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1 Multivariate

1.1 Mahalanobis Distance

The Mahalanobis Distance is a descriptive statistic that provides a relative measure of a data point's distance (residual) from a common point. It is a unitless measure introduced by P. C. Mahalanobis in 1936.[1] The Mahalanobis distance is used to identify and gauge similarity of an unknown sample set to a known one. It differs from Euclidean distance in that it takes into account the correlations of the data set and is scale-invariant. In other words, it has a multivariate effect size.

2 Bartko's Ellipse

As a complement to the Bland-Altman plot, *Bartko* proposes the use of a bivariate confidence ellipse, constructed for a predetermined level. *AltmanEllipse* provides the relevant calculations for the ellipse. This ellipse is intended as a visual guidelines for the scatter plot, for detecting outliers and to assess the within- and between-subject variances.

The minor axis relates to the between subject variability, whereas the major axis relates to the error mean square, with the ellipse depicting the size of both relative to each other. Consequently Bartko's ellipse provides a visual aid to determining the relationship between variances. If $\text{var}(a)$ is greater than $\text{var}(d)$, the orientation of the ellipse is horizontal. Conversely if $\text{var}(a)$ is less than $\text{var}(d)$, the orientation of the ellipse is vertical.

The Bland-Altman plot for the Grubbs data, complemented by Bartko's ellipse, is depicted in Figure 1.7. The fourth observation is shown to be outside the bounds of the ellipse, indicating that it is a potential outlier.

The limitations of using bivariate approaches to outlier detection in the Bland-Altman plot can demonstrated using Bartko's ellipse. A covariate is added to the 'F vs C' comparison that has a difference value equal to the inter-method bias, and an average value that markedly deviates from the rest of the average values in the comparison, i.e. 786. Table 1.8 depicts a 95% confidence ellipse for this manipulated data set. By inspection of the confidence interval, a conclusion would be reached that this extra covariate is an outlier, in spite of the fact that this observation is wholly consistent with the conclusion of the Bland-Altman plot.

Importantly, outlier classification must be informed by the logic of the data's formulation. In the Bland-Altman plot, the horizontal displacement of any observation is supported by two independent measurements. Any observation should not be considered an outlier on the basis of a noticeable horizontal displacement from the main cluster, as in the case with the extra covariate. Conversely, the fourth observation, from the original data set, should be considered an outlier, as it has a noticeable vertical displacement from the rest of the observations.

In classifying whether a observation from a univariate data set is an outlier, many formal tests are available, such as the Grubbs test for outliers. In assessing whether a covariate in a Bland-Altman plot is an outlier, this test is useful when applied to the case-wise difference values treated as a univariate data set. The null hypothesis of the Grubbs test procedure is the absence of any outliers in the data set. Conversely, the alternative hypotheses is that there is at least one outlier present.

The test statistic for the Grubbs test (G) is the largest absolute deviation from the sample mean divided by the standard deviation of the differences,

$$G = \max_{i=1,\ldots,n} \frac{\left|d_i - \bar{d}\right|}{S_d}.$$

For the 'F vs C' comparison it is the fourth observation gives rise to the test statistic, $G = 3.64$. The critical value is calculated using Student's t distribution and the sample size,

$$U = \frac{n-1}{\sqrt{n}} \sqrt{\frac{t^2_{\alpha/(2n),n-2}}{n-2+t^2_{\alpha/(2n),n-2}}}.$$

For this test $U = 0.75$. The conclusion of this test is that the fourth observation in the 'F vs C' comparison is an outlier, with $p-$value $= 0.003$, according with the previous result using Bartko's ellipse.

3 Mountain Plot

Krouwer and Monti have proposed a folded empirical cumulative distribution plot, otherwise known as a Mountain plot.

They argue that it is suitable for detecting large, infrequent errors. This is a non-parametric method that can be used as a complement with the Bland Altman plot. Mountain plots are created by computing a percentile for each ranked difference between a new method and a reference method. (Folded plots are so called because of the following transformation is performed for all percentiles above 50: percentile = 100 - percentile.) These percentiles are then plotted against the differences between the two methods.

Krouwer and Monti argue that the mountain plot offers some following advantages. It is easier to find the central 95% of the data, even when the data are not normally distributed. Also, comparison on different distributions can be performed with ease.

A mountain plot (or "folded empirical cumulative distribution plot") is created by computing a percentile for each ranked difference between a new method and a reference method. To get a folded plot, the following transformation is performed for all percentiles above 50: percentile = 100 - percentile. These percentiles are then plotted against the differences between the two methods (Krouwer and Monti, 1995).

The mountain plot is a useful complementary plot to the Bland and Altman plot. In particular, the mountain plot offers the following advantages: It is easier to find the central 95% of the data, even when the data are not Normally distributed. Different distributions can be compared more easily.

The folded cumulative distribution function for a random variable can be easily obtained by folding down the upper half of the cumulative distribution function (CDF). It is a simple graphical method for summarising distributions, and has been used for the evaluation of laboratory assays, clinical trials and quality control (Monti, 1995; Krouwer and Monti, 1995).

A mountain plot (or "folded empirical cumulative distribution plot") is created by computing a percentile for each ranked difference between a new method and a reference method.

To get a folded plot, the following transformation is performed for all percentiles above 50: percentile = 100 – percentile. These percentiles are then plotted against the differences between the two methods (Krouwer & Monti, 1995). The calculations and plots are simple enough to perform in a spreadsheet.

The mountain plot is a useful complementary plot to the Bland & Altman plot. In particular, the mountain plot offers the following advantages:

- It is easier to find the central 95% of the data, even when the data are not Normally distributed.
- Different distributions can be compared more easily.
- Unlike a histogram, the plot shape is not a function of the intervals.

Compared with the Bland-Altman difference plot, the folded CDF stresses more the median and tails of the difference. If the two assays are 'unbiased' 98 with each other (Krouwer and Monti, 1995), the median would be close to zero.

Bland-Altman and mountain plots each provide complementary perspectives on the data, and the authors recommend both plots.

4 The Identity plot

This is a simple regression based approach. It gives the analyst a cursory examination of how well the measurement methods agree. In the case of good agreement, the covariates of the plot accord closely with the $X = Y$ line.

5 Variations of the BA plot

In light of some potential pitfalls associated with the conventional BA plot, a series of alternative formulations for the Bland-Altman plot have been proposed.

6 Survival Agreement Plot (Luiz et al)

This approach is put forward by *Luiz*. It seeks to extend the agreement evaluation through a graphic approach using step functions' capable of expressing the degree of agreement (or disagreement) as a function of several limits of tolerance.

- It expresses agreement or disagreement as a function of several limits of tolerance.
- Y axis represents the proportion of discordant cases.
- X axis represents the observed differences.

7 Eksborg's Plot

Eksborg proposes a plot of the relative values found by the two Methods being compared (Method 1/Method 2) vs the mean of the Method values.

This approach was discussed as an alternative to the BA approach by

8 Bartko's Ellipse

As an enhancement on the Bland Altman Plot, *bartko* has expounded a confidence ellipse for the covariates. *bartko* proposes a bivariate confidence ellipse as a boundary for dispersion. The stated purpose is to 'amplify dispersion', which presumably is for the purposes of outlier detection.The orientation of the the ellipse is key to interpreting the results.

- The Minor Axis is related to the Variance between-subjects
- The Major Axis is related to the Error Mean Square.

The ellipse illustrates the size of both relative to each other. Furthermore, the ellipse provides a visual aid to determining the relationship between the variance of the means $Var(a_i)$ and the variance of the differences $Var(d_i)$.

- If $Var(a_i)$ is greater than $Var(d_i)$, the orientation of the ellipse is horizontal.
- If $Var(a_i)$ is less than $Var(d_i)$, the orientation of the ellipse is vertical.

The more horizontal the ellipse, the greater the ICC.

9 dewitte et al

Bland ALtman recommend the logarithmic y scale others prefer the precent y scale. generally there is not much difference(except when the data extends over several orders of magnitude) percent method is recommends becuase the numbers can be read directly from the plot without the need for back transfromation.

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absolute - small range
percentage - medium range
log scale - large range
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we observe increasing use of the bland altman plot over the years, from 8

9.1 Survival Plots

- Survival–agreement plots have been suggested as a new graphical approach to assess agreement in quantitative variables. We propose that survival analytical techniques can complement this method, providing a new analytical insight for agreement.
- Two survival–agreement plots are used to detect the bias between to measurements of the same variable. The presence of bias is tested with log-rank test, and its magnitude with Cox regression.
- An example on C-reactive protein determinations shows how survival analytical methods would be interpreted in the context of assessing agreement.
- Log-rank test, Cox regression, or other analytical methods could be used to assess agreement in quantitative variables; correct interpretations require good clinical sense