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Letter to the Editor

Benefits of combining bias and imprecision in quality assurance of clinical chemical procedures

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In clinical chemistry, the concept of three types of error is well established: random error (imprecision), systematic error (bias) and gross error. This concept is very useful for characterizing and monitoring the performance of quantitative analytical procedures. The first two types of error must be checked regularly, whereas gross errors should be avoided by organizational precautions.

Two different proposals have been developed to combine imprecision and bias for the maximal allowable deviation in quality assurance. For patient samples, combination models generally require additional components [1]. The total error concept is the sum of the systematic error and the extended standard deviation [2]. Usually, the k-fold coefficient of variation is added to the bias (as a percentage of the "true value"):

$$TE\ (\%) = k\ CV + bias\ (\%). \quad (1)$$

The total error gives the threshold for the deviation between true and measured values that is exceeded with a probability of 5% if $k = 1.64$. Some authors recommend a coverage factor of 1.96 instead of 1.64, corresponding to a probability of 2.5%. The latter factor was rounded to 2.0 in the guideline of the German Medical Association [3].

Recently, Macdonald [4] suggested a two-vector consideration. In Figure 1, the distance RMSD (root mean square of measurement deviation) is proposed as a combined measure for bias (a) and imprecision (b). In the model of Macdonald, $((n-1)/n)b$ and a can be interpreted as the catheti of a right-angled triangle. According to the Pythagoras theorem:

$$RMSD^2 = ((n-1)/n)b^2 + a^2. \quad (2)$$

Macdonald proposed that the ratio $(n-1)/n$ can be neglected for simplification for $n \geq 15$.

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One reason for advocating the RMSD model in comparison with the total error concept of the guideline of the German Medical Association is that bias and imprecision should be allowed to compensate each other [4]. However, the same effect can be obtained if $k = 1.0$ in Eq. (1).

The difference between the two concepts is illustrated in Table 1 for four practical combinations of bias and imprecision that are allowable according to the guideline of the German Medical Association [3]. For all coverage factors, the allowable limits are similar. Under these conditions, the RMSD concept does not provide any advantage in comparison to the TE approach. If the coverage factor suggested by Macdonald is used ($k = 3.0$), the allowable error range is greater than for the concept in the current guideline [3], leading to lower control efficiency.

In a practical example (Figure 2), both combination models are equally suited due to a low CV of 1.2% and low bias of 1% (example a). If a systematic error of 6% is added (example b), the allowable RMSD (7.8%, combination 2 in Table 1) is exceeded twice (runs 3 and 12), although the bias is still within the allowable limit (6%). If bias and imprecision are increased to 6% and 4.96%, respectively (example c), the allowable RMSD is exceeded six times during the control period, although the empirical imprecision and bias are within the allowable limits according to the current guideline [3].

The concept proposed by Macdonald would lead to considerable tightening of the current control rules. If this is required, a similar effect could be obtained with the TE model, e.g., by reducing the coverage factor to $k = 1.0$, so that introduction of a new quantity such as the RMSD is not necessary.

The true value is not known to the laboratory in most cases. If it is substituted by the value assigned by the manufacturer (conventional true value assigned to control samples), it is known that these values are themselves biased, even if well-standardized procedures (e.g., IFCC procedures) are applied [5]. Furthermore, manufacturers sometimes must correct assigned values after they have been published, causing considerable problems for laboratories and their customers. Therefore, both errors should be controlled separately.

The combination of imprecision and bias into a single parameter appears to simplify daily quality assurance. However, no practical benefit of such a combination in daily quality assurance has been demonstrated in comparison with the well-established separate checks for

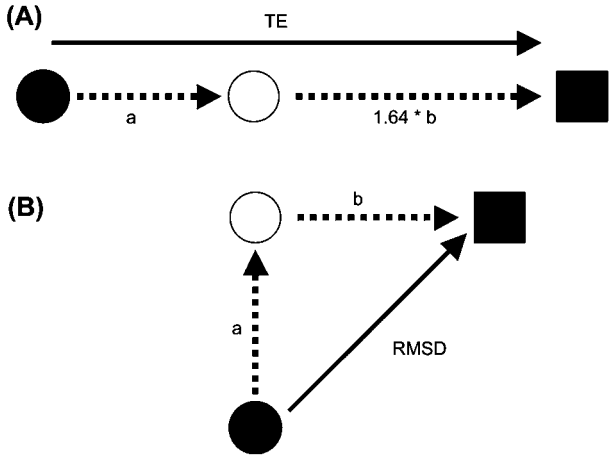

Figure 1 Concepts combining maximal allowable bias (a) and maximal allowable imprecision (b).
(A) TE is the total error and (B) RMSD is the root mean square deviation of the measurement. Filled circles represent the "true" value (or assigned value as a conventional true value), open circles represent the mean of a series of measured values, and rectangles represent the allowable limit for single measured values.

Table 1 Comparison of combined errors for various combinations of imprecision (CV%) and bias (as a percentage of the target value) taken from Table 1 of ref. [4].

Combination	1 (Hb)	2 (glucose)	3 (LDH)	4 (Fetoprotein)
Bias	2	6	8	14
CV, %	2	5	5	10
Total error[1)]				
k=1	4.0	11.0	13.0	24.0
k=2	6.0	16.0	18.0	34.0
k=3	8.0	21.0	23.0	44.0
RMSD[2)]				
k=1	2.8	7.8	9.4	17.2
k=2	5.7	15.6	18.9	34.4
k=3	8.5	23.4	28.3	51.6

k is the coverage factor. [1)]Equation (1). [2)]RMSD × coverage factor.

both errors. Laboratorians are used to thinking in terms of imprecision and bias separately. It has been postulated that clinicians may favor combination models. Many clinicians are well aware that laboratory results vary, but they assume that bias can be neglected. They are not used to combining both errors in any model. Therefore, combination models are probably also of no benefit to clinicians.

Clinicians and laboratorians would profit from situations in which bias can be neglected (e.g., $\leq$1%). Then Eq. (1) can be reduced to:

$$TE = k\ CV. \quad (3)$$

Another method involves the application of intra-laboratory decision limits. In this way, possible bias is included in the decision limit and does not need regular quality assurance checks over short periods of time. It may be sufficient if the laboratory participates in regular external quality schemes.

Intra-laboratory decision limits may be difficult to achieve. However, laboratories with high throughput rates can derive their own decision limits, as demonstrated by various groups [6]. Therefore, it is proposed that for procedures with negligible bias or where intra-laboratory decision limits can be easily derived, only imprecision must be checked regularly (i.e., in each run) and a combination of errors is not necessary.

The last concept has three advantages: 1) it simplifies internal quality assurance; 2) it is consistent with the present theory of three types of error; and 3) it follows the current view of most physicians, who only think in terms of imprecision of laboratory results.

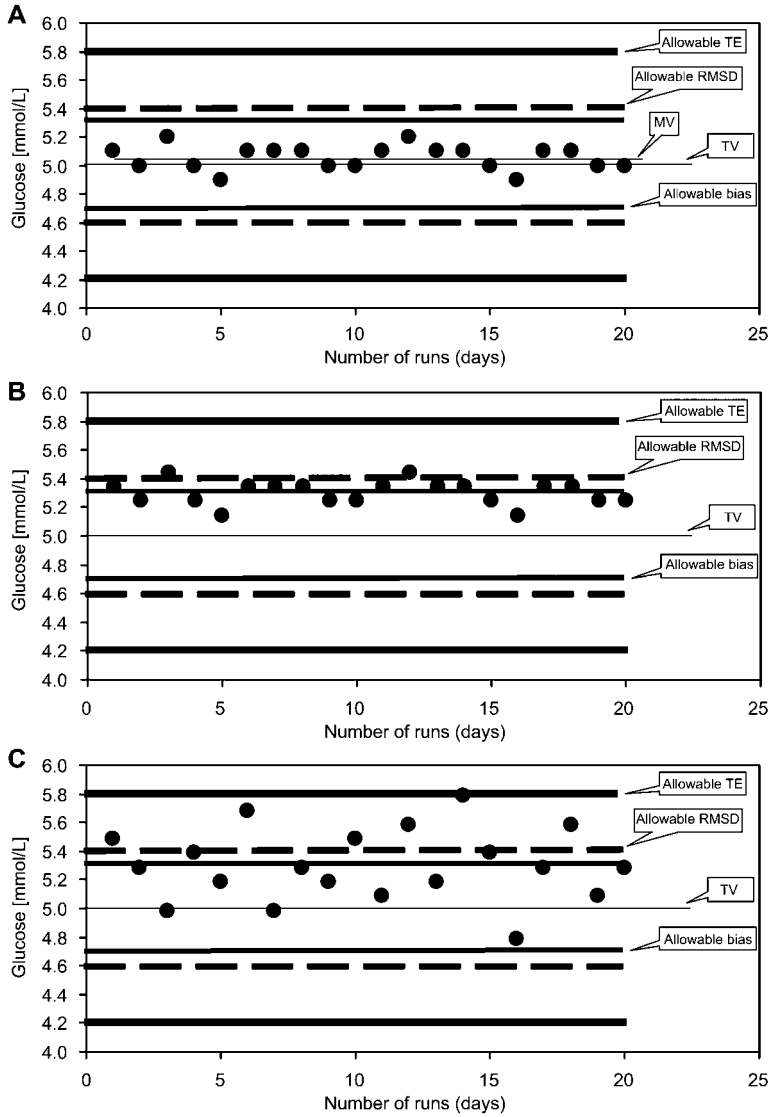

Figure 2 Control chart for the determination of glucose (mmol/L) at 20 days (taken from ref. [7]).
Bold lines represent the allowable limits (total error 16%, bias 6%, CV 5%) according to the current guideline [3] and dashed lines according to the allowable RMSD (7.8%).

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