Calculating the Coefficient of Variation from Duplicate Measurements: A New Method

TO THE EDITOR:

In clinical chemistry, repeatability of analytical methods is sometimes studied by duplicate analyses of patient samples because those specimens are commutable (1). If the analytical standard deviation (SD) varies within a concentration interval, the ordinary Dahlberg method (2) should not be used. In some cases, the coefficient of variation (CV), i.e., SD divided by the mean, may be more constant than SD in a concentration interval (1). Then the relative Dahlberg SD (2) or the method of Bland and Altman (3) could be used to study the imprecision in that interval. However, both these methods are prone to error if there is a bias between the 2 measurements. Here we propose another method, which is straightforward and robust against bias. Accordingly, the 2 measurements of the same specimen do not necessarily have to be done in immediate succession in the same run. Suppose n patient samples are analyzed twice, then:

(a) For each pair (i) of n pairs of measurement results, r_{i1} and r_{i2}, calculate the difference in percentage of the mean (DPM_i): $DPM_i = 100 \times \frac{d_i}{m_i}$ %, where $d_i = r_{i2} - r_{i1}$, and $m_i = \frac{r_{i1}+r_{i2}}{2}$

(b) Calculate the SD of the distribution of all DPM_i (SD_{DPM}):

$$SD_{DPM} = \sqrt{\frac{\sum_{i=1}^{n}(DPM_i - \overline{DPM})^2}{n-1}}$$

(c) Calculate $CV = \frac{SD_{DPM}}{\sqrt{2}}$

Rationale: SD_{DPM} is given as the percentage of the mean, so in fact it is the CV of the distribution of all d_i. However, the value of this CV is due to the imprecision of 2 measurements. To get the corresponding figure for one measurement, one has to divide by $\sqrt{2}$. This procedure is analogous to the "method of moments" variance estimator, which is a bias-robust method for estimating SD when SD rather than CV is supposed to be a constant (4). To see this, one could calculate CV from the method of moments variance estimator formula for SD (4) by dividing by the mean of all m ($\bar{m}$) and multiplying by 100:

$$\begin{aligned} CV &= 100 \times \frac{SD}{\bar{m}}\% \\ &= 100 \times \frac{\sqrt{\frac{\sum_{i=1}^{n}(d_i - \bar{d})^2}{2(n-1)}}}{\bar{m}}\% \\ &= 100 \times \sqrt{\frac{\sum_{i=1}^{n}\left(\frac{d_i}{\bar{m}} - \frac{\bar{d}}{\bar{m}}\right)^2}{2(n-1)}}\% \end{aligned}$$

where $\bar{d}$ is the mean of all d. This is nearly the same as was calculated in steps (a)–(c) previously, which is:

$$CV = 100 \times \sqrt{\frac{\sum_{i=1}^{n}\left(\frac{d_i}{m_i} - \frac{\bar{d}}{\bar{m}}\right)^2}{2(n-1)}}\%$$

because $DPM_i = 100 \times \frac{d_i}{m_i}$, and $\overline{DPM} = 100 \times \frac{\bar{d}}{\bar{m}}$. There is one small difference: If one calculates the CV as $100 \times \frac{SD}{\bar{m}}$, one divides d_i by $\bar{m}$ instead of m_i. Dividing by m_i is more correct.

A bias between the first and second measurement will affect the mean of the DPMs, but should not affect the SD of the DPMs. The limits of the 95% confidence interval (CI) of the CV are equal to the limits of the 95% CI of SD_{DPM} divided by $\sqrt{2}$. The limits of the 95% CI of SD can be derived from the chi-square-distribution (5).

We used data simulation to estimate the accuracy of the CV and its 95% CI as derived from the 3 methods. When calculating the 95% CI of the relative Dahlberg SD, we followed Bland's recommendation and used the t-distribution (3). Each series of paired measurement values was constructed from a uniform distribution of true values from 100 to 200. From each true value, 2 random, Gaussian distributed analytical results were generated with the true value as the mean and with

Table 1. Results from calculating the coefficient of variation (CV) from 20 paired measurements when there is a difference of 2% between the measurements in each pair. The coverage of the 95% confidence interval (CI) of the CV is also given. Three different methods are used: M1 is the relative Dahlberg SD method (2), M2 is the log procedure of Bland and Altman (3), and M3 is our proposed method.

	Estimated CV (%)			Coverage of the 95% CI (%)		
True CV (%)	M1	M2	M3	M1	M2	M3
1	1.7	1.7	1.0	12	10	95
2	2.4	2.4	2.0	91	89	95
3	3.2	3.3	2.9	93	95	95
4	4.2	4.2	3.9	92	95	95
5	5.1	5.2	4.9	91	95	95
6	6.0	6.2	5.9	90	95	95
7	7.0	7.3	6.9	89	95	95
8	8.0	8.3	7.8	89	95	95
9	9.0	9.4	8.8	88	95	95
10	9.9	10.5	9.8	88	95	95

a SD equal to a constant fraction of the mean (the true CV). To simulate bias, we increased the second measurement in each pair by 2% of the true value. For each value of true CV, 100 000 series of 20 paired measurement values were generated. The Stata software (StataCorp, College Station, TX), v.16.1 was used for simulations.

The results are given in Table 1. Compared to the other methods, our proposed method was little affected by proportional bias. For true CVs less than 5%, the calculated CVs were closer to the true values when determined by our method (M3) than by the other methods.

We have observed that the relative Dahlberg SD method (2) and the method of Bland and Altman (3) are not robust against outliers. Neither is our proposed method, so we recommend a graphical inspection of the distribution of the DPMs. The distribution should appear approximately Gaussian, and outlying observations should be excluded. To get reasonably narrow confidence intervals of the CV, the number of pairs of measurement is recommended to be at least 25 (4).

In conclusion, if CV is approximately constant and no outliers are present, our proposed method estimates both the CV and its 95% CI accurately, even in the presence of proportional bias between the 2 measurements.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 4 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; (c) final approval of the published article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.*

Authors' Disclosures or Potential Conflicts of Interest: *No authors declared any potential conflicts of interest.*

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https://doi.org/10.1093/jalm/jfac098