input, with subject identification as the first variable, followed by all the replicated observations of *X* and all the replications of *Y* in this order, as shown in data transformation of Table 1.

3.2 Output

If the variable *Y* has more than one replication, then the output of the program provides the following results: (1) MSD(*X*, *X'*), MSD(*Y*, *Y'*) and MSD(*X*, *Y*); (2) estimate of ψ^N , standard error (SE) of ψ^N and 100(1- α)% CI for ψ^N ; (3) estimate of ψ^R , SE of ψ^R and 100(1- α)% CI for ψ^R . If *Y* does not have replications, only (1) and (3) will be provided. In addition, when the estimated ψ^N is greater than 1, the corresponding confidence interval will not be shown in the result.

4. Examples

Examples of the SAS and R macros input and output are presented in Tables 1 and 2.

4.1 A Quantitative Example – Carotid Stenosis Data

The carotid stenosis screening study was designed to determine the suitability of magnetic resonance angiography (MRA) for noninvasive screening of carotid artery stenosis, compared to invasive intra-arterial angiogram (IA). The main interest was in comparing two MRA techniques, two-dimensional (MRA-2D) and three-dimensional (MRA-3D) MRA time of flight, to the IA, which was considered the “gold standard”. In this example, the three screening methods were considered as the “observers”. Readings were made by three raters using each of the three methods to assess carotid stenosis on each of the 55 patients. For this illustration, the three readings made by different raters were considered as replications. Separate readings were made on the left and right carotid arteries. However, in this example, our interest was restricted to the left side. For more details on this study, the reader is referred to Barnhart and Williamson [22].

Assessing the agreement between MRA-2D and IA, $\hat{\psi}^N$ was 0.592 with 95% CI (0.348, 0.835), while $\hat{\psi}^R$ was 0.231 with 95% CI (0.035, 0.427), using IA as the reference. The agreement between MRA-3D and IA showed similar results with $\hat{\psi}^N = 0.452$ (95% CI: (0.242, 0.661)) and $\hat{\psi}^R = 0.191$ (95% CI: (0.026, 0.357)) [11]. The SAS and R codes, as well as the

output comparing MRA-2D to IA, are shown in Table 1.

4.2 A Binary Example – Data from a Mammography Study

In a mammography study [23], 150 female patients underwent a mammography at the Yale-New Haven Hospital in 1987. Each of ten radiologists read each patient's mammogram and classified it into one of four diagnosis categories: (1) normal, (2) abnormal – probably benign, (3) abnormal – intermediate or (4) abnormal – suggestive of cancer. Four months later, the same films were reviewed again, in a random order, by the same radiologists. We considered the two evaluations as replications. In the present analysis, we considered a radiologist's rating as "positive" if the mammogram was classified into the fourth category, which was abnormal and suggestive of cancer. Otherwise, the rating was considered as "negative". Each of the study participants was followed up for three years, and then a definitive diagnosis was made. The definitive diagnosis was breast cancer if it was histopathologically confirmed within the three years of follow-up. We considered this diagnosis as the patient's "true" breast cancer status. Based on this criterion, 27 of 150 patients (18%) had breast cancer. Ten radiologists were involved. Since the total of sensitivity and specificity was highest for radiologist A, we illustrated the new coefficients by estimating the agreement between radiologist A and each of the remaining nine radiologists. Radiologist A was considered as the reference in estimating ψ^R .

When evaluating the agreement between radiologist A and F, MSD (X, X') was 0.04, MSD (Y, Y') was 0.067 and MSD (X, Y) was 0.070. When neither radiologist was considered as a reference, $\hat{\psi}^N$ was 0.762 with 95% CI (0.476, 1.000); while with radiologist A as the reference, $\hat{\psi}^R$ was 0.571 with 95% CI (0.162, 0.981) [16]. SAS and R codes as well as outputs are shown in Table 2.

5. Summary

In this paper, we provide computer programs to estimate the coefficients of individual agreement (CIA's), which are based on the ratio of within-observers and between-observers disagreement. Both a SAS macro and an R program were used to estimate CIA's along with their SE's and confidence intervals, when one of the observers was considered as a reference and when neither of the observers was a reference. Two examples demonstrated that our programs worked well for both quantitative and binary measurements.

6. Macro Availability and Software Requirement

The CIA programs in SAS and R are available directly from the authors. They can also be found at following website: <http://www.sph.emory.edu/observeragreement/>. The programs were written in SAS V9.1.3 and R 2.8.0. The R users need to download, install and load the package "fSeries" at <http://cran.r-project.org/web/packages/fSeries/index.html> or from CRANmirror. The function "removeNA" in fSeries was used to remove the entire subject if any observation of that subject contains a missing value.

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Table 1 Estimating the agreement between MRA-2D to IA using CIA’s in the stenosis screening study (left side).

Description	The three readings by different raters were treated as replications. The readings of IA were denoted by x1, x2 and x3 while the measurements of MRA-2D were y1, y2 and y3.						
Original Dataset	id	stenL11	stenL12	stenL13	stenL21	stenL22	stenL23
	1	100.000	100.000	100.000	100.000	100.000	100.000
	2	73.077	66.575	77.186	69.472	60.410	72.214
	3	0.000	0.000	3.191	49.324	0.000	0.000
	4	16.612	0.000	0.000	0.187	0.000	0.000
Data Transformation	<pre>data sten_new; set stenosis_left (rename=(stenL11=x1 stenL12=x2 stenL13=x3 stenL21=y1 stenL22=y2 stenL23=y3)); keep id x1 x2 x3 y1 y2 y3; run;</pre>						
Input Dataset	id	x1	x2	x3	y1	y2	y3
	1	100.000	100.000	100.000	100.000	100.000	100.000
	2	73.077	66.575	77.186	69.472	60.410	72.214
	3	0.000	0.000	3.191	49.324	0.000	0.000
	4	16.612	0.000	0.000	0.187	0.000	0.000
SAS code	<pre>%include 'D:\CIA\program\CIA_macro.sas' ; %CIA (id=id, data_name=sten_left, rep_X=3, rep_Y=3, alpha=0.05, title=Comparison between IA and MRA-2D);</pre>						
R code	<pre>sten <- read.csv(file="C:\\ CIA\\data\\sten_left.csv", header=T) out <- CIA(dataname=sten, rep_X=3, rep_Y=3, alpha=0.05)</pre>						
Output	Comparison between IA and MRA-2D Estimate of MSD Functions MSD_XX MSD_YY MSD_XY 279.447 1153.48 1210.77 Estimated Psi_N Est_ SE_Est_ 95.0% CI Psi_N Psi_N for Psi_N 0.592 0.124 (0.348,0.835) Estimated Psi_R Est_ SE_Est_ 95.0% CI Psi_R Psi_R for Psi_R 0.231 0.100 (0.035,0.427)						

Table 2 Estimating the agreement between radiologist A and F using CIA’s in the mammography study.

Description	The two readings of radiologist A were called x1 and x2 since A was treated as the reference for ψ^R . The measurements of radiologist F were y1 and y2.																												
Original Dataset	study_id	A1	A2	F1	F2																								
	1	0	0	0	0																								
	2	0	0	0	0																								
	3	1	1	1	1																								
Data Transformation	<pre>data mammo_new; set mammo (rename=(A1=x1 A2=x2 F1=y1 F2=y2)); keep study_id x1 x2 y1 y2; run;</pre>																												
Input Dataset	study_id	x1	x2	y1	y2																								
	1	0	0	0	0																								
	2	0	0	0	0																								
	3	1	1	1	1																								
SAS code	<pre>%include 'D:\CIA\program\CIA_macro.sas' ; %CIA (id=study_id, data_name=mmg_ab, rep_X=2, rep_Y=2, alpha=0.05, title=Comparison between A and F);</pre>																												
R code	<pre>mammo <- read.csv(file="C:\\ CIA\\data\\mammo.csv", header=T) out <- CIA(dataname=mammo, rep_X=2, rep_Y=1, alpha=0.05)</pre>																												
Output	Comparison between A and F Estimate of MSD Functions <table><tr><td>MSD_XX</td><td>MSD_YY</td><td>MSD_XY</td></tr><tr><td>0.040</td><td>0.067</td><td>0.070</td></tr></table> Estimated Psi_N <table><tr><td>Est_</td><td>SE_Est_</td><td>95.0% CI</td></tr><tr><td>Psi_N</td><td>Psi_N</td><td>for Psi_N</td></tr><tr><td>0.762</td><td>0.146</td><td>(0.476,1.000)</td></tr></table> Estimated Psi_R <table><tr><td>Est_</td><td>SE_Est_</td><td>95.0% CI</td></tr><tr><td>Psi_R</td><td>Psi_R</td><td>for Psi_R</td></tr><tr><td>0.571</td><td>0.209</td><td>(0.162,0.981)</td></tr></table>					MSD_XX	MSD_YY	MSD_XY	0.040	0.067	0.070	Est_	SE_Est_	95.0% CI	Psi_N	Psi_N	for Psi_N	0.762	0.146	(0.476,1.000)	Est_	SE_Est_	95.0% CI	Psi_R	Psi_R	for Psi_R	0.571	0.209	(0.162,0.981)
MSD_XX	MSD_YY	MSD_XY																											
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Psi_N	Psi_N	for Psi_N																											
0.762	0.146	(0.476,1.000)																											
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