ABSTRACT

Before new clinical measurement methods are implemented in clinical practice, it must be confirmed whether their results are equivalent to those of existing methods. The agreement between these methods is evaluated using the four-quadrant plot, which describes the trend of change in each difference of the two measurement methods’ values in sequential time points, and the plot’s concordance rate, which is calculated using the sum of data points that agree with this trend divided by the number of all accepted data points in the plot. However, the conventional concordance rate does not consider the covariance between the data on individuals, which may affect its proper evaluation. Therefore, we proposed a new concordance rate calculated by each individual subject according to the number of agreement. Moreover, to adjust outliers that may exist in clinical data and interfere with the estimation, we adopted the minimum covariance determinant (MCD) estimator when calculating our proposed approach. A numerical simulation conducted with several factors including the estimation methods indicated that the MCD approach resulted in a more accurate evaluation. We also showed a real data and compared the proposed methods with the conventional approach. Finally, we discussed for the implementation in clinical studies.

Keywords Clinical trial, · Method comparison, · Monte Carlo Simulation, · Trending agreement

1 Introduction

New clinical measurements and new technologies such as cardiac output (CO) monitoring continue to be introduced, and it must be verified whether the results of the new testing measurement methods are equivalent to those of the standard measurement methods before implementing them in clinical practice (Cox et al., 2017; Landis et al., 2011; Monnet et al., 2012; Wang et al., 2020).

Several ways have been proposed to assess the equivalence of the new testing methods with the standard methods (e.g., Carstensen, 2010; Choudhary & Nagaraja, 2017). In Altman & Bland (1983), Bland & Altman (1986) and Bland & Altman (1996), the Bland-Altman analysis have been proposed to evaluate the accuracy of a new clinical test based on its difference from a gold standard technique and the mean of the two test values. In addition, a method for calculating the sample size when conducting the Bland-Altman analysis during clinical trials has been proposed by Shieh (2019). The Bland-Altman analysis has also expanded to cases of repeated measurement (e.g., Bland & Altman, 2007; Bartko, 1976; Zou, 2013), which have been used in clinical study (e.g., Asamoto et al., 2017).

Moreover, as the assessment based on the degree of trending of the CO changes at each time point, the use of the four-quadrant plot and concordance rate has been proposed (Perrino et al., 1994; Perrino et al., 1998). These methods focus on the trending ability between two testing values. In a four-quadrant plot, pairs of each difference of two testing values at sequential time points are plotted, and their evaluation is based on whether the trends regarding each
Concordance rate in a four-quadrant plot is calculated by the ratio of the number of agreements to all data points. In general, one subject is measured multiple times in clinical practice. This conventional concordance rate does not consider individual variations, which can influence the calculation. However, concordance rate for the four-quadrant plot has not been expanded for repeated measurement, unlike in the Bland-Altman analysis.

Thus, this study proposes a new concordance rate for the four-quadrant plot based on normal distribution to take into account the individual subjects. This method can be applied to any number of time points. We also added a hyper parameter to the proposed method which allows analysts to set it from a clinical perspective. This parameter is the minimum concordance number between two measurements, which are regarded as being in “agreement” based on how many times an “agreement” is counted. We show the case of three time points in this study.

In addition, the clinical data sometimes contain outliers. This is not necessarily a problem with the testing equipment itself, but possibly a matter of the accuracy of the new measurement methods, for example, slight equipment-specific or accidental errors, mistakes caused by measuring skills, and deviation from a protocol in clinical trials. These problems cause data variations and improper estimations of the mean and variance, because the proposed concordance rate is based on normal distribution (Huber & Ronchetti, 2011).

Thus, for a more accurate evaluation, we apply the new concordance rate to a robust estimation method called the minimum covariance determinant (MCD) estimator (Rousseuw & Van Driessen, 1999) to adjust the effect of outliers when we estimate the mean vectors and variance covariance matrix. From the simulation results, the effectiveness of the proposed methods with MCD is superior to the conventional concordance rate with a consideration of the individuals.

Accordingly, this study first proposes the new concordance rate for the four-quadrant plot in a general framework and then takes the case of the calculation at three time points as an example. In detail, the remainder of this paper is organized as follows; Section 2 explains the general concordance rate for the four-quadrant plot. In Section 3, we introduce the new proposed concordance rate and present the case wherein the maximum number of agreements is two. Then, Section 4 presents the application of the proposed method to simulations and its result. Section 5 describes the results of the application to a real example. We conclude this paper in Section 6.

## 2 Concordance Rate

This section explains the ways to draw the four-quadrant plot and calculate the concordance rate by using the conventional method. The assessment method for the trending agreement of two testing values using the four-quadrant plot was first proposed by Perrino, et al. (1994). The four-quadrant plot uses each pair of differences between the values measured by the two clinical methods being compared. Point $x_{it}^*$, $y_{it}^*$ (where $i = 1, 2, \cdots, n$; $t = 1, 2, \cdots, (T+1)$) indicates the value of the gold standard for individual subject $i$ at time $t^{*th}$, and $y_{it}^*$ is the value of the experimental technique. Then, the $t$th difference of the values measured by the gold standard is

$$x_{it} = x_{i(t+1)}^* - x_{it}^* \quad (t = 1, 2, \cdots, T),$$

and the $t$th difference of the values measured by the experimental technique is

$$y_{it} = y_{i(t+1)}^* - y_{it}^* \quad (t = 1, 2, \cdots, T).$$

Plot 1 in Fig. 1 shows an example of treatment values in a time sequence that compares two tests for one subject. Focusing on the first two data points in Plot 1, the difference between $[2]$ and $[1]$ can be described as $[4]$ of the four-quadrant plot in Plot 2. At this time, both $x$ and $y$ increase, which indicates that the direction of change in $x$ and $y$ is the same. A point such as $[4]$ plotted in the upper-right of the four-quadrant plot can be evaluated as being in “agreement.” In contrast, the difference between $[3]$ and $[2]$ is plotted as $[5]$ in the lower-right of Plot 2. In this case, $x$ increases but $y$ decreases, which means that the trend of $x$ and $y$ is recognized as being in “disagreement.” Similarly, if the difference in both $x$ and $y$ is negative, as plotted in the lower-left, the change is also in “agreement,” while the data points in the upper-left can be assessed as being in “disagreement.”

Fig. 2 is a four-quadrant plot with artificial example data. In the figure, the red points in the upper-right and lower-left sections are counted as being in “agreement.” The blue dots, on the other hand, signify “disagreement.” If there is no difference between the values of the experimental technique and the gold standard, the data dot is on the 45° lines (dotted lines in Fig. 2).
Figure 1: Plots for the step of drawing the four-quadrant plot. The horizontal axis denotes $x$, and the vertical axis denotes $y$. Plot 1: Data plotted for three pairs of values on Cartesian coordinates. Plot 2: Four-quadrant plot of the data in Plot 1.

Figure 2: Four-quadrant plot with artificial example data.
The concordance rate is calculated based on the idea above. The conventional concordance rate (CCR) is defined as follows:

\[ \text{CCR}(a) = \frac{\#SA - \#AEz(a)}{nT - \#Ez(a)}. \]  

where

\[ \begin{align*}
\text{SA} &= \{(x_{it}, y_{it}) | \left( (x_{it} \geq 0, y_{it} \geq 0) \cup (x_{it} < 0, y_{it} < 0) \right), \hfill \\
& \hfill i = 1, 2, \ldots, n; \ t = 1, 2, \ldots, T \}, \\
\text{AEz}(a) &= \{(x_{it}, y_{it}) | \left( (0 \leq x_{it} \leq a, 0 \leq y_{it} \leq a) \cup (-a < x_{it} < 0, -a < y_{it} < 0) \right) \hfill \\
& \hfill i = 1, 2, \ldots, n; \ t = 1, 2, \ldots, T \}, \quad \text{and} \\
\text{Ez}(a) &= \{(x_{it}, y_{it}) | -a \leq x_{it}, x_{it} \leq a, -a \leq y_{it}, y_{it} \leq a, \ t = 1, 2, \ldots, T \}. \end{align*} \]

SA is the set of “agreement” pairs of each difference between the values of the gold standard and experimental technique. Ez(a) is the set of pairs plotted in the exclusion zone. In the four-quadrant plot, the exclusion zone (middle square in Fig. 2) is usually placed to remove data plots close to the origin of the plot, because it is difficult to determine whether such small values have occurred due to the examination or mechanical errors (e.g., Critchley et al., 2010). The gray points plotted in the exclusion zone in Fig. 2 are excluded when calculating the concordance rate. The range of the exclusion zone depends on a, which is set from a clinical point of view (e.g., Saugel et al., 2015). AEz(a) is the set of the “agreement” pairs in the exclusion zone. \# signifies the cardinality of a set. The concordance rate in Eq. (1) is the ratio between the number of data points in the “agreement” sections except exclusion zone with all data points that fall outside the exclusion zone.

This conventional concordance rate uniformly counts the number of data points that show the same trend of change. However, multiple measurements are generally taken for a single patient in a clinical setting. Individual tendencies may thus influence the measurement results for a single subject. Therefore, individuals must be considered to calculate a more precise concordance rate.

3 Concordance Rate for the Four-quadrant Plot

3.1 General framework of the proposed concordance rate

The proposed concordance rate evaluates the equivalence between the experimental technique and the gold standard through calculation that considers the individual subjects. This proposed method includes the exclusion zone as well, and is defined as the conditional probability, which corresponds to the event falling out of the exclusion zone in all time points. We estimate the parameters of the population with all the data.

The approach of the proposal calculation starts with the four-quadrant plot per point t. First, the quadrant sections are named \( A_t \) to \( D_t \). The sample space where the \( t \)-th value falls in each section can be described in four ways:

\[ \begin{align*}
A_t &= \{ \omega | X_t(\omega) \geq 0, Y_t(\omega) \geq 0 \}, \\
B_t &= \{ \omega | X_t(\omega) < 0, Y_t(\omega) < 0 \}, \\
C_t &= \{ \omega | X_t(\omega) < 0, Y_t(\omega) \geq 0 \}, \quad \text{and} \\
D_t &= \{ \omega | X_t(\omega) \geq 0, Y_t(\omega) < 0 \} \quad (t = 1, 2, \ldots, T). \end{align*} \]

Here, \( X_t \) and \( Y_t \) are random variables of each difference of the values of the gold standard and experimental techniques, respectively. \( X_t \) and \( Y_t \) correspond to \( x_{it} \) and \( y_{it} \), respectively. \( X = (X_1, X_2, \ldots, X_T) \) and \( Y = (Y_1, Y_2, \ldots, Y_T) \) are assumed to be distributed from multivariate normal distributions, and \( X \) and \( Y \) are independent of each other. \( A_t \) in the upper-right and \( B_t \) in the lower-left quadrants of the four-quadrant plot (Fig. 2) correspond with “agreement,” whereas \( C_t \) in the upper-left and \( D_t \) in the lower-right quadrants are in “disagreement.”

Here, the family of sets is defined as follows:

\[ \mathcal{W}_t \equiv \{ A_t \cup B_t, C_t \cup D_t \} \quad (t = 1, 2, \ldots, T). \]

Then, exclusion zone at the \( t \)-th time is

\[ \text{Ez}_t(a) = \{ \omega | -a \leq X_t(\omega) \leq a, -a \leq Y_t(\omega) \leq a \} \quad (t = 1, 2, \ldots, T). \]
Ez(a) is also divided into four-quadrant sections:

\[ \text{Ez}_a = \{ \omega | 0 \leq X_t(\omega) \leq a, 0 \leq Y_t(\omega) \leq a \} \],

\[ \text{Ez}_b = \{ \omega | -a \leq X_t(\omega) \leq 0, -a \leq Y_t(\omega) \leq 0 \} ,

\[ \text{Ez}_c = \{ \omega | -a \leq X_t(\omega) \leq 0, 0 \leq Y_t(\omega) \leq a \} ,

\[ \text{Ez}_d = \{ \omega | 0 \leq X_t(\omega) \leq a, -a \leq Y_t(\omega) \leq 0 \} \quad (t = 1, 2, \ldots, T). \]

The assets of the random variables in \( A_t, B_t, C_t, \) and \( D_t \), except the exclusion zone, are defined as follows:

\[ A^*_t = A_t \cap \text{Ez}_a^c, \]

\[ B^*_t = B_t \cap \text{Ez}_b^c, \]

\[ C^*_t = C_t \cap \text{Ez}_c^c, \]

\[ D^*_t = D_t \cap \text{Ez}_d^c, \]

where \( Z^c \) is the complement of arbitrary set \( Z \). \( A^*_t \) and \( B^*_t \) are the events of “agreement” that do not fall into the exclusion zone, whereas \( C^*_t \) and \( D^*_t \) are the events of “disagreement” out of the exclusion zone.

The proposed concordance rate is calculated in the condition when all pairs of \( (X_t, Y_t) \) are not in the exclusion zone. This means that all data of one subject are excluded from the calculation if any pair of data points for that subject drops to the exclusion zone at least once. This can be described as

\[ \text{NEz}(a) = \{ \omega | \forall t (t = 1, 2, \ldots, T); \omega \notin \text{Ez}_a(a) \}. \]

Here, the two clinical testing methods are regarded as equivalent if \( X_t \) and \( Y_t \) show the same direction of trends more than \( m \) times out of \( T \) times per subject. \( m \) is determined from a clinical perspective. Given this idea, we propose the new concordance rate, wherein the probability of “agreement” of more than \( m \) times in \( T \) is defined as follows:

\[ P \left[ \bigcup_{t=m}^{T} \text{H}_t \right] \cap \text{NEz}(a) \]

\[ = \frac{\sum_{t=m}^{T} P \left[ \text{H}_t \cap \text{NEz}(a) \right]}{1 - P \left[ \bigcup_{s=1}^{T} \text{Ez}_s(a) \right]}, \quad (2) \]

where

\[ \text{H}_t = \{ \omega | (W_1(\omega), W_2(\omega), \ldots, W_T(\omega)) \in \prod_{s=1}^{T} \omega_s, \sum_{s=1}^{T} I(W_s(\omega) = A_s(\omega) \cup B_s(\omega)) = t \}. \quad (3) \]

\( H_t \) in Eq. (2) is the subset of the sample space wherein the trend between \( X \) and \( Y \) agrees \( t \) times. \( I \) is the indicator function in the condition wherein the \( s \)th data fall in \( A^1 \) or \( B^1 \). \( \prod_{s=1}^{T} \omega_s \) in Eq. (3) indicates the product.

### 3.2 Example of the proposal index, \( T = 2 \)

Next, we explain the proposed concordance rate in the case of \( m = 1 \) and \( T = 2 \). The probability can be calculated as follows:

\[ P \left[ \left( \bigcup_{t=1}^{2} \text{H}_t \right) \right] \cap \text{NEz}_2(a) \]

\[ = \frac{\sum_{t=1}^{2} P \left[ \text{H}_t \cap \text{NEz}(a) \right]}{1 - P \left[ \bigcup_{s=1}^{2} \text{Ez}_s(a) \right]}, \quad (4) \]

We apply the definition at \( T = 2 \) to a four-quadrant plot. There are three patterns in the case of \( T = 2 \): agreement in \( t = 1 \), agreement in \( t = 2 \), and agreements in \( t = 1 \) and \( t = 2 \). The probability of the numerator in the definition formula is

\[ P[H_1 \cap \text{NEz}(a)] = P[(A^*_1 \cup B^*_1) \cap (C^*_2 \cup D^*_2)] + P[(C^*_1 \cup D^*_1) \cap (A^*_2 \cup B^*_2)] \quad (5) \]

\[ P[H_2 \cap \text{NEz}(a)] = P[(A^*_1 \cup B^*_1) \cap (A^*_2 \cup B^*_2)]. \quad (6) \]
To describe each case, the range wherein the data point enters into each quadrant of the plot is set as $F = \{[0, \infty]^T, [-\infty, 0]^T\}$, and the range of the exclusion zone is $E = \{[0, a]^T, [-a, 0]^T\}$. Vectors to describe the range for the probability calculations are as follows:

$$v_1 = \begin{bmatrix} v_{11} \\ v_{21} \end{bmatrix}, \quad v_2 = \begin{bmatrix} v_{12} \\ v_{22} \end{bmatrix}, \quad z_1 = \begin{bmatrix} z_{11} \\ z_{21} \end{bmatrix}, \quad z_2 = \begin{bmatrix} z_{12} \\ z_{22} \end{bmatrix}.$$ 

The first term of Eq. (5) means the probability with which the trend of $X_1$ and $Y_1$ is in agreement, whereas that of $X_2$ and $Y_2$ is not. This can also be expressed as

$$P\left( (A_1^1 \cup B_1^1) \cap (C_2^1 \cup D_2^1) \right)$$

$$= \sum_{v_1=v_{11}, \ v_2=v_{21}, \ v_1 \neq v_2} P(v_{11} < X_1 < v_{21}, \ v_{12} < X_2 < v_{22}) P(z_{11} < Y_1 < z_{21}, \ z_{12} < Y_2 < z_{22})$$

$$+ \sum_{v_1=v_{11}, \ v_2=v_{21}, \ v_1 \neq v_2} P(v_{11} < X_1 < v_{21}, \ v_{12} < X_2 < v_{22}) P(z_{11} < Y_1 < z_{21}, \ z_{12} < Y_2 < z_{22})$$

$$- \sum_{v_1=v_{11}, \ v_2=v_{21}, \ v_1 \neq v_2} P(v_{11} < X_1 < v_{21}, \ v_{12} < X_2 < v_{22}) P(z_{11} < Y_1 < z_{21}, \ z_{12} < Y_2 < z_{22})$$

$$- \sum_{v_1=v_{11}, \ v_2=v_{21}, \ v_1 \neq v_2} P(v_{11} < X_1 < v_{21}, \ v_{12} < X_2 < v_{22}) P(z_{11} < Y_1 < z_{21}, \ z_{12} < Y_2 < z_{22}).$$

Then, the second term of Eq. (5) is the probability when the trend of $X_1$ and $Y_1$ is in disagreement, but that of $X_2$ and $Y_2$ is in agreement. This can be rewritten similarly as

$$P\left( (C_1^1 \cup D_1^1) \cap (A_2^1 \cup B_2^1) \right)$$

$$= \sum_{v_1=v_{11}, \ v_2=v_{21}, \ v_1 \neq v_2} P(v_{11} < X_1 < v_{21}, \ v_{12} < X_2 < v_{22}) P(z_{11} < Y_1 < z_{21}, \ z_{12} < Y_2 < z_{22})$$

$$+ \sum_{v_1=v_{11}, \ v_2=v_{21}, \ v_1 \neq v_2} P(v_{11} < X_1 < v_{21}, \ v_{12} < X_2 < v_{22}) P(z_{11} < Y_1 < z_{21}, \ z_{12} < Y_2 < z_{22})$$

$$- \sum_{v_1=v_{11}, \ v_2=v_{21}, \ v_1 \neq v_2} P(v_{11} < X_1 < v_{21}, \ v_{12} < X_2 < v_{22}) P(z_{11} < Y_1 < z_{21}, \ z_{12} < Y_2 < z_{22})$$

$$- \sum_{v_1=v_{11}, \ v_2=v_{21}, \ v_1 \neq v_2} P(v_{11} < X_1 < v_{21}, \ v_{12} < X_2 < v_{22}) P(z_{11} < Y_1 < z_{21}, \ z_{12} < Y_2 < z_{22}).$$

Eq. (6) is the probability that the trends of $X_1$ and $Y_1$ and of $X_2$ and $Y_2$ are both concordant:

$$P\left( (A_1^1 \cup B_1^1) \cap (A_2^1 \cup B_2^1) \right)$$

$$= \sum_{v_1=v_{11}, \ v_2=v_{21}, \ v_1 \neq v_2} P(v_{11} < X_1 < v_{21}, \ v_{12} < X_2 < v_{22}) P(z_{11} < Y_1 < z_{21}, \ z_{12} < Y_2 < z_{22})$$

$$+ \sum_{v_1=v_{11}, \ v_2=v_{21}, \ v_1 \neq v_2} P(v_{11} < X_1 < v_{21}, \ v_{12} < X_2 < v_{22}) P(z_{11} < Y_1 < z_{21}, \ z_{12} < Y_2 < z_{22})$$

$$- \sum_{v_1=v_{11}, \ v_2=v_{21}, \ v_1 \neq v_2} P(v_{11} < X_1 < v_{21}, \ v_{12} < X_2 < v_{22}) P(z_{11} < Y_1 < z_{21}, \ z_{12} < Y_2 < z_{22})$$

$$- \sum_{v_1=v_{11}, \ v_2=v_{21}, \ v_1 \neq v_2} P(v_{11} < X_1 < v_{21}, \ v_{12} < X_2 < v_{22}) P(z_{11} < Y_1 < z_{21}, \ z_{12} < Y_2 < z_{22}).$$
Finally, the probability of the denominator in $T = 2$ is

$$1 - P\left[ \bigcup_{s=1}^{2} E z_s(a) \right]$$

$$= 1 - P(-a < X_1 < a, -\infty < X_2 < \infty)P(-a < Y_1 < a, -a < Y_2 < a) - P(-\infty < X_1 < -a, -a < X_2 < a)P(-\infty < Y_1 < -a, -a < Y_2 < a) + P(-a < X_1 < a, -a < X_2 < a)P(-a < Y_1 < a, -a < Y_2 < a).$$

In the proposed concordance rate, we assume that all random variables are distributed from multivariate normal distribution. Therefore, we must estimate the mean vectors and covariance matrices to calculate the concordance rate. The method of estimating these parameters is described next.

### 3.3 Estimation

Since the proposed method assumes that $X_t$ and $Y_t$ are distributed from $T$-dimensional normal distributions, it is necessary to estimate the $T$-dimensional mean vector and variance covariance matrix to calculate the concordance rate. The estimated mean vector in the proposed approach is $\bar{x} = (\bar{x}_1, \bar{x}_2, \cdots, \bar{x}_T)^T (t = 1, 2, \cdots, T)$, where $\bar{x}_t$ is the mean of the $t$th value. The covariance matrix based on the differences between the times is $S = (s_{tk}) (t, k = 1, 2, \cdots, T)$, where $s_{tk}$ is the covariance between $t$ and $k$. The estimation of the parameters for the other test values, $y_t$, can be described similarly as $\bar{x}_1$.

The proposed approach aims at calculating a more precise concordance rate; however, outliers may affect its estimation results, because this new approach follows normal distribution. To reduce the effect of outliers, a robust method was combined with the proposed method to estimate the mean vector and covariance matrix. For the robust mean vector and covariance matrix estimation, we focused on MCD.

**MCD estimator**

MCD automatically selects $h(n/2 \leq h \leq n)$ data for smaller determinant values to calculate the mean vector and variance-covariance matrix. $H$ is determined based on Rousseeuw & Van Driessen (1999), given that $h$ is pre-specified as follows:

$$H \subset \{1, 2, \cdots, n\} \quad \#(H) = h,$$

such that the determinant of the covariance matrix is smaller. The mean vector for the MCD is

$$\bar{x}^{(MCD)} = (\bar{x}_1^{(MCD)}, \bar{x}_2^{(MCD)}, \cdots, \bar{x}_T^{(MCD)})^T,$$

where

$$\bar{x}_t^{(MCD)} = \frac{1}{h} \sum_{i \in H} x_{it} \quad (t = 1, 2, \cdots, T).$$

The covariance matrix for the MCD is

$$S^{(MCD)} = \begin{bmatrix}
    s_{11}^{(MCD)} & s_{12}^{(MCD)} & \cdots & s_{1T}^{(MCD)} \\
    s_{21}^{(MCD)} & s_{22}^{(MCD)} & \cdots & s_{2T}^{(MCD)} \\
    \vdots & \vdots & \ddots & \vdots \\
    s_{T1}^{(MCD)} & s_{T2}^{(MCD)} & \cdots & s_{TT}^{(MCD)}
\end{bmatrix},$$

where

$$s_{tk}^{(MCD)} = ccf_{ccsf} \frac{1}{h - 1} \sum_{i \in H} (x_{it} - \bar{x}_t^{(MCD)})(x_{ik} - \bar{x}_k^{(MCD)}) \quad (t, k = 1, 2, \cdots, T).$$

$ccf$ and $ccsf$ are called the consistency correction factor and small sample correction factor, respectively. For the choice of $ccf$ and $ccsf$, see Butler et al. (1993), Croux & Haesbroeck (1999), and Pison et al. (2002).
4 Numerical Simulation

In this section, we first describe the simulation design and then present the simulation result. We conducted a simulation of how close the concordance rates calculated with the conventional methods and the proposed approaches are to the result of the true concordance rate. The assessment of each concordance rate was expressed as the difference from the true concordance rate. In this simulation, we used R Studio Version 1.1.453 and the robust package (Todorov & Filzmoser, 2009) to estimate parameters of the proposed methods.

4.1 Simulation design

We set $T = 2$, and the data generation procedure was as follows:

$$
X \sim \mathcal{N}(\mu_X, \Sigma_X) \quad Y \sim \mathcal{N}(\mu_Y, \Sigma_Y),
$$

where $X = (X_1, X_2)^T$ and $Y = (Y_1, Y_2)^T$. $X_t$ is the difference in the measurement values of the gold standard between the $t$th and $(t+1)$th times ($t = 1, 2, 3$), and $Y_t$ is that of experimental technique.

In addition,

$$
\mu_X = \begin{bmatrix} \mu_{X1} \\ \mu_{X2} \end{bmatrix}, \quad \mu_Y = \begin{bmatrix} \mu_{Y1} \\ \mu_{Y2} \end{bmatrix},
$$

$$
\Sigma_X = \begin{bmatrix} \sigma_{X1} & \rho_X \\ \rho_X & \sigma_{X2} \end{bmatrix}, \quad \Sigma_Y = \begin{bmatrix} \sigma_{Y1} & \rho_Y \\ \rho_Y & \sigma_{Y2} \end{bmatrix},
$$

where $\mu_X$ and $\mu_Y$ are the mean vectors of the gold standard and experimental technique, and $\Sigma_X$ and $\Sigma_Y$ are the covariance matrices, respectively. Here, we set $\sigma_{x1} = \sigma_{x2} = \sigma_{y1} = \sigma_{y2} = 1$.

Factors set in the simulation are presented in Table 1. The number of total patterns is $30 \times 3 \times 2 \times 2 \times 2 \times 2 \times 7 = 10080$. For each pattern, corresponding artificial data were generated 100 times and the results were evaluated. The levels of the seven factors were set as follows.

**Factor 1: Type of means**

The mean was of 30 types, as shown in Table 2. The setting depended on the combination of the magnitude of the mean value and the direction of change in $x$ and $y$.

**Factor 2: Covariance of the difference between the two consecutive values**

Covariance of the difference between values that were sequentially measured was set as $0, 1/3$ and $2/3$ in both $X$ and $Y$.

**Factor 3: Number of agreements**

Factor 3 was the number of trending agreements between $X$ and $Y$. We set two different situations: (1) agreement more than once at two time points, and (2) agreement at both time points.

**Factor 4: Outlier**

Two patterns were set: generated data (1) not including the outlier or (2) including the outlier. In (2), we replaced the observation values of 20% of the subjects in $Y_1$ with the outlier:

$$
Y_1^* \sim \mathcal{N}(-10, 0.5^2).
$$

That is, the outlier is given the value of 3 if there are 15 subjects and 8 if there are 40 subjects.

**Factor 5: Exclusion zone**

$a$ of the exclusion zone $Ez(a)$ was set as 0.5 and 1.0.
Table 1: Factors of the simulation design

| Factor No. | Factor name                                | Number of levels |
|------------|--------------------------------------------|------------------|
| Factor 1   | Type of means                              | 30               |
| Factor 2   | Covariance of the difference between the consecutive values | 3               |
| Factor 3   | Number of agreements                       | 2                |
| Factor 4   | Outlier                                    | 2                |
| Factor 5   | Exclusion zone                             | 2                |
| Factor 6   | Number of subjects                         | 2                |
| Factor 7   | Methods                                    | 7                |

**Factor 6: Number of subjects**

The number of subjects was set as 15 and 40.

**Factor 7: Methods**

We calculated the concordance rate by seven methods: control1, control2, the proposed method and its method with four robust approaches. We denoted the proposed concordance rate without robust methods as the “normal” approach to distinguish it from the robust. For robust methods, we applied MCD, weighted, M and PairwiseGK.

Control1, based on binomial distribution, is calculated as follows:

$$\sum_{s=m}^{2} 2C_s p^s (1-p)^{(2-s)},$$

where

$$p = \frac{k_1 + k_2}{n_1 + n_2}.$$

$k_1 (t = 1, 2)$ is the number of data that show the same trend between $X_t$ and $Y_t$ out of the exclusion zone. $n_t^1$ is the number of subjects whose data points fall out of the exclusion zone. The concordance rate in control2 is calculated by the probability at each number of agreement: twice in two time points is $p_1 p_2$, and once in two time points $p_1 (1 - p_2) + (1 - p_1)p_2$.

where

$$p_t = \frac{k_t}{n_t^1} \quad (t = 1, 2).$$

The calculation of the exclusion zone in control1 and control2 is simple. If the data point falls into the exclusion zone once in two time points, the number of agreements for one subject is counted as 1.

Besides MCD, we applied three other robust methods to the proposed concordance rate for its estimation of the mean and covariance matrices. First, we used weighted MCD proposed by Pison et al. (2002), called “weighted,” and it uses the correction factor as the weight for the estimation in case of a small number of subjects. The second method estimates based on the M estimator proposed by Rocke (1996), and it is named “M.” Finally, “PairwiseGK,” proposed by Maronna & Zamar (2002), was based on a robust covariance estimation originally proposed by Gnanadesikan & Kettenring (1972).

The evaluation index for the simulation result included the absolute values of the difference between the concordance rate computed using the true mean vector and true covariance matrix and the concordance rate based on each estimated parameters. We concluded that the estimation methods deserved better assessment if the difference with the true value was smaller in the absolute value among all concordance rate approaches.

**4.2 Simulation results**

In all simulation results except some patterns of Factor1, MCD approach was the closest to the true value. The result of this simulation (Fig. 3) also showed a tendency similar to the results above. We described the simulation results
Table 2: Type of means in Factor 1

| Pattern No. | $\mu_X^1$ | $\mu_X^2$ | $\mu_Y^1$ | $\mu_Y^2$ |
|-------------|----------|----------|----------|----------|
| Pattern1    | -1.5     | -1.5     | 1.5      | 1.5      |
| Pattern2    | -0.5     | -0.5     | 0.5      | 0.5      |
| Pattern3    | -1.5     | 1.5      | 1.5      | 1.5      |
| Pattern4    | 0.5      | -0.5     | 0.5      | 0.5      |
| Pattern5    | 1.5      | 1.5      | 1.5      | 1.5      |
| Pattern6    | 0.5      | 0.5      | 0.5      | 0.5      |
| Pattern7    | -0.5     | -1.5     | 0.5      | 1.5      |
| Pattern8    | 0.5      | -1.5     | 0.5      | 1.5      |
| Pattern9    | -0.5     | 1.5      | -0.5     | 1.5      |
| Pattern10   | 0.5      | 1.5      | -0.5     | 1.5      |
| Pattern11   | -1.5     | -1.5     | -1.5     | -1.5     |
| Pattern12   | -0.5     | -0.5     | -0.5     | -0.5     |
| Pattern13   | -1.5     | 1.5      | -1.5     | -1.5     |
| Pattern14   | 0.5      | -0.5     | -0.5     | -0.5     |
| Pattern15   | 1.5      | 1.5      | -1.5     | -1.5     |

Comparing the results in Fig. 7, there was no significant difference in terms of covariance. MCD resulted more closely to the true values in both $m = 1$ and $m = 2$ than control1 (Fig. 9), which means that MCD evaluates more properly in any number of agreement in the case of T=2. Regarding exclusion zone (Fig. 10) and the number of subjects (Fig. 11), neither of these factors specifically affected the results in almost all methods. As for the outlier, the MCD method was stable even when the data included the outlier (Fig. 9). Table 3 shows the quartile range of the results for the outlier. The quartile range of MCD was narrower than that of the normal approach when the outlier was included in the data. As actual laboratory results sometimes include outliers, it can be said that the MCD method provides a more accurate concordance rate than the normal method.
Figure 4: Result of the simulation for Factor 1: Type of mean, patterns 1-10. c1: control1, c2: control2, N: normal method, mcd: MCD method, W: weighted, M: M, and GK: pairwiseGK.

Figure 5: Result of the simulation for Factor 1: Type of mean, patterns 11-20. c1: control1, c2: control2, N: normal method, mcd: MCD method, W: weighted, M: M, and GK: pairwiseGK.
Figure 6: Result of the simulation for Factor 1: Type of mean, patterns 21-30. c1: control1, c2: control2, N: normal method, mcd: MCD method, W: weighted, M: M, and GK: pairwiseGK.

Figure 7: Result of the simulation for Factor 2: Covariance

Table 3: Quartile range of the result for Factor 4: Outlier

| Factor 4 | c1   | c2   | normal | MCD  | weighted | M    | pairwiseGK |
|----------|------|------|--------|------|----------|------|------------|
| w/o outlier | 0.1758 | 0.1472 | 0.1381 | 0.1404 | 0.1407 | 0.1439 | 0.1406 |
| w/ outlier | 0.1643 | 0.1472 | 0.1415 | 0.1327 | 0.1322 | 0.1401 | 0.1400 |

c1: control1, c2: control2, N: normal method, mcd: MCD method, W: weighted, M: M, and GK: pairwiseGK
5 Real Example

We applied the proposed methods to the oximetry data of package “MethComp” in R software, as proposed by Carstensen et al. (2020). The data comprise the oxygen content of blood for 61 children based on two types of tests: examining blood gas by collecting blood (CO) and percutaneous measurement using a pulse oximeter (pulse). The study was performed at three time points for each subject. Since 57 cases had data of these clinical examinations in all time points, we adopted these data for this practical example. The four-quadrant plots generated from the real data are presented in Fig. 12 here, (1) plots $t = 1$ and (2) plots $t = 2$. We chose the normal approach and MCD, and we compared them with control1 and control2 as described in Section 4. The concordance rate was calculated in the two cases when the trend of change agreed once in two time points and twice all time points. $Ez(a)$ was set as 1.

Table 4: Estimated mean for a real example

|       | $t = 1$ | $t = 2$ |
|-------|---------|---------|
| $X$   | -0.444  | 1.048   |
| $Y$   | 1.250   | 0.518   |
Based on the data, first, the outliers were found in both plots in Fig. 12. These estimated means were all close to the center of the plot; however, the estimated mean of $X$ in $t = 1$ was negative, as shown in Table 4. As for the covariance, it was negative for both $X$ and $Y$, as shown in Table 5, which indicated a different trend between the time points.

Table 6 shows the result of the concordance rate using each method. The concordance rate for the conventional method was 0.449. Compared with this result, the result was higher for the approaches with $m = 1$ and lower for those with $m = 2$. The conventional concordance rate did not consider the number of agreements per individual subject. Moreover, this calculation method does not depend on the number of “agreements.” Among these methods, the control methods underestimated by about 0.05 compared with the normal approach and MCD for both $m = 1$ and $m = 2$. As Table 4 shows, the trend of change between the mean $X$ and $Y$ were opposite in $t = 1$, which means that the trend between $X$ and $Y$ in $t = 1$ is in “disagreement.” In addition, the simulation results clarified that MCD
corrected the outliers and estimated the value. If these outliers are not caused by the equipment of pulse, MCD could adjust the outliers this time as well and enhance the accuracy of its calculation.

6 Discussion

The conventional concordance rate for a four-quadrant plot is one of the methods for evaluating the equivalence between a new testing method and a standard measurement method. In many clinical practice situations, these values are observed repeatedly for the same subjects. However, the conventional concordance rate for the four-quadrant plot does not consider individual subjects when evaluating the trend of measurement values between two clinical testing methods being compared. Therefore, we proposed a new concordance rate based on normal distribution that is calculated using all the differences between the two testing values depending on the number of agreements. The minimum number of agreements to evaluate the equivalence can be set according to the total number of time points in the data and the clinical point of view. As another problem in clinical trials, the data contain outliers since some researchers may make mistakes in the use of the equipment or the patient may be mismatched to the eligibility criteria. Therefore, we combined this method with the MCD estimator to modify the outliers.

In most factors set in the simulation, the proposed concordance rate with MCD was mostly closer to the true value than the conventional method, while the results of the control method were superior to the proposed methods in some situations of the simulation. Concretely, the true values of the control method were concordant once in two time points, and all these absolute mean values were the same at all time points. However, such a situation occurs rarely in actual clinical practice. Therefore, the proposed MCD method is found to be effective. In addition, through the real example using oximetry data, we showed the various results on the trending ability of the proposed methods since we can choose $m$. We also provided only the results of the numerical simulations and a real example for the case of time point $T = 2$ in this study; however, this proposed concordance rate can be calculated as a case of any $T$.

We further discuss the four points of future work of this study. First, for the values of the proposed concordance rate, there are no absolute criteria, similar to the conventional concordance rate. Although various criteria have been proposed, there are no common acceptable criteria for the conventional concordance rate (e.g., Saugel et al., 2015). Therefore, it is difficult to determine the result as good, acceptable, or poor. Second, the results of the proposed concordance rate may also face the problem at time intervals between the measurement values, similar to the conventional concordance rate (e.g., Saugel et al., 2015). Third, we have to determine the parameters of the exclusion zone (e.g.,
Critchley et al., 2011). Finally, in the proposed method, we introduced hyper parameter $m$, which allows us to arrive at a flexible interpretation of the results. While the Bland-Altman analysis was sometimes used in confirmatory clinical trials based on the statistical inference (e.g., Asamoto et al., 2017), the our proposed concordance rate for the four-quadrant plot has not been established yet in this regard. The estimation of the confidence interval will be needed.

In this study, we found that the conventional concordance rate was not so proper indicator in repeated measurements, while the proposed concordance rate could enhance the accuracy by calculating depending on the number of agreement. Moreover, MCD method can adjust the errors that may occur in actual clinical trials. As the proposed concordance rate provides the trending agreement from various perspectives, this new method is expected to contribute to clinical decisions as an exploratory analysis. Further consideration is thus required from these points of view.

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