Using ANOVA to Estimate Limits of Agreement for MRMC study

1. Definition

Suppose X_{ijk} denotes the score for case k ($k = 1, ..., K$) from the reader j ($j = 1, .., J$) under modality i ($i = 1, 2$) in a Multi-reader Multi-case study comparing two different modalities, where $i = 1$ and $i = 2$ indicate test modality and reference modality respectively. The difference score between the two modalities is given by $D^{12}_{jj'k} = X_{1jk} - X_{2j'k}$. If $j = j'$, the difference score $D^{12}_{jj,k}$, or simply Y_{jk}, denotes the within-reader between-modality (WRBM) difference.That is, the difference score from the same reader under different modalities. Given the mean difference $\overline{D^{12}_{WR}} = E[Y_{jk}]$ and the variance of the difference $V^{12}_{WR} = Var[Y_{jk}]$, the WRBM limits of agreement is defined as:

$$\overline{D^{12}_{WR}} \pm 2\sqrt{V^{12}_{WR}}$$

When $j \neq j'$, the difference score $D^{12}_{jj'k}$ denotes the between-reader between-modality (BRBM) difference. Similarly, we have the mean difference $\overline{D^{12}_{BR}} = E[D^{12}_{jj'k}]$ and the variance of the difference $V^{12}_{BR} = Var[D^{12}_{jj'k}]$. Thus, the BRBM limits of agreement is defined as:

$$\overline{D^{12}_{BR}} \pm 2\sqrt{V^{12}_{BR}}$$

To construct the WRBM and BRBM limits of agreement, we need to calculate $\overline{D^{12}_{WR}}$, V^{12}_{WR}, $\overline{D^{12}_{BR}}$, and V^{12}_{BR}. The two mean differences are easy to estimate.

$$\hat{\overline{D^{12}_{WR}}} = \frac{1}{JK}\sum_j\sum_k D^{12}_{jj,k} = \frac{1}{JK}\sum_j\sum_k (X_{1jk} - X_{2jk}) = \overline{X_{1}..} - \overline{X_{2}..}$$

where $\overline{X_{i}..} = \frac{1}{JK}\sum_j\sum_k X_{ijk}$ $i = 1, 2$ denotes the average score across all the readers and cases for a single modality. Similarly,

$$\hat{\overline{D^{12}_{BR}}} = \frac{1}{J(J-1)K}\sum_j\sum_{j\neq j'}\sum_k D^{12}_{jj'k} = \frac{1}{J(J-1)K}\sum_j\sum_{j\neq j'}\sum_k (X_{1jk} - X_{2j'k}) = \overline{X_{1}..} - \overline{X_{2}..}$$

Therefore, $\hat{\overline{D^{12}_{WR}}} = \hat{\overline{D^{12}_{BR}}} = \overline{X_{1}..} - \overline{X_{2}..}$.. The WRBM and BRBM limits of agreement will be different only by V^{12}_{WR} and V^{12}_{BR}. In the following tow sections, we will discuss how to use two-way random effect ANOVA to estimate V^{12}_{WR} and use three-way mixed effect ANOVA to estimate V^{12}_{BR}

2. Using two-way random effect ANOVA to estimate V_{WRBM}

To estimate $V^{12}_{WR} = Var[Y_{jk}]$, we build up a two-way random effect model for the WRBM difference Y_{jk}

$$Y_{jk} = \mu + R_j + C_k + \varepsilon_{jk}$$

where $R_j \sim N(0, \sigma^2_R)$, $C_k \sim N(0, \sigma^2_C)$, and $\varepsilon_{jk} \sim N(0, \sigma^2_\varepsilon)$ are independent random variables. Then, the variance of Y_{jk} can be expressed as

$$V^{12}_{WR} = Var[Y_{jk}] = Var(R_j + C_k + \varepsilon_{jk}) = \sigma^2_R + \sigma^2_C + \sigma^2_\varepsilon$$

The two-way random effect ANOVA table is given by

Source	DF	Sum of Square (SS)	Mean Square (MS)	E(MS)
Reader	$J-1$	$SSR = K\sum_j(\overline{Y_{j.}} - \overline{Y_{..}})^2$	$MSR = SSR/(J-1)$	$\sigma_\varepsilon^2 + K\sigma_R^2$
Case	$K-1$	$SSC = J\sum_k(\overline{Y_{.k}} - \overline{Y_{..}})^2$	$MSR = SSC/(K-1)$	$\sigma_\varepsilon^2 + J\sigma_C^2$
Error	$(J-1)(K-1)$	$SSE = SST - SSR - SSC$	$MSE = SSE/(J-1)(K-1)$	σ_ε^2
Total	$JK-1$	$SST = \sum_j\sum_k(Y_{jk} - \overline{Y_{..}})^2$		

In the table above, $\overline{Y_{j.}} = \frac{1}{K}\sum_k Y_{jk}$, $\overline{Y_{.k}} = \frac{1}{J}\sum_j Y_{jk}$, $\overline{Y_{..}} = \overline{D_{WR}^{12}}$ are the marginal and overall mean of difference score. Hence, the sum of squares (SS) and mean squares (MS) can be calculated from the data. From the last column of the ANOVA table, we can find the relationship between the variance components (σ_R^2, σ_C^2, σ_ε^2) and the mean squares. So the unbiased estimation for the variance components are

$$\hat{\sigma}_\varepsilon^2 = MSE$$
$$\hat{\sigma}_R^2 = \frac{MSR - MSE}{K}$$
$$\hat{\sigma}_C^2 = \frac{MSC - MSE}{J}$$

Therefore, the estimation of variance of Y_{jk},

$$\hat{V}_{WR}^{12} = \hat{V}ar[Y_{jk}] = \hat{\sigma}_R^2 + \hat{\sigma}_C^2 + \hat{\sigma}_\varepsilon^2 = \frac{1}{JK}(J * MSR + K * MSC + (JK - J - K) * MSE)$$

Following is an example of using function laWRBM.anova to compute the WRBM limits of agreement for the simulated MRMC data

```
# Simulate MRMC data
config <- sim.new.Hierarchical.config(modalityID = c("testA","testB"))
set.seed(1)
data.sim <- sim.new.Hierarchical(config)

# Using ANOVA to calculate WRBM limits of agreement
laWRBM.anova_result <- laWRBM.anova(data.sim)
print(laWRBM.anova_result)
```

```
##      meanDiff var.MeanDiff var.1obs ci95meanDiff.bot ci95meanDiff.top    la.bot
## 1 -0.04556717   0.02126542 2.257737       -0.3313822        0.2402479 -3.050721
##     la.top
## 1 2.959586
```

The var.1obs in the result is the estimation of variance of WRBM difference, $\hat{V}_{WR}^{12}$.The limits of agreement is given by [la.bot, la.top]. Since both the ANOVA method and U-statistics method provide unbiased estimation to the variance components, the above result is the same as the one calculated by using U-statistics method. laWRBM is a function in iMRMC package that using U-statistics method to construct WRBM limits of agreement.

```
# Compare the result with laWRBR in iMRMC package
print(laWRBM(data.sim,modalitiesToCompare = c("testA","testB")))
```

```
##            meanDiff var.MeanDiff var.1obs ci95meanDiff.bot ci95meanDiff.top
## AminusB -0.04556717   0.02126542 2.257737       -0.3313822        0.2402479
##            la.bot   la.top
## AminusB -3.050721 2.959586
```

3. Using three-way mixed effect ANOVA to calculate V_{WRBM}

To estimate $V_{BR}^{12} = Var[D_{jj'k}^{12}]$, we build up a three-way mixed effect model for the score X_{ijk}

$$X_{ijk} = \mu + m_i + R_j + C_k + RC_{jk} + mR_{ij} + mC_{ik} + \varepsilon_{ijk}$$

where m_i denotes the fixed effect for modality and $\sum_i m_i = 0$,and the other variables are independently normal distributed: $R_j \sim N(0, \sigma_R^2)$, $C_k \sim N(0, \sigma_C^2)$, $RC_{jk} \sim N(0, \sigma_{RC}^2)$, $mR_{ij} \sim N(0, \sigma_{mR}^2)$, $mC_{ik} \sim N(0, \sigma_{mC}^2)$, and $\varepsilon_{ijk} \sim N(0, \sigma_\varepsilon^2)$.

The mixed effect model we applied is the unrestrict mixed model. Compared to the restricted model, the interaction term of the mixed effect and random effect in the unrestricted model will not be correlated at the same random level. This makes the model easier to work with.

Then, the BRBM difference $D_{jj'k}^{12}$ can be expressed as

$$D_{jj'k}^{12} = X_{1jk} - X_{2j'k} = m_1 - m_2 + R_j - R_j' + RC_{jk} - RC_{j'k} + mR_{1j} - mR_{2j'} + mC_{1k} - mC_{2k} + \varepsilon_{1jk} - \varepsilon_{2j'k}$$

The variance of $D_{jj'k}^{12}$ is as following

$$V_{BR}^{12} = Var[D_{jj'k}^{12}] = 2\sigma_R^2 + 2\sigma_{RC}^2 + 2\sigma_{mR}^2 + 2\sigma_{mC}^2 + 2\sigma_\varepsilon^2$$

The three-way mixed effect ANOVA table is given by

Source	DF	Sum of Square (SS)	E(MS)
Modality	$I-1$	$SSM = JK\sum_i(\overline{X_{i..}} - \overline{X_{...}})^2$	$\sigma_\varepsilon^2 + K\sigma_{mR}^2 + J\sigma_{mC}^2 + \frac{JK}{I-1}\sum_i m_i^2$
Reader	$J-1$	$SSR = IK\sum_j(\overline{X_{.j.}} - \overline{X_{...}})^2$	$\sigma_\varepsilon^2 + I\sigma_{RC}^2 + K\sigma_{mR}^2 + IK\sigma_R^2$
Case	$K-1$	$SSC = IJ\sum_k(\overline{X_{..k}} - \overline{X_{...}})^2$	$\sigma_\varepsilon^2 + I\sigma_{RC}^2 + J\sigma_{mC}^2 + IJ\sigma_C^2$
Reader:Case	$(J-1)(K-1)$	$SSRC = I\sum_j\sum_k(\overline{X_{.jk}} - \overline{X_{.j.}} - \overline{X_{..k}} + \overline{X_{...}})^2$	$\sigma_\varepsilon^2 + I\sigma_{RC}^2$
Reader:Modality	$(J-1)(I-1)$	$SSMR = K\sum_i\sum_j(\overline{X_{ij.}} - \overline{X_{i..}} - \overline{X_{.j.}} + \overline{X_{...}})^2$	$\sigma_\varepsilon^2 + K\sigma_{mR}^2$
Case:Modality	$(K-1)(I-1)$	$SSMC = J\sum_i\sum_k(\overline{X_{i.k}} - \overline{X_{i..}} - \overline{X_{..k}} + \overline{X_{...}})^2$	$\sigma_\varepsilon^2 + J\sigma_{mC}^2$
Error	df_E	$SSE = SST - otherSS$	σ_ε^2
Total	$IJK-1$	$SST = \sum_i\sum_j\sum_k(X_{ijk} - \overline{X_{...}})^2$	

where $\overline{X_{i..}}$, $\overline{X_{.j.}}$, $\overline{X_{..k}}$, $\overline{X_{ij.}}$, $\overline{X_{i.k}}$, $\overline{X_{.jk}}$, and $\overline{X_{...}}$ are marginal or overall mean of the score X_{ijk}. The df_E denotes the degree of freedom for the error, $df_E = IJK - IJ - JK - IK + I + J + K - 1$. Similar to the two-way ANOVA table, the last column shows the relationship between the variance components with the mean squares. So the unbiased estimation for the variance components are

$$\hat{\sigma}_\varepsilon^2 = MSE$$
$$\hat{\sigma}_{RC}^2 = \frac{MSRC - MSE}{I}$$
$$\hat{\sigma}_{mC}^2 = \frac{MSMC - MSE}{J}$$
$$\hat{\sigma}_{mR}^2 = \frac{MSMR - MSE}{K}$$
$$\hat{\sigma}_R^2 = \frac{MSR - MSRC - MSMR + MSE}{IK}$$
$$\hat{\sigma}_C^2 = \frac{MSC - MSRC - MSMC + MSE}{IJ}$$

Therefore, the estimation of variance of $Y_{jj'k}$ is

$$\begin{aligned}\hat{V}_{BR}^{12} = \hat{V}ar[D_{jj'k}^{12}] &= 2\hat{\sigma}_R^2 + 2\hat{\sigma}_{RC}^2 + 2\hat{\sigma}_{mR}^2 + 2\hat{\sigma}_{mC}^2 + 2\hat{\sigma}_\varepsilon^2 \\ &= \frac{2}{IJK}(J * MSR + J(K-1) * MSRC + J(I-1) * MSMR \\ &\quad + IK * MSMC + (IJK - IJ - IK - JK + J) * MSE)\end{aligned}$$

Following is an example of using function laBRBM.anova to compute the BRBM limits of agreement for the simulated MRMC data

```
# Using ANOVA to calculate BRBM limits of agreement
laBRBM.anova_result <- laBRBM.anova(data.sim)
print(laBRBM.anova_result)
```

```
##      meanDiff var.MeanDiff var.1obs ci95meanDiff.bot ci95meanDiff.top    la.bot
## 1 -0.04556717   0.02126542 2.468746       -0.3313822        0.2402479 -3.188016
##     la.top
## 1 3.096882
```

We can compare the above result with the result from laBRBM function in iMRMC package. Again, the ANOVA method and the U-statistics method shows the same result.

```
# Compare the result with laWRBR in iMRMC package
print(laBRBM(data.sim,modalitiesToCompare = c("testA","testB")))
```

```
##            meanDiff var.MeanDiff var.1obs ci95meanDiff.bot ci95meanDiff.top
## AminusB -0.04556717   0.02126542 2.468746       -0.3313822        0.2402479
##            la.bot   la.top
## AminusB -3.188016 3.096882
```

4. Relationship between the two-way random effect ANOVA and the three-way mixed effect ANOVA

Since the WRBM difference score, $Y_{jk} = X_{1jk} - X_{2jk}$, is a linear combination of the individual score, the variance of Y_{jk} can also be expressed by the mean squares in the three-way mixed effect ANOVA. First, we put the three-way ANOVA model into the WRBM difference score definition.

$$Y_{jk} = X_{1jk} - X_{2jk} = m_1 - m_2 + mR_{1j} - mR_{2j} + mC_{1k} - mC_{2k} + \varepsilon_{1jk} - \varepsilon_{2jk}$$

Then, the variance of Y_{jk} is as following:

$$V_{WR}^{12} = Var[Y_{jk}] = 2\sigma_{mR}^2 + 2\sigma_{mC}^2 + 2\sigma_\varepsilon^2$$

Therefore, by plug in the unbiased estimation of the variance components, we get the estimation of V_{WRBM}

$$\hat{V}_{WR}^{12} = 2\hat{\sigma}_{mR}^2 + 2\hat{\sigma}_{mC}^2 + 2\hat{\sigma}_\varepsilon^2 = \frac{2}{JK}(J * MSMR + K * MSMC + (JK - J - K) * MSE)$$

By comparing this result with the one from the two-way random effect ANOVA, we notice that there is a linear relationship between the sum of squares in the two ANOVA models. In the following we use subscirpt

$2w$ to denote the MS or SS for the two-way ANOVA.

$$\begin{aligned}
SSR_{2w} &= K\sum_j(\overline{Y_{j.}}-\overline{Y_{..}})^2\\
&= K\sum_j\left(\overline{X_{1j.}}-\overline{X_{2j.}}-\overline{X_{1..}}+\overline{X_{2..}}\right)^2\\
&= K\sum_j[(\overline{X_{1j.}}-\overline{X_{1..}}-\overline{X_{.j.}}+\overline{X_{...}})^2+(\overline{X_{2j.}}-\overline{X_{2..}}-\overline{X_{.j.}}+\overline{X_{...}})^2\\
&\quad -2(\overline{X_{1j.}}-\overline{X_{1..}}-\overline{X_{.j.}}+\overline{X_{...}})(\overline{X_{2j.}}-\overline{X_{2..}}-\overline{X_{.j.}}+\overline{X_{...}})]\\
&= K\sum_j\left[\sum_i(\overline{X_{ij.}}-\overline{X_{i..}}-\overline{X_{.j.}}+\overline{X_{...}})^2+2\cdot\frac{1}{2}\cdot\frac{1}{2}(\overline{Y_{j.}}-\overline{Y_{..}})^2\right]\\
&= SSMR_{3w}+\frac{1}{2}SSR_{2w}
\end{aligned}$$

Thus,

$$SSR_{2w} = 2SSMR_{3w}$$

Similarly,

$$SSC_{2w} = 2SSMC_{3w}$$

$$SST_{2w} = 2\sum_i\sum_j\sum_k(X_{ijk}-\overline{X_{i..}}-\overline{X_{.jk}}+\overline{X_{...}})^2$$

For the total sum of square in the three-way ANOVA,

$$\begin{aligned}
SST_{3w} &= \sum_i\sum_j\sum_k(X_{ijk}-\overline{X_{...}})^2\\
&= \sum_i\sum_j\sum_k\left[(X_{ijk}-\overline{X_{i..}}-\overline{X_{.jk}}+\overline{X_{...}})+(\overline{X_{i..}}-\overline{X_{...}})+(\overline{X_{.jk}}-\overline{X_{...}})\right]^2\\
&= \sum_i\sum_j\sum_k(X_{ijk}-\overline{X_{i..}}-\overline{X_{.jk}}+\overline{X_{...}})^2+SSM_{3w}+I\sum_j\sum_k(\overline{X_{.jk}}-\overline{X_{...}})^2
\end{aligned}$$

The last term on the right hand side of the above fomular can continue to be decomposed as

$$\begin{aligned}
&I\sum_j\sum_k(\overline{X_{.jk}}-\overline{X_{...}})^2\\
&= I\sum_j\sum_k\left[(\overline{X_{.jk}}-\overline{X_{.j.}}-\overline{X_{..k}}+\overline{X_{...}})+(\overline{X_{.j.}}-\overline{X_{...}})+(\overline{X_{..k}}-\overline{X_{...}})\right]^2\\
&= SSRC_{3w}+SSR_{3w}+SSC_{3w}
\end{aligned}$$

Thus,

$$\begin{aligned}
SSE_{2w} &= SST_{2w}-SSR_{2w}-SSC_{2w}\\
&= 2(SST_{3w}-SSM_{3w}-SSR_{3w}-SSC_{3w}-SSRC_{3w})-2SSMR_{3w}-2SSMC_{3w} = 2SSE_{3w}
\end{aligned}$$

Since $I=2$, the degree of freedom for $SSMR_{3w}$ is $(J-)(I-1)=J-1$ and for $SSMC_{3w}$ is $(K-)(I-1)=K-1$. $df_E = IJK-IJ-JK-IK+I+J+K-1 = JK-J-K+1$ is the degree of freedom for SSE_{3w}. We have the same mean square relationship as that for the sum of squares

$$\begin{aligned}
MSR_{2w} &= 2MSMR_{3w}\\
MSC_{2w} &= 2MSMR_{3w}\\
MSE_{2w} &= 2MSE_{3w}
\end{aligned}$$

Therefore,

$$\begin{aligned}
\hat{V}_{WRBM} &= \frac{2}{JK}(J*MSMR_{3w}+K*MSMC_{3w}+(JK-J-K)*MSE_{3w})\\
&= \frac{1}{JK}(J*MSR_{2w}+K*MSC_{2w}+(JK-J-K)*MSE_{2w})
\end{aligned}$$