Assessment of Agreements

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Introduction

What's Agreement?

Agreement

It is mainly aimed to answer one question, **whether the reading from one rater/instrument agree with those from other raters/instruments**.

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Agreement

It is mainly aimed to answer one question, **whether the reading from one rater/instrument agree with those from other raters/instruments**.

- Compare several laboratory results collected in various labs.
- Evaluate the performance between two medical devices.
- Find out if new/old methods are interchangeable.

What's Agreement?

id	X	Y
1	1.15	1.23
2	1.90	2.03
3	2.54	2.01
4	2.70	2.75
5	3.68	2.98
6	3.85	4.37
7	3.99	3.87
8	4.20	4.31
9	5.85	6.47
10	6.42	6.64

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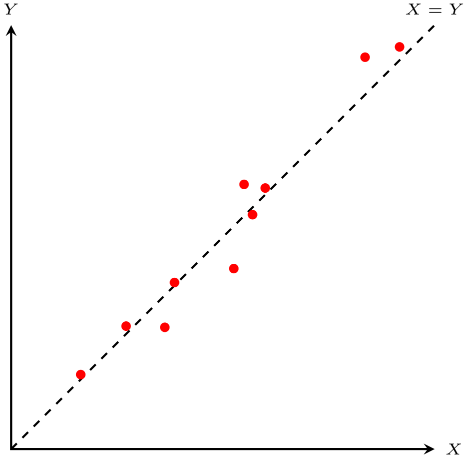
- $\sum_{i=1}^{n}(X_i - Y_i)^2$
- $E(X) = E(Y)$
- $var(X)/var(Y) = 1$
- ρ_{XY}
- Paired t-test
- $X_i = Y_i$?

What's Agreement?

id	
1	1
2	1
3	2
4	2
5	3
6	3
7	3
8	4
9	5
10	6



$Y_i)^2$

$Y)$

$r(Y) = 1$

t

What's Agreement?

id	
1	1
2	1
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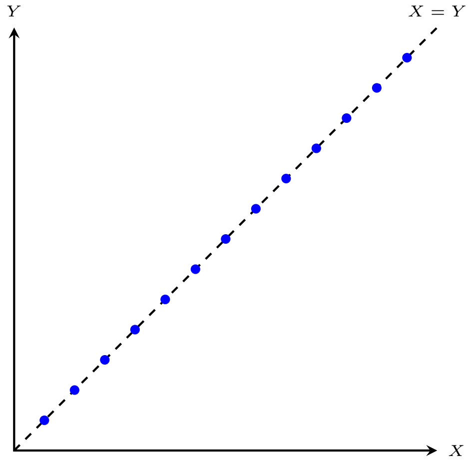

Perfect Agreed

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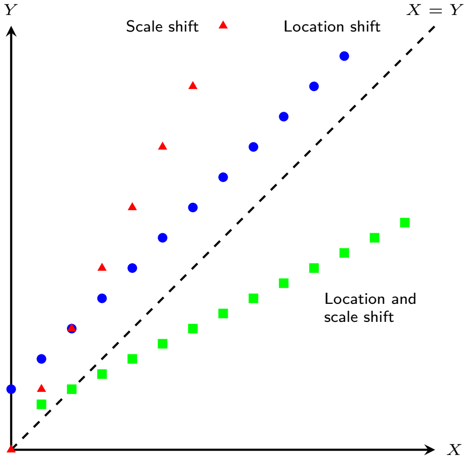
$- Y_i)^2$

$ar(Y) = 1$

(Y)

st



Pearson Correlation Coefficient Failed

What's Agreement?

id	
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2	1
3	2
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6	3
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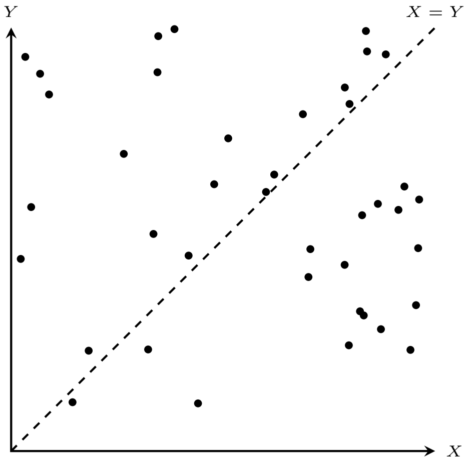
10	6

$Y_i)^2$

$r(Y) = 1$

(Y)

st



Paired t-test is misleading

Some Statistics

X and Y are assumed to have a bivariate distribution with mean μ_x and μ_y, variances σ_x^2 and σ_x^2, and covariance σ_{xy}.

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Mean Square Deviation

$$\text{MSD} = E(X-Y)^2 = (\mu_x - \mu_y)^2 + \sigma_x^2 + \sigma_y^2 - 2\sigma_{xy}$$

Precision Coefficient

$$\rho = \frac{\sigma_{xy}}{\sigma_x \sigma_y}$$

Accuracy Coefficient

$$\chi_a = \frac{2}{\varpi + 1/\varpi + \upsilon^2}$$

which can be decomposed into two parts, location shift $\upsilon = \frac{\mu_x - \mu_y}{\sqrt{\sigma_y \sigma_x}}$, and scale shift $\varpi = \frac{\sigma_y}{\sigma_x}$ or $\frac{\sigma_x}{\sigma_y}$.

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Mean Square De

$\sigma_y^2 - 2\sigma_{xy}$

Precision Coeffici

Accuracy Coefficient

- If $\mu_x = \mu_y$ and $\sigma_x^2 = \sigma_y^2$, $\chi_a = 1$,
- If one of the variance approach infinity or there is a huge difference in means, $\chi_a \to 0$.

Accuracy Coefficient

$$\chi_a = \frac{2}{\varpi + 1/\varpi + \upsilon^2}$$

which can be decomposed into two parts, location shift $\upsilon = \frac{\mu_x - \mu_y}{\sqrt{\sigma_y \sigma_x}}$, and scale shift $\varpi = \frac{\sigma_y}{\sigma_x}$ or $\frac{\sigma_x}{\sigma_y}$.

Concordance Correlation Coefficient (CCC)

Concordance correlation coefficient is another measure for comparing the differences between two variables proposed by Lin [10].

CCC

$$\begin{aligned} \text{CCC} &= 1 - \frac{\text{Expected squared perpendicular deviation from 45°line}}{\text{Expected squared perpendicular deviation from 45°line when X and Y are uncorrelated}} \\ &= 1 - \frac{E(X-Y)^2}{E(X-Y)^2|_{\rho=0}} \\ &= \frac{2\sigma_{xy}}{(\mu_x - \mu_y)^2 + \sigma_x^2 + \sigma_y^2} \end{aligned}$$

[10] L. Lin, A concordance correlation coefficient to evaluate reproducibility, *Biometrics*, 45(1):255, 1989.

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- $\frac{E(X-Y)^2}{E(X-Y)^2|_{\rho=0}}$ is the ratio of the mean square of within-sample total deviation and the total deviation.
- CCC is a standardization of MSD, which indicates whether these two vectors of observations are agreed along the concordance line.
- CCC can be written as the product of the accuracy and the precision coefficients $\text{CCC} = \rho \cdot \chi_a$.

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- CCC take the range from -1 to 1.
- 1 means perfect agreement, -1 means perfect reverse agreement, and 0 means totally uncorrelated ($\sigma_{xy} = 0$).
- $\text{CCC} = \pm 1$ if and only if $\rho = \pm 1$, $\sigma_x = \sigma_y$, and $\mu_x = \mu_y$.

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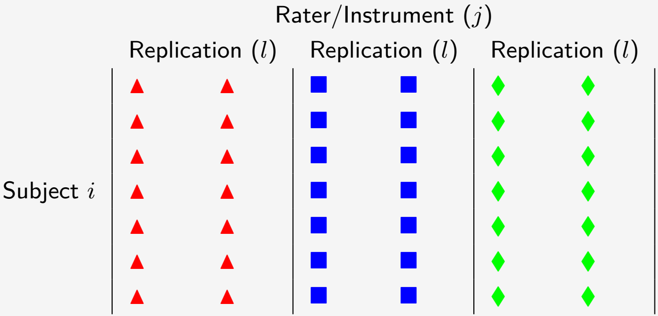
Agreement for Linear Mixed Models

Linear Additive Mixed Effects Model

Model [8]

$$y_{ijl} = \mu + \mathbf{x}_{ij}^{c\prime}\boldsymbol{\theta} + \beta_j + \alpha_i + \gamma_{ij} + \epsilon_{ijl}$$



[8] L. Lin, A.S. Hedayat, and W. Wu, A unified approach for assessing agreement for continuous and categorical data, *Journal of biopharmaceutical statistics*, 17(4):629, 2007.

Linear Additive Mixed Effects Model

Model [8]

$$y_{ijl} = \mu + \mathbf{x}_{ij}^{c\prime}\boldsymbol{\theta} + \beta_j + \alpha_i + \gamma_{ij} + \epsilon_{ijl}$$

- μ is the overall mean;
- $\mathbf{x}_{ij}^{c}$ is the $p \times 1$ design vector for $p \times 1$ covariate coefficients $\boldsymbol{\theta}$;
- β_j is the fixed inter-rater effect;
- α_i is the random subject effect with mean 0 and variance σ_α^2;
- γ_{ij} is the random subject-rater interaction effect with mean 0 and variance σ_γ^2;
- ϵ_{ijl} is the random error with mean 0 and variance σ_ϵ^2.

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- μ is the ove
- $\mathbf{x}_{ij}^c$ is the p ... $\boldsymbol{\theta}$;
- β_j is the fix

The fixed inter-rater effect β_j can be included in the covariates $\boldsymbol{\theta}$.

- α_i is the random subject effect with mean 0 and variance σ_α^2;
- γ_{ij} is the random subject-rater interaction effect with mean 0 and variance σ_γ^2;
- ϵ_{ijl} is the random error with mean 0 and variance σ_ϵ^2.

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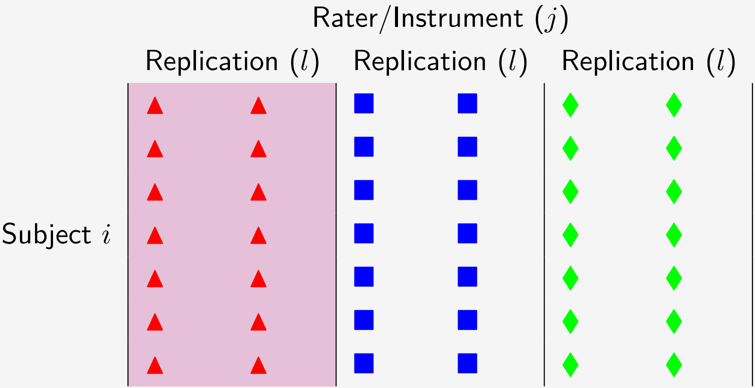
Linear Additive Mixed Effects Model

Model (Updated)

$$y_{ijl} = \mu + \mathbf{x}'_{ij}\boldsymbol{\vartheta} + \alpha_i + \gamma_{ij} + \epsilon_{ijl}$$

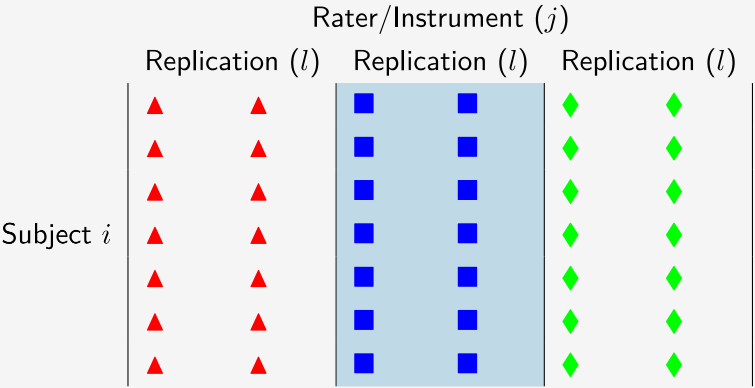
- $\boldsymbol{\vartheta}' = (\beta_1, \beta_2, \ldots, \beta_k, \boldsymbol{\theta}')$ **and $\mathbf{x}_{ij}$ is the corresponding design matrix;**
- i is the index of subjects, $i = 1, 2, \ldots, n$.
- j is the index of raters, $j = 1, 2, \ldots, k$.
- l is the index of replications for each subject and rater, $l = 1, 2, \ldots, m_{ij}$.

Intra-, Inter-, and Total-Rater Agreement



Intra-rater Agreement

Intra-, Inter-, and Total-Rater Agreement



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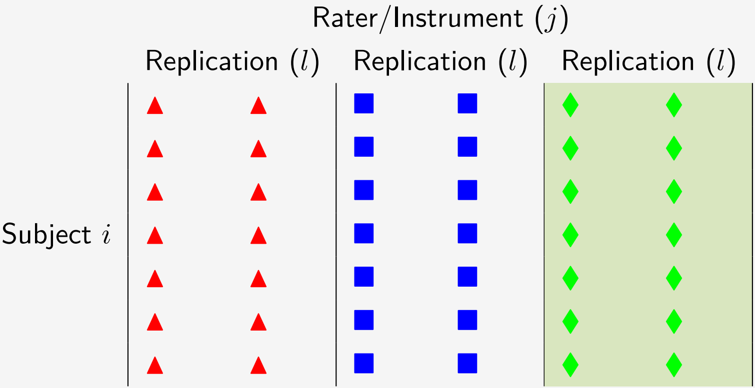

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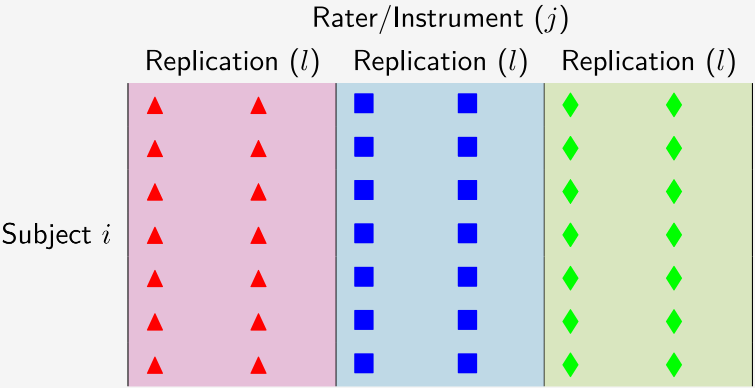

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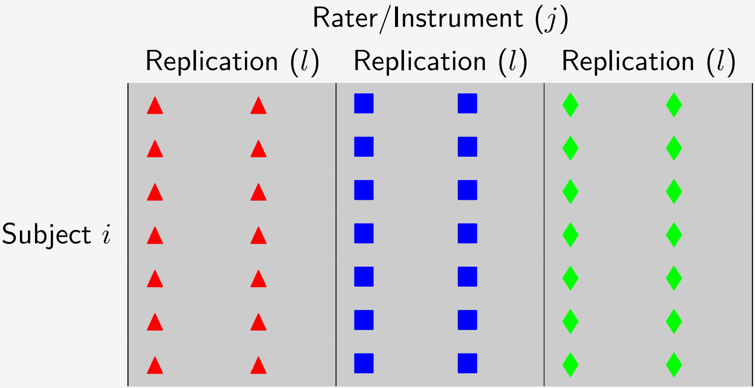

Total-rater Agreement

Intra-, Inter-, and Total-Rater Agreement

Individual Agreement Statistics

For given subject i, and rater j.

Intra-rater Agreement Statistics

$$\begin{aligned}
\text{MSD}_{\text{intra}}|i,j &= E(y_{ijl} - y_{ijl'})^2 \\
&= (\mathbf{x}'_{ij}\boldsymbol{\vartheta} - \mathbf{x}'_{ij}\boldsymbol{\vartheta})^2 + 2(\sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2) - 2(\sigma_\alpha^2 + \sigma_\gamma^2) \\
&= 2\sigma_\epsilon^2 \\
\text{CCC}_{\text{intra}}|i,j &= 1 - \frac{E(y_{ijl} - y_{ijl'})^2}{E(y_{ijl} - y_{ijl'})^2|_{\rho=0}} = \frac{\sigma_\alpha^2 + \sigma_\gamma^2}{\sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2} \\
\rho_{\text{intra}}|i,j &= \frac{\sigma_\alpha^2 + \sigma_\gamma^2}{\sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2} \\
\chi_{\alpha,\text{intra}}|i,j &= 1
\end{aligned}$$

Intra-, Inter-, and Total-Rater Agreement

Individual Agreement Statistics

For given subject i, and any two raters j and j', $j, j' = 1, 2, \ldots, k, j \neq j'$.

Inter-rater Agreement Statistics

$$\begin{aligned}
\text{MSD}_{\text{inter}}|i,j,j' &= E(\bar{y}_{ij\cdot} - \bar{y}_{ij'\cdot})^2 = 2\Big(\boldsymbol{\vartheta}'\mathbf{A}_{\mathbf{x}ijj'}\boldsymbol{\vartheta} + \sigma_\gamma^2 + \frac{\sigma_\epsilon^2}{m_{ijj'}}\Big) \\
\text{CCC}_{\text{inter}}|i,j,j' &= 1 - \frac{E(\bar{y}_{ij\cdot} - \bar{y}_{ij'\cdot})^2}{E(\bar{y}_{ij\cdot} - \bar{y}_{ij'\cdot})^2|_{\rho=0}} \\
&= \frac{\sigma_\alpha^2}{\boldsymbol{\vartheta}'\mathbf{A}_{\mathbf{x}ijj'}\boldsymbol{\vartheta} + \sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2/m_{ijj'}} \\
\rho_{\text{inter}}|i,j,j' &= \frac{\sigma_\alpha^2}{\sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2/m_{ijj'}} \\
\chi_{\alpha,\text{inter}}|i,j,j' &= \frac{\sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2/m_{ijj'}}{\boldsymbol{\vartheta}'\mathbf{A}_{\mathbf{x}ijj'}\boldsymbol{\vartheta} + \sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2/m_{ijj'}}
\end{aligned}$$

where $\mathbf{A}_{\mathbf{x}ijj'} = (\mathbf{x}_{ij} - \mathbf{x}_{ij'})(\mathbf{x}_{ij} - \mathbf{x}_{ij'})'/2$, and $m_{ijj'} = 2m_{ij}m_{ij'}/(m_{ij} + m_{ij'})$

Intra-, Inter-, and Total-Rater Agreement

Individual Agreement Statistics

For given subject i, and any two raters j and j', $j, j' = 1, 2, \ldots, k, j \neq j'$.

Total-rater Agreement Statistics

$$\text{MSD}_{\text{total}}|i,j,j' = E(y_{ijl} - y_{ij'l'})^2 = 2(\boldsymbol{\vartheta}'\mathbf{A}_{\mathbf{x}ijj'}\boldsymbol{\vartheta} + \sigma_\gamma^2 + \sigma_\epsilon^2)$$

$$\text{CCC}_{\text{total}}|i,j,j' = 1 - \frac{E(y_{ijl} - y_{ij'l'})^2}{E(y_{ijl} - y_{ij'l'})^2|_{\rho=0}} = \frac{\sigma_\alpha^2}{\boldsymbol{\vartheta}'\mathbf{A}_{\mathbf{x}ijj'}\boldsymbol{\vartheta} + \sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2}$$

$$\rho_{\text{total}}|i,j,j' = \frac{\sigma_\alpha^2}{\sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2}$$

$$\chi_{\alpha,\text{total}}|i,j,j' = \frac{\sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2}{\boldsymbol{\vartheta}'\mathbf{A}_{\mathbf{x}ijj'}\boldsymbol{\vartheta} + \sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2}$$

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Overall Agreement Statistics

- Barnhart, et al. [1] generalized the individual CCC to an overall CCC using

$$\text{Overall CCC} = 1 - \frac{E\sum_{i=1}^{k-1}\sum_{j=i+1}^{k}(Y_i - Y_j)^2}{E\left[\sum_{i=1}^{k-1}\sum_{j=i+1}^{k}(Y_i - Y_j)^2 | Y_1, \ldots, Y_k \text{ are uncorrelated}\right]}$$

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- It turned out to be a weighted mean of pairwise CCCs. The weight ξ for a pair of observations X and Y is $\xi = E(X - Y)^2|_{\rho=0}$.

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- It penalizes the pairs of observations which have higher variances and larger mean differences.

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- It turned out to be a weighted mean of pairwise CCCs. The weight ξ for a pair of observations X and Y is $\xi = E(X-Y)^2|_{\rho=0}$.
- It penalizes the pairs of observations which have higher variances and larger mean differences.
- Hence,

$$\begin{aligned}\xi_{\text{inter}}|i,j,j' &= 2\left(\boldsymbol{\vartheta}'\mathbf{A}_{\mathbf{x}_{ijj'}}\boldsymbol{\vartheta} + \sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2/m_{ijj'}\right)\\ \xi_{\text{total}}|i,j,j' &= 2\left(\boldsymbol{\vartheta}'\mathbf{A}_{\mathbf{x}_{ijj'}}\boldsymbol{\vartheta} + \sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2\right)\end{aligned}$$

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Overall Agreement Statistics

Selected Overall Agreement Statistics

$$
\begin{aligned}
\text{CCC}_{\text{inter}} &= \frac{\sigma_\alpha^2}{\boldsymbol{\vartheta}'\mathbf{A_x}\boldsymbol{\vartheta} + \sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2/m} \\
\text{CCC}_{\text{total}} &= \frac{\sigma_\alpha^2}{\boldsymbol{\vartheta}'\mathbf{A_x}\boldsymbol{\vartheta} + \sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2} \\
\rho_{\text{inter}} &= \frac{\sigma_\alpha^2}{\boldsymbol{\vartheta}'\mathbf{A_x}\boldsymbol{\vartheta} + \sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2/m} \\
&+ \frac{2}{nk(k-1)} \cdot \frac{\sum_{i=1}^{n}\sum_{j=1}^{k-1}\sum_{j'=j+1}^{k} \boldsymbol{\vartheta}'\mathbf{A}_{\mathbf{x}ijj'}\boldsymbol{\vartheta}/(\sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2/m_{ijj'})}{\boldsymbol{\vartheta}'\mathbf{A_x}\boldsymbol{\vartheta} + \sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2/m} \\
\chi_{a,\text{inter}} &= \frac{\sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2/m}{\boldsymbol{\vartheta}'\mathbf{A_x}\boldsymbol{\vartheta} + \sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2/m} \\
\chi_{a,\text{total}} &= \frac{\sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2}{\boldsymbol{\vartheta}'\mathbf{A_x}\boldsymbol{\vartheta} + \sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2}
\end{aligned}
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Selected Overall Agreement Statistics

$$\text{CCC}_{\text{inter}} = \frac{\sigma_\alpha^2}{\boldsymbol{\vartheta}'\mathbf{A}_\mathbf{x}\boldsymbol{\vartheta} + \sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2/m}$$

$$\text{CCC}_{\text{total}} = \frac{\sigma_\alpha^2}{\boldsymbol{\vartheta}'\mathbf{A}_\mathbf{x}\boldsymbol{\vartheta} + \sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2}$$

$$\rho_{\text{inter}} = \frac{\sigma_\alpha^2}{\boldsymbol{\vartheta}'\mathbf{A}_\mathbf{x}\boldsymbol{\vartheta} + \sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2/m} + \frac{2}{nk(k-1)} \cdot \frac{\sum_{i=1}^{n}\sum_{j=1}^{k-1}\sum_{j'=j+1}^{k} \boldsymbol{\vartheta}'\mathbf{A}_{\mathbf{x}ijj'}\boldsymbol{\vartheta}/(\sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2/m_{ijj'})}{\boldsymbol{\vartheta}'\mathbf{A}_\mathbf{x}\boldsymbol{\vartheta} + \sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2/m}$$

$$\chi_{a,\text{inter}} = \frac{\sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2/m}{\boldsymbol{\vartheta}'\mathbf{A}_\mathbf{x}\boldsymbol{\vartheta} + \sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2/m}$$

$$\chi_{a,\text{total}} = \frac{\sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2}{\boldsymbol{\vartheta}'\mathbf{A}_\mathbf{x}\boldsymbol{\vartheta} + \sigma_\alpha^2 + \sigma_\gamma^2 + \sigma_\epsilon^2}$$

where

- $\mathbf{A}_\mathbf{x} = \sum_{i=1}^{n}\sum_{j=1}^{k-1}\sum_{j'=j+1}^{k}(\mathbf{x}_{ij} - \mathbf{x}_{ij'})(\mathbf{x}_{ij} - \mathbf{x}_{ij'})'/nk(k-1)$,
- m is the harmonic mean of $m_{ijj'}$'s.

Restricted Agreement Statistics

- **All the (overall) agreement statistics are functions of ϑ, σ_α, σ_γ, and σ_ϵ.**
- $\mathbf{A}_{\mathbf{x}} = \sum_{i=1}^{n} \sum_{j=1}^{k-1} \sum_{j'=j+1}^{k} (\mathbf{x}_{ij} - \mathbf{x}_{ij'})(\mathbf{x}_{ij} - \mathbf{x}_{ij'})'/nk(k-1)$.

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Model

$$y_{ijl} = \mu + \mathbf{x}_{ij}'\boldsymbol{\vartheta} + \alpha_i + \gamma_{ij} + \epsilon_{ijl}$$

- $\boldsymbol{\vartheta}' = (\beta_1, \beta_2, \ldots, \beta_k, \boldsymbol{\theta}')$ and $\mathbf{x}_{ij}$ is the corresponding design matrix, which includes covariate matrix $\mathbf{x}_{ij}^c$.

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$$y_{ijl} = \mu + \mathbf{x}'_{ij}\boldsymbol{\vartheta} + \alpha_i + \gamma_{ij} + \epsilon_{ijl}$$

- $\boldsymbol{\vartheta}' = (\beta_1, \beta_2, \ldots, \beta_k, \boldsymbol{\theta}')$ and $\mathbf{x}_{ij}$ is the corresponding design matrix, which includes covariate matrix $\mathbf{x}^c_{ij}$.

In many cases, one may not be interested in the covariates, but the inter- and total-rater effects or variabilities. Therefore, we eliminate the covariate effects in the computation of $\mathbf{A_x}$ by assuming $\mathbf{x}^c_{ij} = 0$ (or $= \mathbf{x}^c_0$) in the $\mathbf{x}_{ij}$.

Estimations

Rewrite the model in vector form,

$$y = X\boldsymbol{\beta} + Z_1\boldsymbol{\alpha} + Z_2\boldsymbol{\gamma} + Z_0\boldsymbol{\epsilon}$$

with

$$\boldsymbol{\alpha} = \begin{pmatrix} \alpha_1 \\ \alpha_2 \\ \vdots \\ \alpha_n \end{pmatrix}, \quad \boldsymbol{\gamma} = \begin{pmatrix} \gamma_{11} \\ \gamma_{12} \\ \vdots \\ \gamma_{1k} \\ \gamma_{21} \\ \vdots \\ \gamma_{ij} \\ \vdots \\ \gamma_{nk} \end{pmatrix}, \quad \boldsymbol{\beta} = \begin{pmatrix} \mu \\ \boldsymbol{\vartheta} \end{pmatrix}$$

Estimations

Fixed Effects

$$\boldsymbol{\beta} = (X'V^{-1}X)^{-}X'V^{-1}y$$

Asymptotic variance matrix is

$$V_{\boldsymbol{\beta}} = var(\boldsymbol{\beta}) = (X'V^{-1}X)^{-}$$

Estimations

Fixed Effects

$$\boldsymbol{\beta} = (X'V^{-1}X)^{-}X'V^{-1}y$$

Asymptotic variance matrix is

$$V_{\boldsymbol{\beta}} = var(\boldsymbol{\beta}) = (X'V^{-1}X)^{-}$$

Variance Components

Restricted maximum likelihood (REML) is used.

Let $N = \sum m_{ij}$, and K be an $N \times (N - p + 1)$ matrix with rank $N - p + 1$, $K'X = 0$.

$$\begin{pmatrix} tr(Z_0'PZ_0Z_0'PZ_0) & tr(Z_0'PZ_1Z_1'PZ_0) & tr(Z_0'PZ_2Z_2'PZ_0) \\ tr(Z_1'PZ_0Z_0'PZ_1) & tr(Z_1'PZ_1Z_1'PZ_1) & tr(Z_1'PZ_2Z_2'PZ_1) \\ tr(Z_2'PZ_0Z_0'PZ_2) & tr(Z_2'PZ_1Z_1'PZ_2) & tr(Z_2'PZ_2Z_2'PZ_2) \end{pmatrix} \begin{pmatrix} \sigma_\epsilon^2 \\ \sigma_\alpha^2 \\ \sigma_\gamma^2 \end{pmatrix} = \begin{pmatrix} y'PZ_0Z_0'Py \\ y'PZ_1Z_1'Py \\ y'PZ_2Z_2'Py \end{pmatrix}$$

where

$$P = V^{-1} - V^{-1}X(X'V^{-1}X)^{-}X'V^{-1} = K(K'VK)^{-1}K'$$

Asymptotic Variances of Variance Components

With Normality

With Normality

The estimated variance of variance components can be calculated from the second derivatives of the log likelihood function. Let $\varsigma = \left(\sigma_\epsilon^2, \sigma_\alpha^2, \sigma_\gamma^2\right)'$,

$$V_\varsigma = var\begin{pmatrix} \sigma_\epsilon^2 \\ \sigma_\alpha^2 \\ \sigma_\gamma^2 \end{pmatrix} = 2\begin{pmatrix} tr(PZ_0Z_0'PZ_0Z_0') & tr(PZ_0Z_0'PZ_1Z_1') & tr(PZ_0Z_0'PZ_2Z_2') \\ tr(PZ_1Z_1'PZ_0Z_0') & tr(PZ_1Z_1'PZ_1Z_1') & tr(PZ_1Z_1'PZ_2Z_2') \\ tr(PZ_2Z_2'PZ_0Z_0') & tr(PZ_2Z_2'PZ_1Z_1') & tr(PZ_2Z_2'PZ_2Z_2') \end{pmatrix}^{-1}$$

Without Normality

Richardson and Welsh [12]

For hierarchical models, observations y can be partitioned into g vectors y_i so that V is block diagonal with g blocks V_j. Each $Z_i Z_i'$ is also block diagonal, we denote the jth diagonal block as $[Z_i Z_i']_j$.

Assume some mild conditions hold, there is a solution $\hat{\varsigma} = \left(\sigma^2_\epsilon, \sigma^2_\alpha, \sigma^2_\gamma\right)'$ of the estimating equations satisfying $|\hat{\varsigma} - \varsigma| = O_p(N^{-1/2})$ as $N \to \infty$. Moreover,

$$N^{1/2}(\hat{\varsigma} - \varsigma) \xrightarrow{D} \mathcal{N}(0, G^{-1}FG^{-1}),$$

where the elements of G and F can be estimated by,

$$
\begin{aligned}
[\hat{G}]_{ik} &= (2N)^{-1} \sum_{j=1}^{g} tr(\hat{V}_j^{-1}[Z_{i-1}Z'_{i-1}]_j \hat{V}_j^{-1}[Z_{k-1}Z'_{k-1}]_j) \\
[\hat{F}]_{ik} &= (4N)^{-1} \sum_{j=1}^{g} \Big\{ \Big[(y_j - X_j\hat{\boldsymbol{\beta}})'\hat{V}_j^{-1}[Z_{i-1}Z'_{i-1}]_j \hat{V}_j^{-1}(y_j - X_j\hat{\boldsymbol{\beta}})(y_j - X_j\hat{\boldsymbol{\beta}})'\hat{V}_j^{-1} \\
&\quad \times [Z_{k-1}Z'_{k-1}]_j \hat{V}_j^{-1}(y_j - X_j\hat{\boldsymbol{\beta}})\Big] - tr(\hat{V}_j^{-1}[Z_{i-1}Z'_{i-1}]_j) tr(\hat{V}_j^{-1}[Z_{k-1}Z'_{k-1}]_j) \Big\}
\end{aligned}
$$

[12] A.M. Richardson and A.H. Welsh, Asymptotic properties of restricted maximum likelihood (reml) estimates for hierarchical mixed linear models, *Australian & New Zealand Journal of Statistics*, 36(1):31–43, 1994.

Asymptotic Properties of Agreement Statistics

- Let $\boldsymbol{\tau} = (\boldsymbol{\vartheta}, \boldsymbol{\varsigma})'$,

$$V_{\boldsymbol{\tau}} = N \cdot \begin{pmatrix} V_{\boldsymbol{\vartheta}} & 0 \\ 0 & V_{\boldsymbol{\varsigma}} \end{pmatrix}$$

[12] A.M. Richardson and A.H. Welsh, Asymptotic properties of restricted maximum likelihood (reml) estimates for hierarchical mixed linear models, *Australian & New Zealand Journal of Statistics*, 36(1):31–43, 1994.

Asymptotic Properties of Agreement Statistics

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$$N^{1/2}(\hat{\boldsymbol{\tau}} - \boldsymbol{\tau}) \xrightarrow{D} \mathcal{N}(0, V_{\boldsymbol{\tau}})$$

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Asymptotic Properties of Agreement Statistics

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- From Richardson and Welsh [12], we know that

$$N^{1/2}(\hat{\boldsymbol{\tau}} - \boldsymbol{\tau}) \xrightarrow{D} \mathcal{N}(0, V_{\boldsymbol{\tau}})$$

- Delta method is used to obtain the asymptotic normality for all agreement statistics.

$$N^{1/2}(f(\hat{\boldsymbol{\tau}}) - f(\boldsymbol{\tau})) \xrightarrow{D} \mathcal{N}(0, \triangledown f(\boldsymbol{\tau})' V_{\boldsymbol{\tau}} \triangledown f(\boldsymbol{\tau}))$$

where $f(\cdot)$ can be any agreement functions.

---

[12] A.M. Richardson and A.H. Welsh, Asymptotic properties of restricted maximum likelihood (reml) estimates for hierarchical mixed linear models, *Australian & New Zealand Journal of Statistics*, 36(1):31–43, 1994.

Asymptotic Properties of Agreement Statistics

- Let $\boldsymbol{\tau} = (\boldsymbol{\vartheta}, \varsigma)'$,

For example

$$var(\mathsf{CCC}_{\mathsf{inter}}) =$$

$$\begin{pmatrix} \frac{-2\mathbf{A_x}\boldsymbol{\vartheta}}{(\boldsymbol{\vartheta}'\mathbf{A_x}\boldsymbol{\vartheta}+\sigma_\alpha^2+\sigma_\gamma^2+\sigma_\epsilon^2/m)^2} \\ \frac{-1/m}{(\boldsymbol{\vartheta}'\mathbf{A_x}\boldsymbol{\vartheta}+\sigma_\alpha^2+\sigma_\gamma^2+\sigma_\epsilon^2/m)^2} \\ \frac{\theta'\mathbf{A_x}\boldsymbol{\vartheta}+\sigma_\gamma^2+\sigma_\epsilon^2/m}{(\boldsymbol{\vartheta}'\mathbf{A_x}\boldsymbol{\vartheta}+\sigma_\alpha^2+\sigma_\gamma^2+\sigma_\epsilon^2/m)^2} \\ \frac{-1}{(\boldsymbol{\vartheta}'\mathbf{A_x}\boldsymbol{\vartheta}+\sigma_\alpha^2+\sigma_\gamma^2+\sigma_\epsilon^2/m)^2} \end{pmatrix}^T \times \frac{V_{\boldsymbol{\tau}}}{N} \times \begin{pmatrix} \frac{-2\mathbf{A_x}\boldsymbol{\vartheta}}{(\boldsymbol{\vartheta}'\mathbf{A_x}\boldsymbol{\vartheta}+\sigma_\alpha^2+\sigma_\gamma^2+\sigma_\epsilon^2/m)^2} \\ \frac{-1/m}{(\boldsymbol{\vartheta}'\mathbf{A_x}\boldsymbol{\vartheta}+\sigma_\alpha^2+\sigma_\gamma^2+\sigma_\epsilon^2/m)^2} \\ \frac{\theta'\mathbf{A_x}\boldsymbol{\vartheta}+\sigma_\gamma^2+\sigma_\epsilon^2/m}{(\boldsymbol{\vartheta}'\mathbf{A_x}\boldsymbol{\vartheta}+\sigma_\alpha^2+\sigma_\gamma^2+\sigma_\epsilon^2/m)^2} \\ \frac{-1}{(\boldsymbol{\vartheta}'\mathbf{A_x}\boldsymbol{\vartheta}+\sigma_\alpha^2+\sigma_\gamma^2+\sigma_\epsilon^2/m)^2} \end{pmatrix}$$

where $f(\cdot)$ can be any agreement functions.

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Simulations

Normal Data with Covariates and 10% Missing Values

- The following formula was used to generate data.

$$\begin{aligned} y_{ijl} &= \mu + x_{ij} + \beta_j + \alpha_i + \gamma_{ij} + \epsilon_{ijl} \\ & \quad i = 1, 2, \ldots, 200, \; j = 1, 2, 3, \; l = 1, 2. \end{aligned}$$

- where $x_{ij} = \ln(i) + \ln(j)$, $\mu = 10$, $\beta_1 = 0$. $\beta_2 = -1$, $\beta_3 = -2$.
- α_i, γ_{ij} and ϵ_{ijl} were independently normally distributed with mean zeros and variances $\sigma_\alpha^2 = 1$, $\sigma_\gamma^2 = 0.5^2$ and $\sigma_\epsilon^2 = 0.1^2$.
- 10% randomly missing values was conducted.

Simulations

Normal Data with Covariates and 10% Missing Values

Simulation Results for 1000 Runs

		True	Mean(Est)	Std(Est)	Mean(Std)	SIG(%)
Intra	MSD	0.020	0.020	0.003	0.003	4.6
	CCC	0.992	0.992	0.002	0.002	5.2
Inter	MSD	2.510	2.523	0.439	0.430	5.1
	CCC	0.443	0.440	0.069	0.070	5.2
	Precision	0.797	0.803	0.059	0.057	5.4
	Accuracy	0.557	0.555	0.067	0.063	5.5
Total	MSD	2.520	2.532	0.439	0.430	5.1
	CCC	0.442	0.439	0.068	0.070	5.2
	Precision	0.794	0.787	0.046	0.047	4.9
	Accuracy	0.558	0.556	0.067	0.063	5.7

d

Simulations

Non-normal Skew Cases

- Gamma distribution with a small shape parameter was used for the skew case. The data generating formula is

$$\begin{aligned} y_{ijl} &= \mu + \beta_j + \alpha_i + \gamma_{ij} + \epsilon_{ijl} \\ & \quad i = 1, 2, \ldots, 200,\ j = 1, 2,\ l = 1, 2. \end{aligned}$$

- where $\mu = 10$, $\beta_1 = 0$. $\beta_2 = -1$.
- ϵ_{ijl} was normally distributed with mean zero and variance $\sigma_\epsilon^2 = 0.5^2$.
- α_i and γ_{ij} were independently gamma distributed,

$$\alpha_i \sim \text{Gamma}(\text{shape} = 2, \text{scale} = 2/\sqrt{2})$$
$$\gamma_{ij} \sim \text{Gamma}(\text{shape} = 2, \text{scale} = 1/\sqrt{2})$$

Simulations

Non-normal Skew Cases

Simulation Results for 1000 Runs

		True	Mean(Est)	Std(Est)	Mean(Std)	SIG(%)
Intra	MSD	0.500	0.496	0.071	0.068	5.9
	CCC	0.952	0.950	0.013	0.015	4.6
Inter	MSD	3.250	3.287	0.718	0.680	6.3
	CCC	0.711	0.701	0.082	0.081	6.3
	Precision	0.780	0.773	0.074	0.070	6.5
	Accuracy	0.911	0.905	0.041	0.038	7.8
Total	MSD	3.500	3.535	0.718	0.681	6.0
	CCC	0.696	0.691	0.082	0.084	5.6
	Precision	0.762	0.755	0.074	0.070	6.6
	Accuracy	0.913	0.907	0.040	0.037	7.5

Simulations

Non-linear Case

- Multivariate negative binomial data was generated using Gamma–Poisson mixture with parameters $r = 10$ and $p = 0.91$.
- The dimensions were set as $n = 50$, $k = 2$, $m = 2$, and Pearson correlation coefficient matrix for the four data series was

$$\begin{pmatrix} 1 & 0.9 & 0.8 & 0.8 \\ 0.9 & 1 & 0.8 & 0.8 \\ 0.8 & 0.8 & 1 & 0.9 \\ 0.8 & 0.8 & 0.9 & 1 \end{pmatrix}$$

- After generating the multivariate negative binomial series, an additional inter-rater effect $\beta_2 = 20$ was added to the series of the second rater, in order to make a between rater location shift.

Simulations

Non-linear Case

Simulation Results for 1000 Runs

		True	Mean(Est)	Std(Est)	Mean(Std)	SIG(%)
Intra	MSD	224.788	223.807	33.057	33.350	3.1
	CCC	0.900	0.897	0.025	0.027	3.0
Inter	MSD	735.476	741.954	127.160	123.183	5.1
	CCC	0.709	0.701	0.064	0.067	3.3
	Precision	0.842	0.839	0.046	0.047	3.7
	Accuracy	0.842	0.834	0.046	0.044	6.3
Total	MSD	847.870	850.858	128.879	124.753	2.2
	CCC	0.679	0.671	0.065	0.067	2.6
	Precision	0.800	0.796	0.050	0.052	3.4
	Accuracy	0.849	0.842	0.043	0.041	7.4

er

to make a between rater location shift.

Cardiac Function Measurements Case Study

- This example (Bowling, et al. [4]) was used to determine the limits of agreement between left ventricular ejection fraction estimated by impedance cardiography (IC) and radionuclide ventriculography (RV).
- Sixty measurements of cardiac ejection fraction by these two methods were made on 12 patients, with unbalanced number of replicates per patient.

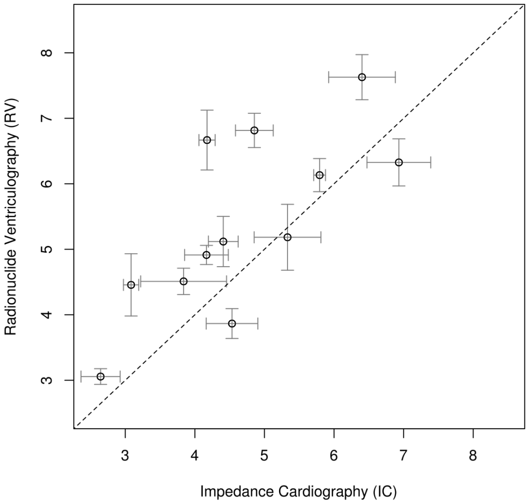
---

[4] L.S. Bowling, W.S. Sageman, S.M. O'Connor, R. Cole, and D.E. Amundson, Lack of agreement between measurement of ejection fraction by impedance cardiography versus radionuclide ventriculography, *Critical care medicine*, 21(10):1523, 1993.

Cardiac Outputs by RV and IC for 12 Patients

Patients	Method	Outputs					
1	IC	6.57	5.62	6.90	6.57	6.35	
	RV	7.83	7.42	7.89	7.12	7.88	
2	IC	4.06	4.29	4.26	4.09		
	RV	6.16	7.26	6.71	6.54		
3	IC	4.71	5.50	5.08	5.02	6.01	5.67
	RV	4.75	5.24	4.86	4.78	6.05	5.42
4	IC	4.14	4.20	4.61	4.68	5.04	
	RV	4.21	3.61	3.72	3.87	3.92	
5	IC	3.03	2.86	2.77	2.46	2.32	2.43
	RV	3.13	2.98	2.85	3.17	3.09	3.12
6	IC	5.90	5.81	5.70	5.76		
	RV	5.92	6.42	5.92	6.27		
7	IC	5.09	4.63	4.61	5.09		
	RV	7.13	6.62	6.58	6.93		
8	IC	4.72	4.61	4.36	4.20	4.36	4.20
	RV	4.54	4.81	5.11	5.29	5.39	5.57
9	IC	3.17	3.12	2.96			
	RV	4.48	4.92	3.97			
10	IC	4.35	4.62	3.16	3.53	3.53	
	RV	4.22	4.65	4.74	4.44	4.50	
11	IC	7.20	6.09	7.00	7.10	7.40	6.80
	RV	6.78	6.07	6.52	6.42	6.41	5.76
12	IC	4.50	4.20	3.80	3.80	4.20	4.50
	RV	5.06	4.72	4.90	4.80	4.90	5.10

Means of the Cardiac Outputs for each Subject with Error Bars



Cardiac Function Measurements Case Study

Estimated Agreement Statistics for Cardiac Outputs

		Est	Std	95% C.I.
Intra	CCC	0.932	0.024	$(0.865, 0.967)$
	Precision	0.932	0.024	$(0.865, 0.967)$
Inter	CCC	0.642	0.153	$(0.245, 0.855)$
	Precision	0.716	0.141	$(0.322, 0.898)$
	Accuracy	0.874	0.061	$(0.700, 0.954)$
Total	CCC	0.612	0.153	$(0.229, 0.830)$
	Precision	0.695	0.149	$(0.285, 0.890)$
	Accuracy	0.880	0.055	$(0.724, 0.953)$

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- The intra-rater CCC estimate **0.932** indicates good agreement within each method.

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- The intra-rater CCC estimate **0.932** indicates good agreement within each method.
- The inter-rater CCC estimate **0.642** indicates worse agreement between these two methods.

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- The intra-rater CCC estimate **0.932** indicates good agreement within each method.
- The inter-rater CCC estimate **0.642** indicates worse agreement between these two methods.
- Those low inter-rater agreement statistics values reveal that these two methods impedance cardiography and radionuclide ventriculography are not interchangeable.

Agreement for Generalized Linear Mixed Models

Generalized Linear Mixed Models (GLMM)

Model

$$
\begin{aligned}
f(y_{ij}|\alpha_i, \gamma_{ij}) &= exp\left(\frac{y_{ij}\tau_{ij} - b(\tau_{ij})}{a(\phi)} + c(y_{ij}, \phi)\right), \\
E(y_{ij}|\alpha_i, \gamma_{ij}) &= \mu_{ij}, \\
g(\boldsymbol{\mu}) &= X\boldsymbol{\beta} + Z_1\boldsymbol{\alpha} + Z_2\boldsymbol{\gamma}.
\end{aligned}
$$

Generalized Linear Mixed Models (GLMM)

Model

$$
\begin{aligned}
f(y_{ij}|\alpha_i,\gamma_{ij}) &= exp\left(\frac{y_{ij}\tau_{ij}-b(\tau_{ij})}{a(\phi)}+c(y_{ij},\phi)\right),\\
E(y_{ij}|\alpha_i,\gamma_{ij}) &= \mu_{ij},\\
g(\boldsymbol{\mu}) &= X\boldsymbol{\beta}+Z_1\boldsymbol{\alpha}+Z_2\boldsymbol{\gamma}.
\end{aligned}
$$

$$
\boldsymbol{\alpha}=\begin{pmatrix}\alpha_1\\ \alpha_2\\ \vdots\\ \alpha_n\end{pmatrix},\quad
\boldsymbol{\gamma}=\begin{pmatrix}\gamma_{11}\\ \gamma_{12}\\ \vdots\\ \gamma_{1k}\\ \gamma_{21}\\ \vdots\\ \gamma_{ij}\\ \vdots\\ \gamma_{nk}\end{pmatrix},\quad
\boldsymbol{\beta}=\begin{pmatrix}\mu\\ \beta_1\\ \vdots\\ \beta_k\\ \boldsymbol{\theta}\end{pmatrix},
$$

Generalized Linear Mixed Models (GLMM)

Model

$$\begin{aligned} f(y_{ij}|\alpha_i, \gamma_{ij}) &= exp\left(\frac{y_{ij}\tau_{ij} - b(\tau_{ij})}{a(\phi)} + c(y_{ij}, \phi)\right), \\ E(y_{ij}|\alpha_i, \gamma_{ij}) &= \mu_{ij}, \\ g(\boldsymbol{\mu}) &= X\boldsymbol{\beta} + Z_1\boldsymbol{\alpha} + Z_2\boldsymbol{\gamma}. \end{aligned}$$

- It is known that

$$\begin{aligned} b'(\tau_{ij}) &= E(y_{ij}|\alpha_i, \gamma_{ij}) = \mu_{ij}, \\ var(y_{ij}|\alpha_i, \gamma_{ij}) &= a(\phi)v(\mu_{ij}), \end{aligned}$$

  where $v(\cdot)$ is the variance function for μ.

- Assuming the linear predictor $\boldsymbol{\eta} = X\boldsymbol{\beta} + Z_1\boldsymbol{\alpha} + Z_2\boldsymbol{\gamma}$, and the inverse link function $h(\cdot) = g^{-1}(\cdot)$, we have

$$E(y|\boldsymbol{\alpha}, \boldsymbol{\gamma}) = h(X\boldsymbol{\beta} + Z_1\boldsymbol{\alpha} + Z_2\boldsymbol{\gamma}).$$

Generalized Linear Mixed Models (GLMM)

There are some well-developed methods to estimate the fixed and random effects via maximum likelihood (ML) or restricted maximum likelihood (REML) approach.

- Penalized quasi-likelihood (Breslow and Clayton, 1993);
  (R: glmmPQL)
- **Laplace approximation (Lin and Breslow, 1996);**
  (R library: lme4, lme4a)
- Pseudo likelihood (Wolfinger, 1993);
- Gauss-Hermite quadrature;
  (R library: lme4, lme4a)
- Markov chain Monte Carlo.
  (R library: MCMCglmm)

$$E(y|\boldsymbol{\alpha}, \boldsymbol{\gamma}) = h(X\boldsymbol{\beta} + Z_1\boldsymbol{\alpha} + Z_2\boldsymbol{\gamma}).$$

Individual Agreement Statistics

For given subject i, and rater j.

Intra-rater Agreement Statistics

$$\begin{aligned}\text{MSD}_{\text{intra}}|i,j &= E(y_{ijl} - y_{ijl'})^2 \\ &= \left[E(y_{ijl}) - E(y_{ijl'})\right]^2 + var(y_{ijl}) + var(y_{ijl'}) - 2cov(y_{ijl}, y_{ijl'})\end{aligned}$$

Individual Agreement Statistics

For given subject i, and rater j.

Intra-rater Agreement Statistics

$$\text{MSD}_{\text{intra}}|i,j = E(y_{ijl} - y_{ijl'})^2$$
$$= \left[E(y_{ijl}) - E(y_{ijl'})\right]^2 + var(y_{ijl}) + var(y_{ijl'}) - 2cov(y_{ijl}, y_{ijl'})$$

$$\uparrow$$

$$var(y_{ijl}) = var(E(y_{ijl}|\mu_{ij})) + E(var(y_{ijl}|\mu_{ij})) = var(\mu_{ij}) + E(a(\phi)v(\mu_{ij}))$$

Individual Agreement Statistics

For given subject i, and rater j.

Intra-rater Agreement Statistics

$$cov(y_{ijl}, y_{ijl'}) = var(\mu_{ij})$$

$$\downarrow$$

$$\begin{aligned} \text{MSD}_{\text{intra}}|i,j &= E(y_{ijl} - y_{ijl'})^2 \\ &= \left[E(y_{ijl}) - E(y_{ijl'})\right]^2 + var(y_{ijl}) + var(y_{ijl'}) - 2cov(y_{ijl}, y_{ijl'}) \end{aligned}$$

$$\uparrow$$

$$var(y_{ijl}) = var(E(y_{ijl}|\mu_{ij})) + E(var(y_{ijl}|\mu_{ij})) = var(\mu_{ij}) + E(a(\phi)v(\mu_{ij}))$$

Individual Agreement Statistics

For given subject i, and rater j.

Intra-rater Agreement Statistics

$$\begin{aligned}
\mathsf{MSD}_{\mathsf{intra}}|i,j &= E(y_{ijl} - y_{ijl'})^2 \\
&= \left[E(y_{ijl}) - E(y_{ijl'})\right]^2 + var(y_{ijl}) + var(y_{ijl'}) - 2cov(y_{ijl}, y_{ijl'}) \\
&= 2E\big(a(\phi)v(\mu_{ij})\big)
\end{aligned}$$

Individual Agreement Statistics

For given subject i, and rater j.

Intra-rater Agreement Statistics

$$
\begin{aligned}
\text{MSD}_{\text{intra}}|i,j &= 2E\big(a(\phi)v(\mu_{ij})\big),\\
\text{CCC}_{\text{intra}}|i,j &= \frac{cov(y_{ijl}, y_{ijl'})}{var(y_{ijl})}\\
&= \frac{var(\mu_{ij})}{var(\mu_{ij}) + E(a(\phi)v(\mu_{ij}))},\\
\rho_{\text{intra}}|i,j &= \frac{var(\mu_{ij})}{var(\mu_{ij}) + E(a(\phi)v(\mu_{ij}))},\\
\chi_{a,\text{intra}}|i,j &= 1.
\end{aligned}
$$

Individual Agreement Statistics

Similarly, we have

- $$\begin{aligned} var(\bar{y}_{ij\cdot}) &= var(E(\bar{y}_{ij\cdot}|\mu_{ij})) + E(var(\bar{y}_{ij\cdot}|\mu_{ij})) \\ &= var(\mu_{ij}) + \frac{E\big(a(\phi)v(\mu_{ij})\big)}{m} \end{aligned}$$

- $$\begin{aligned} cov(\bar{y}_{ij\cdot}, \bar{y}_{ij'\cdot}) &= cov(E(\bar{y}_{ij\cdot}|\mu_{ij}), E(\bar{y}_{ij'\cdot}|\mu_{ij'})) \\ &= cov(\mu_{ij}, \mu_{ij'}) \end{aligned}$$

- $$\begin{aligned} cov(y_{ijl}, y_{ij'l'}) &= cov(E(\bar{y}_{ijl}|\mu_{ij}), E(\bar{y}_{ij'l'}|\mu_{ij'})) \\ &= cov(\mu_{ij}, \mu_{ij'}) \end{aligned}$$

Individual Agreement Statistics

For given subject i, and any two raters j and j', $j, j' = 1, 2, \ldots, k, j \neq j'$.

Inter-rater Agreement Statistics

$$\text{MSD}_{\text{inter}}|i,j,j' = \left[E(\mu_{ij}) - E(\mu_{ij'})\right]^2 + var(\mu_{ij}) + \frac{E\big(a(\phi)v(\mu_{ij})\big)}{m} + var(\mu_{ij'}) + \frac{E\big(a(\phi)v(\mu_{ij'})\big)}{m} - 2cov(\mu_{ij}, \mu_{ij'}),$$

$$\text{CCC}_{\text{inter}}|i,j,j' = \frac{2cov(\mu_{ij}, \mu_{ij'})}{\left[E(\mu_{ij}) - E(\mu_{ij'})\right]^2 + var(\mu_{ij}) + \frac{1}{m}E\big(a(\phi)v(\mu_{ij})\big) + var(\mu_{ij'}) + \frac{1}{m}E\big(a(\phi)v(\mu_{ij'})\big)},$$

$$\rho_{\text{inter}}|i,j,j' = \frac{cov(\mu_{ij}, \mu_{ij'})}{\sqrt{var(\mu_{ij}) + \frac{1}{m}E\big(a(\phi)v(\mu_{ij})\big)}\sqrt{var(\mu_{ij'}) + \frac{1}{m}E\big(a(\phi)v(\mu_{ij'})\big)}},$$

$$\chi_{a,\text{inter}}|i,j,j' = \frac{\text{CCC}_{\text{inter}}|i,j,j'}{\rho_{\text{inter}}|i,j,j'}.$$

Individual Agreement Statistics

For given subject i, and any two raters j and j', $j, j' = 1, 2, \ldots, k, j \neq j'$.

Total-rater Agreement Statistics

$$\text{MSD}_{\text{total}}|i,j,j' = \left[E(\mu_{ij}) - E(\mu_{ij'})\right]^2 + var(\mu_{ij}) + E\big(a(\phi)v(\mu_{ij})\big) + var(\mu_{ij'}) + E\big(a(\phi)v(\mu_{ij'})\big) - 2cov(\mu_{ij}, \mu_{ij'}),$$

$$\text{CCC}_{\text{total}}|i,j,j' = \frac{2cov(\mu_{ij}, \mu_{ij'})}{\left[E(\mu_{ij}) - E(\mu_{ij'})\right]^2 + var(\mu_{ij}) + E\big(a(\phi)v(\mu_{ij})\big) + var(\mu_{ij'}) + E\big(a(\phi)v(\mu_{ij'})\big)},$$

$$\rho_{\text{total}}|i,j,j' = \frac{cov(\mu_{ij}, \mu_{ij'})}{\sqrt{var(\mu_{ij}) + E\big(a(\phi)v(\mu_{ij})\big)}\sqrt{var(\mu_{ij'}) + E\big(a(\phi)v(\mu_{ij'})\big)}},$$

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Individual Agreement Statistics

For given subject i, and any two raters j and j', $j, j' = 1, 2, \ldots, k, j \neq j'$.

Total-rater Agreement Statistics

MSD$_{\text{total}}|i$

CCC$_{\text{total}}|i$

$$\overline{[E(\mu_{ij}) - \quad\quad v(\mu_{ij'}))},$$

$$\rho_{\text{total}}|i \quad \overline{\sqrt{var(\mu_{ij}) + E\big(a(\phi)v(\mu_{ij})\big)}\sqrt{var(\mu_{ij'}) + E\big(a(\phi)v(\mu_{ij'})\big)}},$$

$$\chi_{a,\text{total}}|i,j,j' = \frac{\text{CCC}_{\text{total}}|i,j,j'}{\rho_{\text{total}}|i,j,j'}.$$

All the agreement statistics are functions of

- $E(\mu_{ij})$,
- $var(\mu_{ij}) = E(\mu_{ij}^2) - E(\mu_{ij})^2$,
- $cov(\mu_{ij}, \mu_{ij'}) = E(\mu_{ij}\mu_{ij}) - E(\mu_{ij})E(\mu_{ij'})$,
- $E\big(a(\phi)v(\mu_{ij})\big)$.

Dispersion Parameters and Variance Functions

List of Dispersion Parameters and Variance Functions for Selected Distributions

Distribution	$a(\phi)$	$v(\mu)$
Gaussian(μ,σ_ϵ^2)	σ_ϵ^2	1
Gamma(μ, ϕ)	ϕ	μ^2
Binomial(p, N)	1	$\mu(1-\mu)/N$
Poisson(μ)	1	μ
Negative Binomial(r, p)	1	$\mu + \mu^2 r$

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- All we need are $E(\mu_{ij})$, $E(\mu_{ij}^2)$, and $E(\mu_{ij}\mu_{ij'})$.

$$\mu_{ij} = g^{-1}(X_{ij}\boldsymbol{\beta} + \alpha_i + \gamma_{ij})$$

Link Functions

List of the Canonical Links for Selected Distributions

Distribution	Canonical Link	Inverse of Canonical Link
Gaussian(μ,σ_ϵ^2)	μ	η
Gamma(μ, ϕ)	$1/\mu$	$1/\eta$
Binomial(p, N)	$ln(\mu/(1-\mu))$	$exp(\eta)/(1+exp(\eta))$
Poisson(μ)	$ln(\mu)$	$exp(\eta)$
Negative Binomial(r, p)	$-ln(r/\mu+1)$	$r/\big(exp(-\eta)-1\big)$

Link Function

- For natural log link, the expressions for $E(\mu_{ij})$, $E(\mu_{ij}^2)$, and $E(\mu_{ij}\mu_{ij'})$ are easy to find.

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$$\begin{aligned} E(\mu_{ij}) &= E(exp(X_{ij}\boldsymbol{\beta} + \alpha_i + \gamma_{ij})) \\ &= exp(X_{ij}\boldsymbol{\beta})E(exp(\alpha_i))E(exp(\gamma_{ij})) \\ &= exp(X_{ij}\boldsymbol{\beta})M_{\boldsymbol{\alpha}}(1)M_{\boldsymbol{\gamma}}(1) \end{aligned}$$

◇ where $M_{\dagger}(\cdot)$ is the moment generation function for variable † at $\cdot$.

Link Function

- For ... $\mu_{ij}\mu_{ij'})$ are

If $\boldsymbol{\alpha} \sim \mathcal{N}(0, \sigma_\alpha^2 \cdot I_n)$, $\boldsymbol{\gamma} \sim \mathcal{N}(0, \sigma_\gamma^2 \cdot I_{n\times k})$

$$\begin{aligned} E(\mu_{ij}) &= exp(X_{ij}\boldsymbol{\beta})exp\left(\frac{\sigma_\alpha^2 + \sigma_\gamma^2}{2}\right) \\ E(\mu_{ij}^2) &= exp(2X_{ij}\boldsymbol{\beta} + 2\sigma_\alpha^2 + 2\sigma_\gamma^2) \\ E(\mu_{ij}\mu_{ij'}) &= exp(X_{ij}\boldsymbol{\beta} + X_{ij'}\boldsymbol{\beta} + 2\sigma_\alpha^2 + \sigma_\gamma^2) \end{aligned}$$

◇ where $M_\dagger(\cdot)$ is the moment generation function for variable † at ·.

Link Function

- For other links, like logit, square root or inverse links, we use the adaptive numerical integration algorithm [3] to calculate the $E(\mu_{ij})$, $E(\mu_{ij}^2)$, and $E(\mu_{ij}\mu_{ij'})$ directly for all the link functions.

[3] J. Berntsen, T.O. Espelid, and A. Genz, An adaptive algorithm for the approximate calculation of multiple integrals, *ACM Transactions on Mathematical Software (TOMS)*, 17(4):437–451, 1991.

Confidence Intervals

- The asymptotic behavior of the variance components estimates from GLMM is problematic.

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Confidence Intervals

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- 95% percentile interval is used based on parametric bootstrap.

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Simulation

Compare with Lin's Unified Approach

- The unified approach proposed by Lin, et al. [8] can also be used in categorical case.
- Unlike our generalized linear mixed model, the unified approach does not require any model assumptions.
- It uses analysis of variances (ANOVA) technique to estimate all the variance components, and calculates the CCC using linear additive model.

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CCC for Negative Binomial Distribution with Log Link for 1000 runs

		GLMM Approach		Unified Approach	
	TRUE	Mean (EST)	STD(EST)	Mean (EST)	STD(EST)
Intra-CCC	0.853	0.832	0.012	0.820	0.035
Inter-CCC	0.618	0.616	0.075	0.521	0.050
Total-CCC	0.573	0.570	0.024	0.476	0.046

[8] L. Lin, A.S. Hedayat, and W. Wu, A unified approach for assessing agreement for continuous and categorical data, *Journal of biopharmaceutical statistics*, 17(4):629, 2007.

Antihypertensive Patch Dataset

- This dataset is an example given by the FDA (`http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Biostatistics/ucm081434.htm`) and had been used in [6] for the population and individual bioequivalence.

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- AUC values are studied from that dataset, which was collected by a four-period, two-sequence crossover trial to a total of 37 subjects.

Summary of the Crossover Design

Sequence	Number of Subjects	Period
1	18	TRRT
2	19	RTTR

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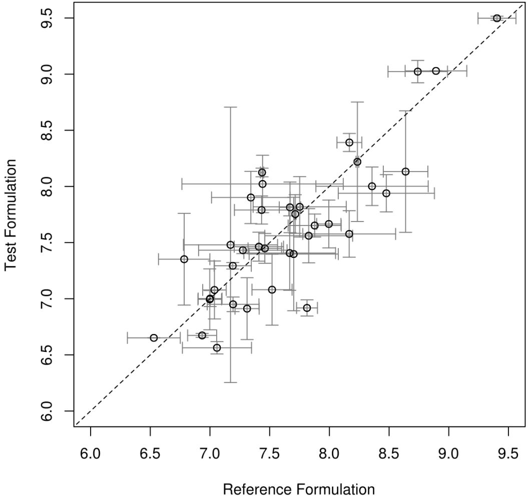
Antihyp

- This … v/Drugs/ Scie… m) and had b… e.
- AUC … four-…

Means of the log(AUC) for each Subject with Error Bars



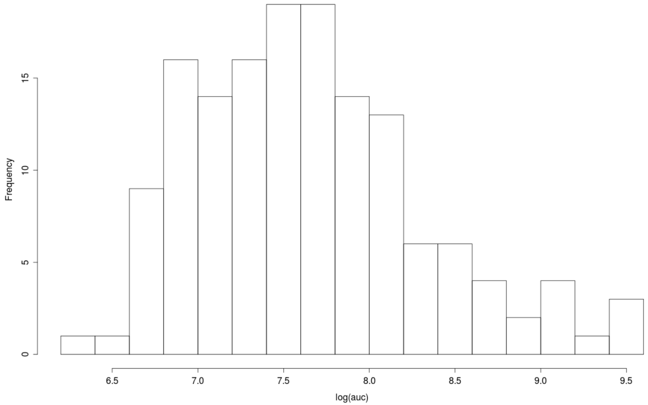
Antihypertensive Patch Dataset

◇ gs/

d

◇

Histogram of log(AUC)



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Antihypertensive Patch Dataset

Using GLMM with Gamma distribution family and log link function. Assume the linear predictor,

$$\eta_{ijl} = \mu + \beta_j + s_i + p_l + \rho_{i,l-1} + \alpha_i + \gamma_{ij}$$

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- The subscript i is the index of subjects, j is the index of formulations (T/R), and l is the index of periods.
- μ is the overall mean, β_j is the fixed formulation effects, s_i is the fixed sequence effects, p_l is the fixed period effects, and $\rho_{i,l-1}$ is the first order carryover effect.
- α_i is the random subject effect nested in sequences, γ_{ij} is the random subject-formulation interaction effect.

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- α_i is the random subject effect nested in sequences, γ_{ij} is the random subject-formulation interaction effect.

Likelihood ratio tests show that the period effects and carryover effects are not statistical significant. The linear predictor can be reduced to

$$\eta_{ij} = \mu + \beta_j + s_i + \alpha_i + \gamma_{ij}$$

Antihypertensive Patch Dataset

Estimated Agreement Statistics for AUC

		Est	95% C.I.
Intra	CCC	0.914	$(0.861, 0.949)$
Inter	CCC	0.954	$(0.925, 0.973)$
	Precision	0.955	$(0.925, 0.974)$
	Accuracy	0.999	$(0.998, 1.000)$
Total	CCC	0.913	$(0.859, 0.948)$
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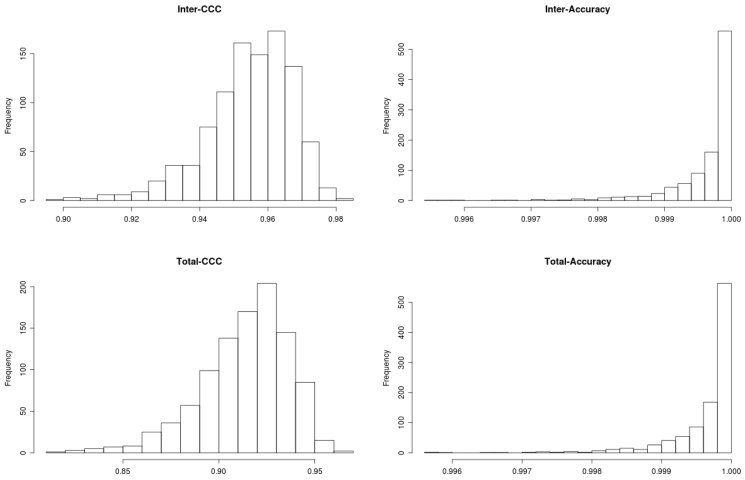
- All the accuracy coefficients are very close to 1, which indicate no major location shift for the marginal distributions of reference and test formulations.
- If an allowance 0.950 is used for CCC, we can see that the inter-CCC is 0.954, which exceeds the allowance 0.950. Therefore, the agreement between the reference and test formulations are satisfactory, they can be considered interchangeable.

Antihypertensive Patch Dataset

Histogram of Selected Agreements for 1000 Bootstrap Simulations



interchangeable.

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The End