Assessing Individual Agreement

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Outline

- Introduction
- ICC and CCC for assessing agreement
- Individual equivalence and coefficient of individual agreement (CIA)
- Comparison of CCC and CIA
- Application to data examples
- Discussion

Introduction

Accurate and precise measurement is important in clinical diagnosis. A method comparison study or reliability study is usually conducted to evaluate agreement between methods or observers. We are often interested in

- Whether the methods/observers can be used interchangeably at individual level
- Whether a new method that is easy to use can replace an existing standard method that may be expensive or invasive at individual level.

Introduction

Traditionally, if there is no reference method, assessing agreement for continuous measurement has been based on

- Intraclass correlation coefficient (ICC) (Inter- and Intra-ICC)

$$ICC = \frac{\sigma_B^2}{\sigma_B^2 + \sigma_W^2} = \frac{\text{Between-subject variability}}{\text{Total variability}}$$

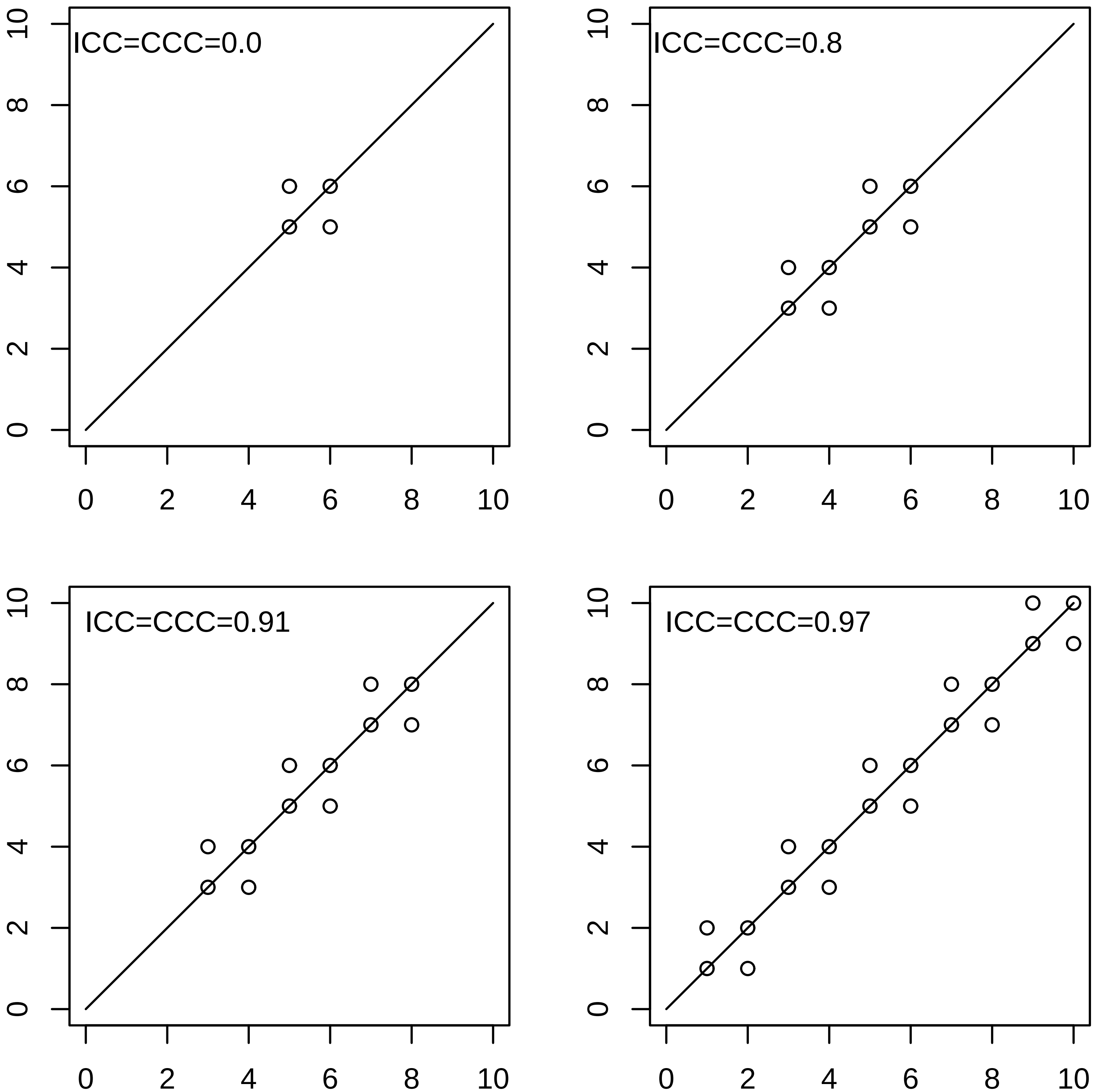
for model $Y_{ij} = \alpha_i + e_{ij}, j = 1, \ldots, J$

- Concordance correlation coefficient (CCC)

$$\begin{aligned} CCC &= 1 - \frac{E(Y_{i1} - Y_{i2})^2}{E(Y_{i1} - Y_{i2})^2 | Y_{i1}, Y_{i2} \quad \text{are independent})} \\ &= \frac{2\sigma_{B1}\sigma_{B2}\rho_\mu}{\sigma_{B1}^2 + \sigma_{W1}^2 + \sigma_{B2}^2 + \sigma_{W2}^2 + (\mu_1 - \mu_2)^2} \end{aligned}$$

for model $Y_{ij} = \mu_{ij} + e_{ij}, j = 1, \ldots, J$

- With fixed within-subject variability σ_W^2, ICC and CCC increase as between-subject variability σ_B^2 increases.


ICC=CCC=0.0
ICC=CCC=0.8
ICC=CCC=0.91
ICC=CCC=0.97

Introduction

- It is questionable whether ICC or CCC is adequate in assessing agreement at individual level.
- We propose the concept of individual agreement

Individual Agreement

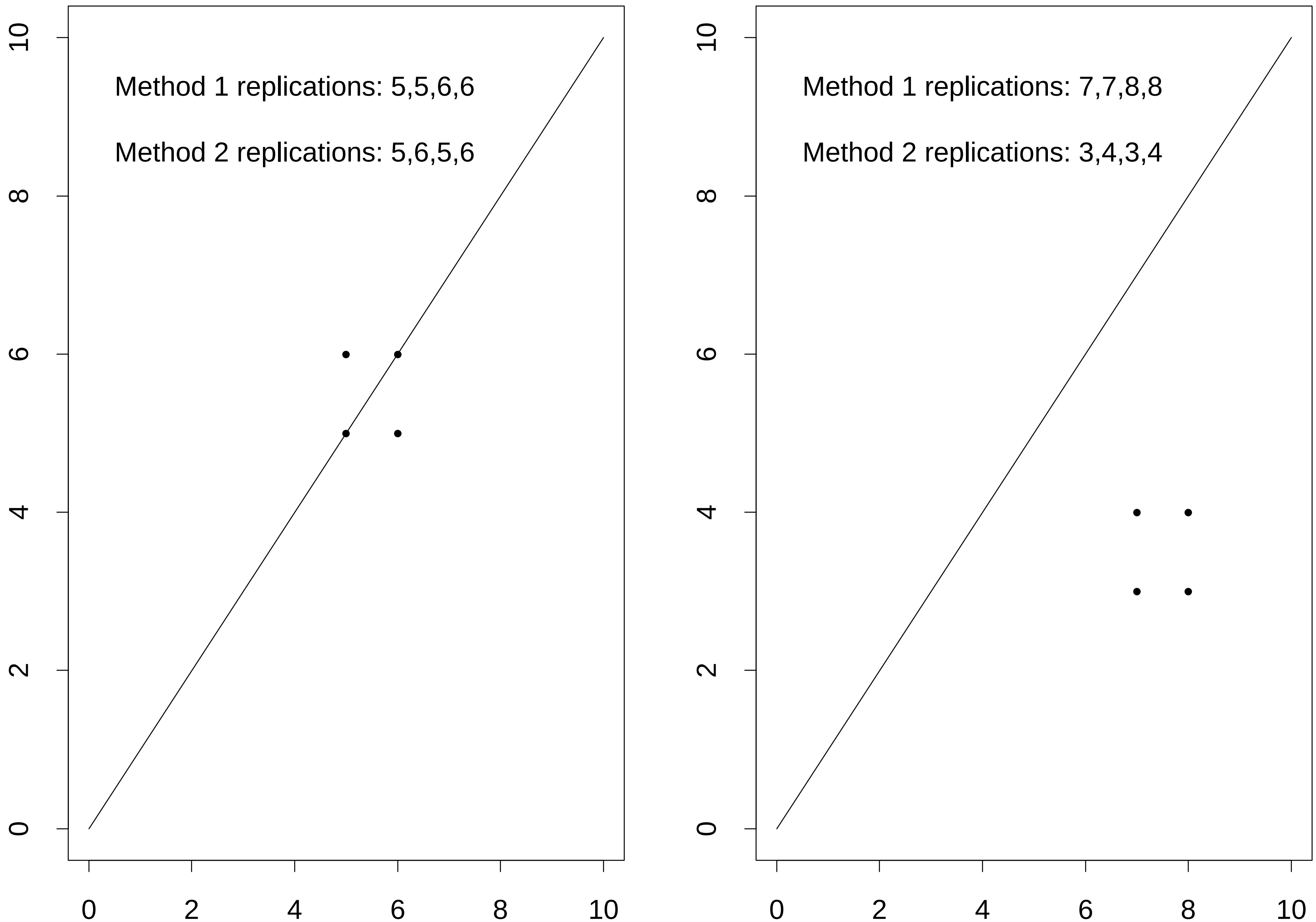
- Assume that the replication error is acceptable, we define good **"Individual Agreement"** in the following sense:

  individual **difference between readings from different methods** is close to the **difference between replicated readings within the method**.

- Two cases are considered and compared:

  (1) Existence of a reference method

  (2) There is no method.



Method 1 replications: 5,5,6,6
Method 2 replications: 5,6,5,6
Method 1 replications: 7,7,8,8
Method 2 replications: 3,4,3,4
0
2
4
6
8
10

Individual Bioequivalence

- For comparing a new with a reference method, “individual agreement” here is similar to individual bioequivalence in bioequivalence studies that assess agreement between a test drug against reference drug.
- Individual bioequivalence was first introduced by Anderson and Hauck (1990) using probability criterion.
- Schall and Luus (1993) extended to general case that includes the probability and moment criteria as special cases.
- FDA modified and adopted the moment criterion in their guidelines (2001) for establishing individual bioequivalence (IBE).

Individual Bioequivalence Criterion

FDA (2001)

Existence of a reference

- Reference-scaled IBC

$$IBC = \frac{E(Y_{iT} - Y_{iR})^2 - E(Y_{iR} - Y_{iR'})^2}{E(Y_{iR} - Y_{iR'})^2/2} \leq \theta_I$$

θ_I is the bioequivalence limit set by the regulatory agency.

- $Y_{ij} = \mu_{ij} + \epsilon_{ij}, j =$T (test drug), R (reference drug)

Within-subject: $\sigma^2_{WT} = Var(\epsilon_{iT}), \sigma^2_{WR} = Var(\epsilon_{iR})$
Between-subject: $\sigma^2_{BT} = Var(\mu_{iT}), \sigma^2_{BR} = Var(\mu_{iR})$.

Subject-by-formulation interaction: $\sigma^2_D = Var(\mu_{iT} - \mu_{iR})$

$$IBC = \frac{(\mu_T - \mu_R)^2 + \sigma^2_D + \sigma^2_{WT} - \sigma^2_{WR}}{\sigma^2_{WR}} \leq \theta_I$$

Proposed Individual Equivalence Criterion (IEC)

Existence of a reference

For a total of J methods with first $J-1$ new methods and J method as a reference

$$IEC^R = \frac{(\sum_{j=1}^{J-1} E(Y_{ij} - Y_{iJ})^2)/(J-1) - E(Y_{iJk} - Y_{iJk'})^2}{E(Y_{iJk} - Y_{iJk'})^2/2} \leq \theta_I$$

Coefficient of Individual Agreement (CIA)

Existence of a reference

$$CIA^R = \psi^R = \frac{E(Y_{iJk} - Y_{iJk'})^2}{\sum_{j=1}^{J-1} E(Y_{ij} - Y_{iJ})^2/(J-1)} = \frac{\sigma^2_{WJ}}{\tau^2_{*R} + \sigma^2_{*R}}$$

"True" inter-method variability: $\tau^2_{*R} = \frac{E(\sum_{j=1}^{J-1} (\mu_{ij} - \mu_{iJ})^2/2)}{J-1}$

Weighted within-method variability: $\sigma^2_{*R} = \frac{1}{2}(\frac{\sum_{j=1}^{J-1} \sigma^2_{Wj}}{J-1} + \sigma^2_{WJ})$

$$CIA^R = \frac{2}{IEC^R + 2}$$

J Methods without Reference

$$IEC^N = \frac{\frac{2\sum_{j=1}^{J-1}\sum_{j'=j+1}^{J} E(Y_{ij}-Y_{ij'})^2}{J(J-1)} - \frac{\sum_j E(Y_{ijk}-Y_{ijk'})^2}{J}}{\frac{\sum_j E(Y_{ijk}-Y_{ijk'})^2}{2J}}$$

$$CIA^N = \psi^N = \frac{\sum_{j=1}^{J} E(Y_{ijk} - Y_{ijk'})^2/2}{\sum_{j=1}^{J-1}\sum_{j'=j+1}^{J} E[(Y_{ij} - Y_{ij'})^2]/(J-1)} = \frac{\sigma_*^2}{\tau_*^2 + \sigma_*^2}$$

$$CIA^N = \frac{2}{IEC^N + 2}$$

$$\tau_*^2 = E(\frac{\sum_j (\mu_{ij} - \mu_{i\bullet})^2}{J-1}), \sigma_*^2 = \sum_j \sigma_{Wj}^2/J$$

Guideline on IEC and CIA values

- In general, low value of IEC or high value of CIA are needed for satisfactory individual agreement.
- FDA's boundary: $\theta_I = 2.4948$. This corresponds to
  $IEC \leq 2.4948$ or
  $CIA \geq 0.445$

  i.e., the "true" inter-method variability is within 125% of the within-subject variability.
- $CIA \geq 0.8$

  if the total variability is within 125% of the within-subject variability
  or the "true" inter-mathod is within 25% of the within-subject variability.

Comparison of CIA^N and CCC

In general,

$$\psi^N = \frac{\rho_c}{1-\rho_c}\frac{J-1}{\gamma} \qquad \text{or} \qquad \rho_c = \frac{\gamma\psi^N}{(J-1)+\gamma\psi^N}, \quad \text{if} \quad \rho_c \neq 0, 1.$$

- Both CIA^N and CCC are decreasing funcitons of location shift ($\sum_{jj'}(\mu_j - \mu_{j'})^2$) and scale shift ($\sum_{jj'}(\sigma_{Bj} - \sigma_{Bj'})^2$)
- Both CIA^N and CCC are increasing functions of the "true" correlation ($\rho_{\mu jj'} = corr(\mu_{ij}, \mu_{ij'})$)
- CIA^N is a decreasing function of between-subject variability (σ_{Bj}) and CCC is an incrasing function of σ_{Bj}.
- CIA^N is an increasing function of within-subject variability (σ_{Wj}) and CCC is a descreasing function of σ_{Wj}.

Dependency of CIA^N and CCC on $d = \sigma_B^2/\sigma_W^2$

For simplicity, consider $\sigma_{Bj}^2 = \sigma_B^2, \sigma_{Wj}^2 = \sigma_W^2, j = 1, 2$ and let $d = \sigma_B^2/\sigma_W^2$. Then

$$CCC = \rho_c = \frac{d\rho_\mu}{d + (\mu_1 - \mu_2)^2/(2\sigma_W^2) + 1}$$

$$CIA^N = \psi^N = \frac{1}{(1 - \rho_\mu)d + (\mu_1 - \mu_2)^2/(2\sigma_W^2) + 1}$$

Figure 1. CIA and CCC as function of d with $(\mu_1 - \mu_2)^2 = 9, \sigma_W^2 = 9/2, \rho_\mu = 1$

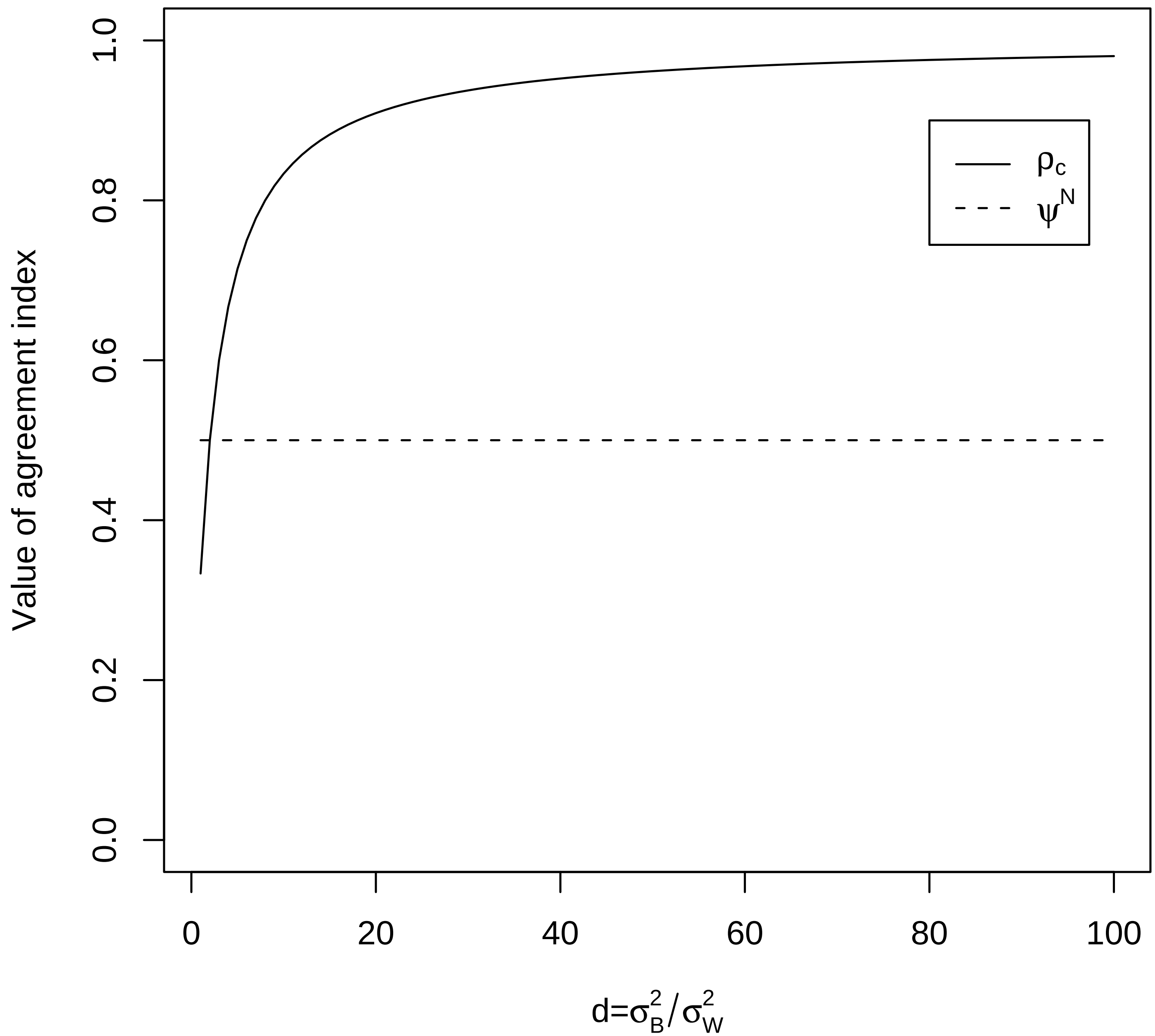


Figure 1. CIA and CCC as function of d with $(\mu_1 - \mu_2)^2 = 9, \sigma_W^2 = d, \rho_\mu = 1$

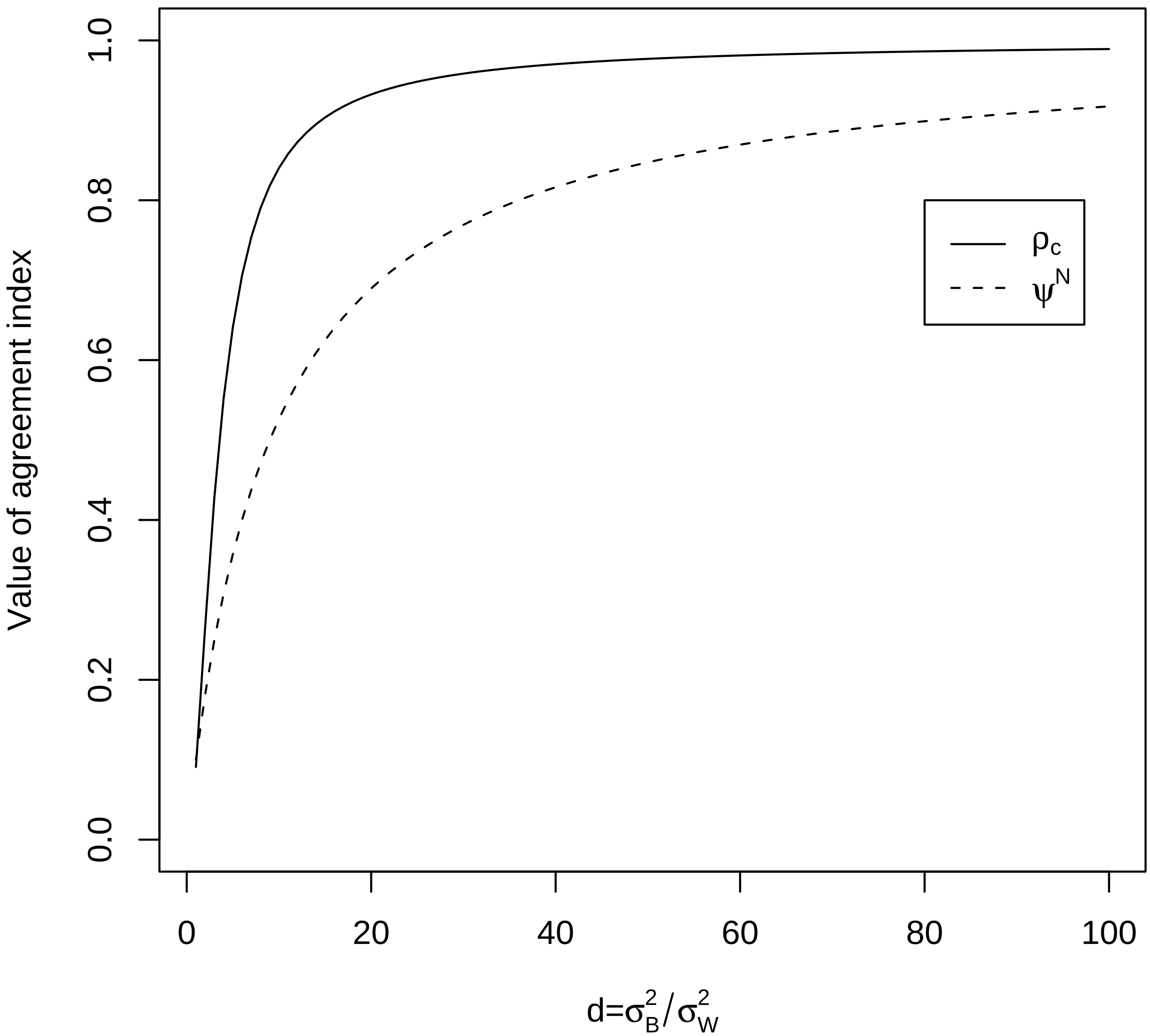


Figure 1.CIA and CCC as function of d with
$(\mu_1 - \mu_2) = 0, \sigma_W^2 = d, \rho_\mu = 1$

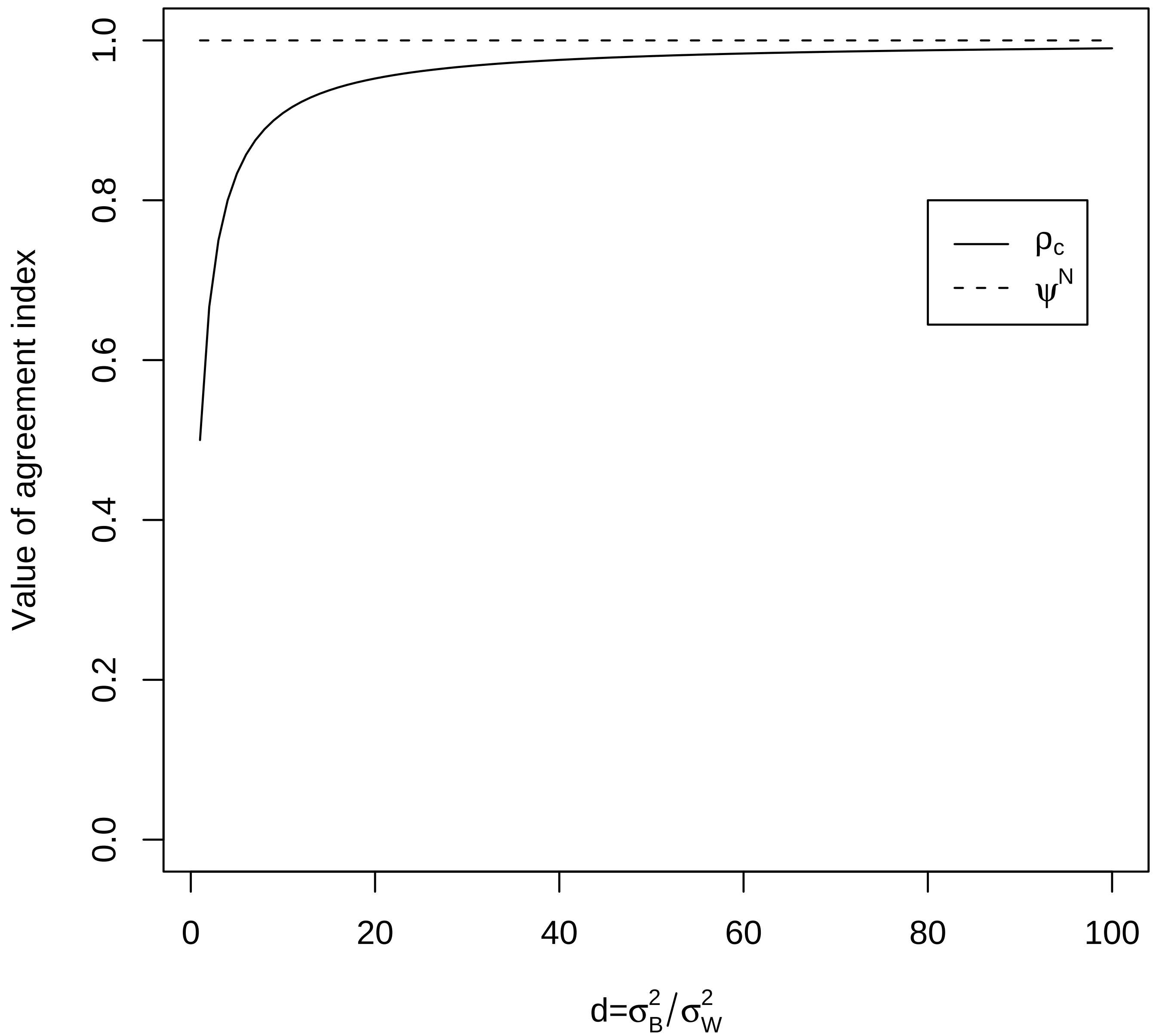


Figure 1.CIA and CCC as function of d with
$(\mu_1 - \mu_2)^2 = 9, \sigma_W^2 = 9/2, \rho_\mu = 0.8$

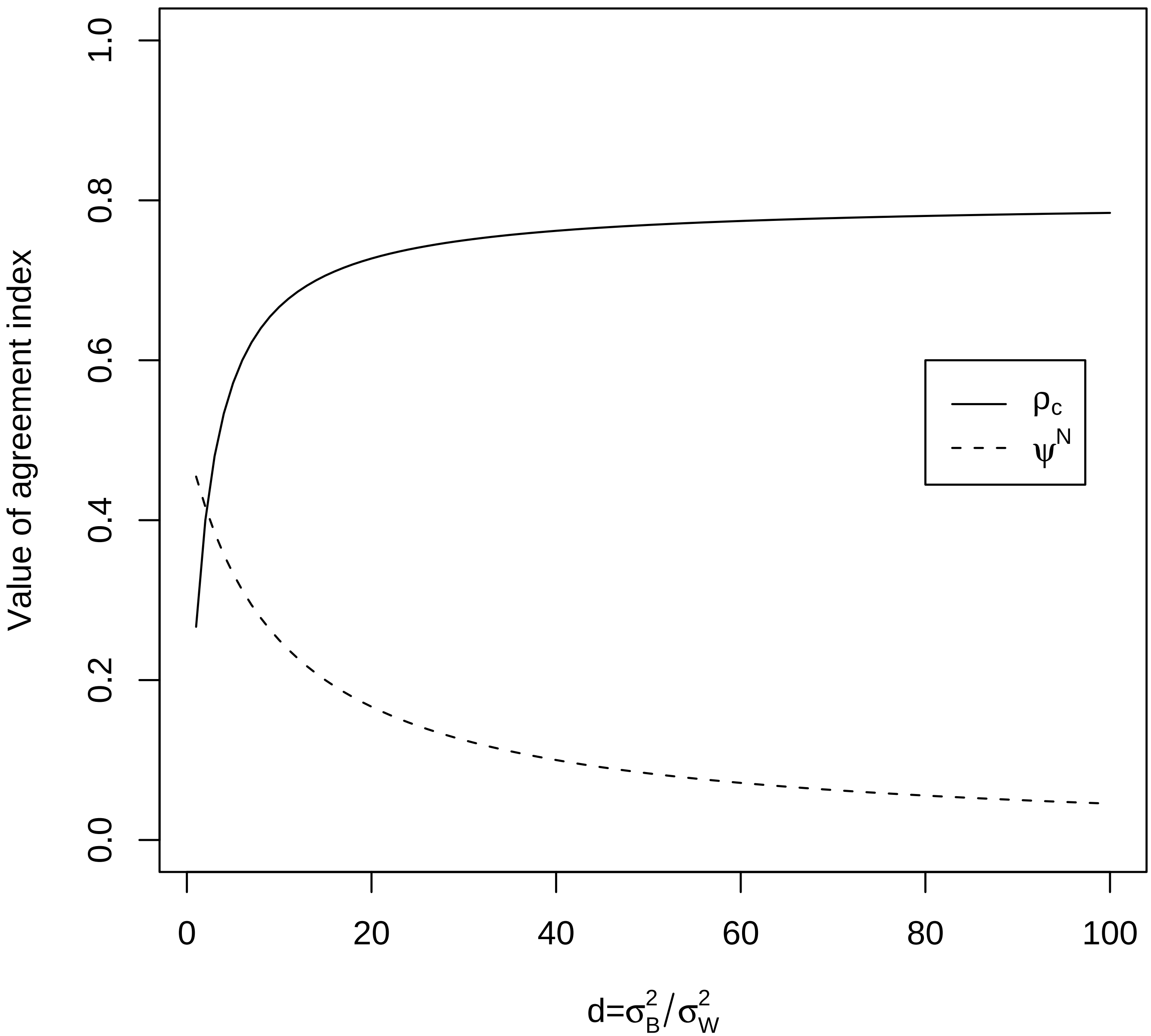


Figure 1.CIA and CCC as function of d with
$\mu_1 - \mu_2 = 0, \sigma_W^2 = d, \rho_\mu = d/(d+1)$

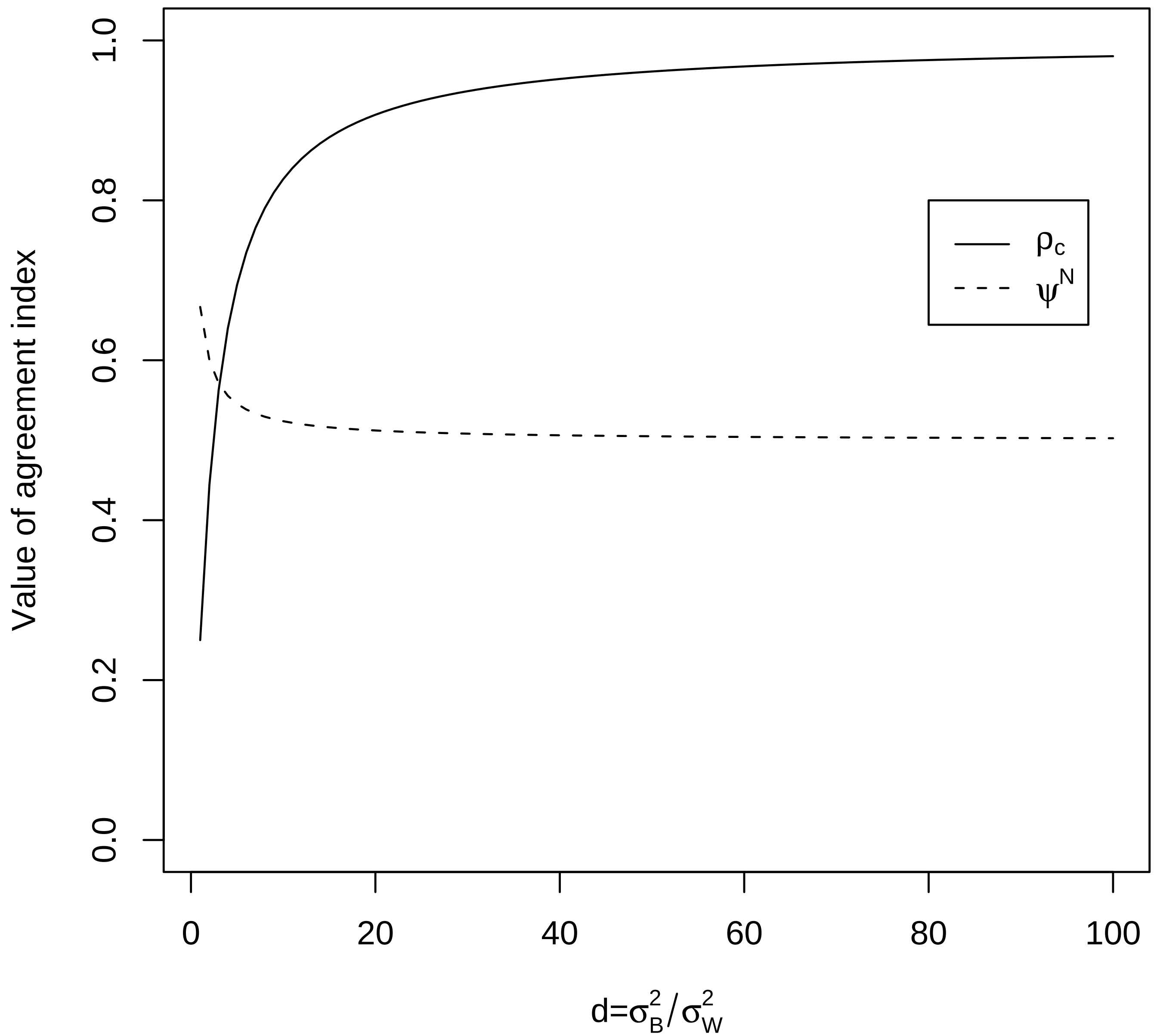
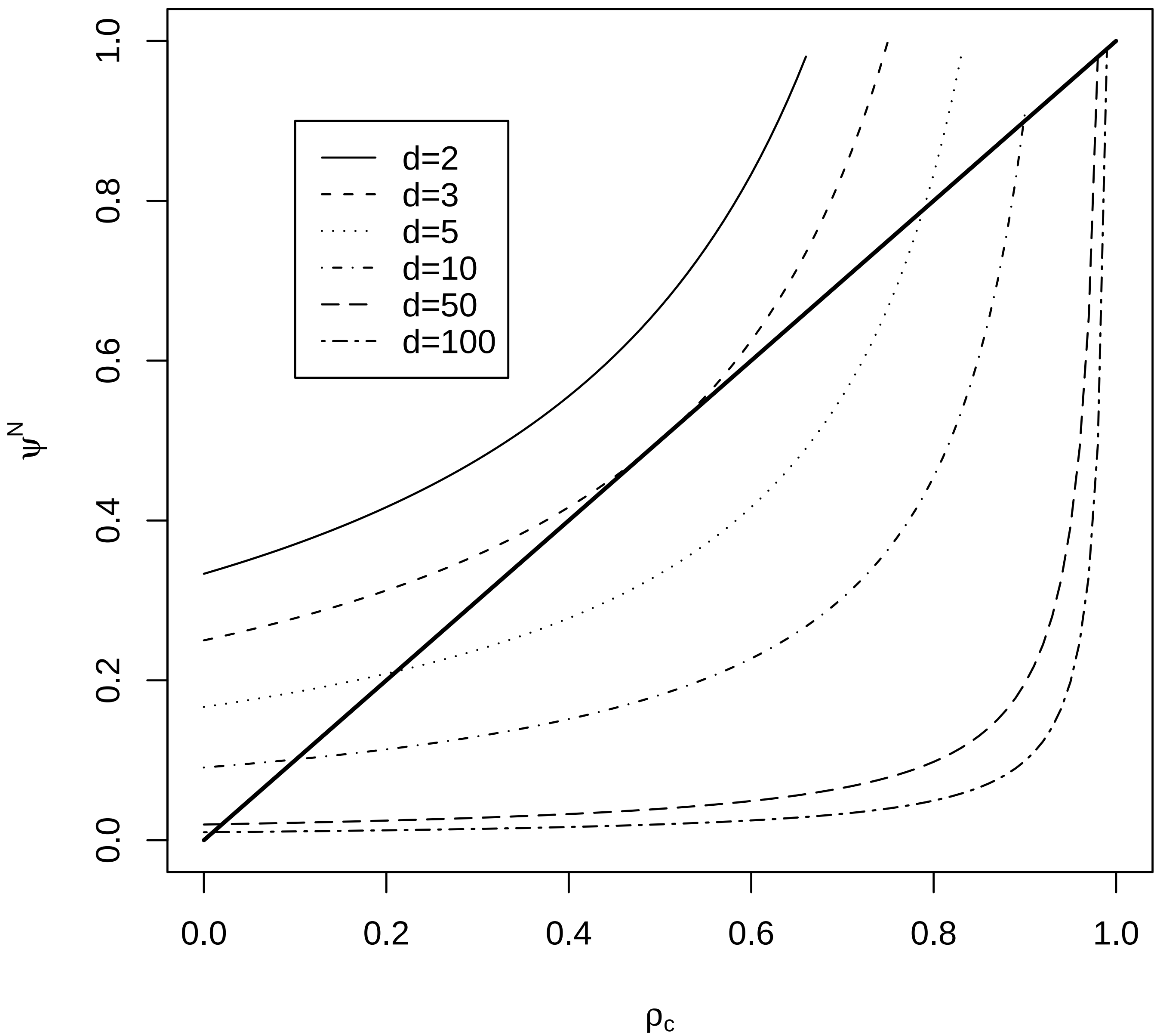


Figure 2. CIA as a function of CCC for fixed d and $\mu_1 - \mu_2 = 0$



Estimation and Inference

Based on method of moment,

- Existence of a reference

$$\hat{IEC}^R = \frac{2(\hat{\tau}^2_{*R} + \hat{\sigma}^2_{*R} - MSE_{WJ})}{MSE_{WJ}}, \quad \hat{CIA}^R = \frac{MSE_{WJ}}{\hat{\tau}^2_{*R} + \hat{\sigma}^2_{*R}}.$$

$$\hat{\sigma}^2_{*R} = (\frac{\sum_{j=1}^{J-1} MSE_{Wj}}{J-1} + MSE_{WJ})/2.$$

$$Y_{ijk} = \mu + \alpha_i + \epsilon_{ijk}, j = 1, \ldots, J.$$

$$\hat{\tau}^2_{*R} = \frac{\sum_j (MS_{jJ} - MSE_{jJ})}{K(J-1)}.$$

$$Y_{ijk} = \mu + \alpha_i + \gamma_{ij} + \epsilon_{ijk}, j = j, \quad \text{or} \quad J$$

Estimation and Inference

Based on method of moment,

- No reference

$$\hat{IEC}^N = \frac{2(MS - MSE)}{K * MSE}$$

$$\hat{CIA}^N = \frac{K * MSE}{MS + (K-1) * MSE}.$$

$$\hat{\tau}_*^2 = \frac{MS - MSE}{K}, \quad \text{and} \quad \hat{\sigma}_*^2 = MSE.$$

$$Y_{ijk} = \mu + \alpha_i + \gamma_{ij} + \epsilon_{ijk},$$

- We use the bootstrap percentile method for one sided confidence bound

Table 1. Description and estimates for the four data examples.

	μ_j	σ^2_{Wj}	σ^2_{Bj}	Intra ICC	Rep. coef.
Goniometers					
Manual Goniometer	1.437	0.736	53.8	0.986	2.38
Electro-goniometer	0.046	0.977	53.8	0.982	2.74
Calcium Scoring					
Radiologist A	35.833	7.667	1025.7	0.993	7.67
Radiologist B	36.125	0.125	1116.2	0.999	0.98
Carotid Stenosis					
Right MRA-2D	45.9	568.5	887.7	0.610	66.0
Right MRA-3D	43.9	550.0	903.6	0.622	65.0
Right IA	33.8	88.0	965.2	0.916	26.0
Systolic Blood Pressure					
Observer 1	127.4	37.4	936.0	0.962	17.0
Observer 2	127.3	38.0	917.1	0.960	17.0
Machine	143.0	83.1	983.2	0.922	25.3

Table 2. Estimates of CCC and CIA

	CCC	CIA^N	CIA^R	W. Average
	ρ_c	ψ^N	ψ^R	$d = \frac{\sigma_B^2}{\sigma_W^2}$
Goniometers (J=2, K=3)				
Manual* vs. Electro Goniometer	0.944	0.287	0.246	61.4
Calcium Scoring (J=2, K=2)				
Radiologist A vs. B	0.995	0.754	-	274.9
Carotid Stenosis (J=3, K=3)				
Overall (IA*) for right artery	0.597	0.738	0.172	2.28
Systolic Blood Pressure (J=3, K=3)				
Overall	0.782	0.225	0.111	17.9
Observer 1 vs. 2	0.973	1.0	–	24.6
Observer 1* vs. Machine	0.703	0.178	0.110	15.9
Ovserver 2* vs. Machine	0.700	0.179	0.112	15.7

* Reference method

Discussion

We proposed CIA for assessing individual agreement of continuous measures between multiple methods for scenarios of existing reference or no reference.

- We found that the CIA is less dependent on the between-subject variability than the CCC.
- The concept of individual agreement can be extended to binary data where KAPPA has the same property as the CCC.
- Before considering any method for comparison, one needs to ensure that its replication error is acceptable.

  Repeatability Coefficient
- Acceptable new method can then be compared with the existing method using the concept of individual agreement.