The Evaluation of Accuracy of Measurement Results in Medical Analytical Laboratory

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Abstract. *Problem of the reliability estimation of measurement methods used to medical diagnostic laboratory, given the example of blood morphology, was presented in the present paper. Measurement method was presented and statistical methods used to evaluation of measurement results were discussed.*

Keywords: Accuracy of Measurement Results, Standard Deviation, Blood Cells Counting

1. Introduction

The result of every measurement is errored, i.e. it contains an error the value of which depends on the accuracy of the applied measurement method. According to [1], the measurement error is a difference of the measurement result and the true value of a measurand. The basic problem in the estimation of measurement error is the fact that we never know the exact true value of a measurand. When we carry out a series of measurements, it is necessary to carry out also a statistical analysis of results obtained with the use of appropriate mathematical procedures. When carrying out a research or test, we should be certain that the applied measuring instrument gives reliable results. The instrument may be checked using a standard, or it may be calibrated by a series of quantities with known yet different values. In terms of medical diagnostic laboratory, a series of control determinations is done every day, and their aim is to check a series of parameters, among them first of all the reproducibility of the results of measuring the same quantity in time. Reproducibility should be understood as the degree of accordance of the results of measuring the same measurand in different measuring conditions. For intra- and interlaboratory control, additional samples with precise value of the examined parameter are used in repeated series of routine determinations. Correct, regular results of this measuring process are significant part of the procedure of laboratory accreditation. This publication is an attempt to take a penetrating look – from the metrological point of view – inside the applied methods and criteria of evaluating the analytical phase accuracy in medical analytical laboratory.

2. The Methods of classifications and counting of blood cells

Measuring equipment used in medical diagnostic lab for blood tests should make it possible to select blood cells and count their number in a unit of 1 mm^3 volume. Blood cells can be divided into three types: erythrocytes, leukocytes and thrombocytes. Regardless of the method applied for measuring, a blood sample is usually diluted in physiological saline, and then a precisely measured volume of the so prepared blood sample is transmitted through a tube with a very small diameter, ca 100 μm; thanks to that, cells in the stream of the diluted sample are arranged one after another (hydrodynamic focusing). The stream of blood sample passes then through the measuring region, in which a detection system detects successively passing blood cells, and transmits information to a data processing and acquisition system. Blood dilution is an indispensable technical operation because, otherwise, more than one cell could pass through the measuring region simultaneously, which causes counting errors.

There are mainly four methods for counting and classification of blood cells. The hemacytometer method - a manual counting method, the photoelectric nephelometric method, can be used only to count normal red blood cells. The other two available methods for blood cell counting and classification use either a Coulter counter or a flow cytometer [2]. They measure single cell flowing through the measuring region based on the electrical impedance, the so-called Coulter principle, or the laser scattering principle respectively.

The resistance method (Coulter's method) is developed to count the blood cells and classify their sizes. It is based on measuring variations in the resistance generated by non-conducting particles, diluted in electrolyte. Fig. 1 shows a simplified diagram illustrating the principle of measuring the number of blood cells with the use of the resistance method. A diluted blood sample moves from a bigger vessel through an aperture with ca 100 μm diameter to a tube in which a hypotension pump is installed, which results in the effect of sucking in the solution from the vessel. There is one electrode in the vessel with the diluted blood sample, whereas the other one is located inside the tube. There is a current generator added to the electrodes, which makes the current pass through the solution. At the moment when a blood cell appears in the aperture region, conductance rapidly decreases and, as a result, a voltage pulse is generated between the electrodes. A detection system with properly set value of actuation threshold allows different types of blood particles to be discriminated. The optic method uses the property that a blood cell placed in liquid medium has a different light absorption coefficient than the solution in which it is placed. Blood cells move in the tube with a very small diameter and pass through the measuring region illuminated by a light source and observed by a photodetector. At the moment when a blood cell crosses the light beam, a voltage pulse is generated at the output of the photodetector [3]. There are a few reasons causing measuring errors during the classification and counting of cells; the most important of them are the following: contamination, incorrect dilution of samples, reduction of the aperture diameter, caused by contamination deposition, incorrect detection threshold. It should be emphasised that even with complete idealization of the measuring apparatus, the analysed biomaterial – because of its heterogeneity – causes a scatter of measuring results, therefore, statistical analysis of the measuring results is a condition sine qua non.

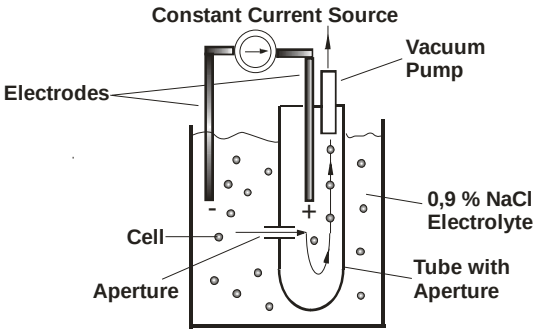

Fig. 1. A scheme illustrating the principle of blood cells measurement using the resistance method

3. Reliability of measurements in medical analytical laboratory

Measurement results obtained in diagnostic lab require an interpretation that makes it possible to determine if the inspected method is accurate and the result reliable. In the classical measuring theory two basic parameters are used (their role is to estimate the distribution quality): an expected value, the estimator of which is most often the mean value of population, being the concentration measure of a random variable, as well as the standard deviation, being the scatter measure. In diagnostic labs, due to a specific character of the examined biomaterial, and also due to a specific character of technical solutions in measuring apparatus, we use any method for estimating the measurement reliability in a modified form – as compared to standard recommendations. In order to determine the quality of a given

measurement method, we use the knowledge of the values of three parameters: arbitrarily matched total allowable measuring error, inaccuracy and bias.

Total error allowable – TE_A – is an acceptable difference between the obtained result and the true value of a measurand. This is an idea applied in medical diagnostic labs to determine the requirements that should be met by the used measuring method, so that it could be regarded as reliable [4]. The value of TE_A makes it possible to determine such a confidence interval in which with assumed probability the obtained measuring results are located. The determination of concrete values of this parameter for particular measurands allows us to decide if a given method, with its inaccuracy and bias, is, nevertheless, a reliable method. Because of random errors that accompany every measurement, the results obtained during repeated measuring of the same sample vary. The degree of accordance among independent measurement results in the literature concerning quality analysis in medical diagnostic laboratory, e.g. in [4], is called precision. The quantity coefficient of inaccuracy is the value of standard deviation, or coefficient of variation defined as a ratio of standard deviation and percentage mean value. The correctness of measurements, as a quality factor, is described by means of a number which is the difference between the mean value and assumed reference value. According to the ISO 3534-1 document, quantity information about correctness, presented in the form of that difference, is defined as bias [4]. In practice, as the reference value we most often assume the mean value of a sample of a specified population of measurement results, and determined e.g. in the model sample of control material designed for inter-laboratory control.

One of the most widespread methods of statistical quality control in medical diagnostic lab is the method applying a control chart, on which particular measurement results are plotted; it is known as the Levey-Jennings chart. This method applies control material as a sample which is analysed in order to carry out quality control. The most relevant question is the interpretation of obtained measurement results by the determination of such limits for the allowable error that cannot be exceeded if the method should not be regarded as out-of-control. In this respect, estimations vary in answering the question if the investigated method is within allowable limits or not. We can distinguish here simple rules and complex rules. The most simple way to estimate control results is the method based on a simple interpretative rule, e.g. rules $1_{2.5S}$, where S means standard deviation. In this rule we assume that the method remains out-of-control in the situation when at least one control result obtained in a measurement exceeds the limits ± 2.5S. In the respective literature we can also find rules 1_{2S}, 1_{3S}, $1_{3.5S}$, that differ from one another in the width of an interval in which the measurement results should be contained. The interpretation of the results of control measurement using complex rules consists in applying a few rules simultaneously, which makes it possible to improve the effectiveness of estimating the control results. One of the most well-known and widespread ones is rule $1_{3S}/2_{2S}/R_{4S}/4_{1S}/10_X$, which has taken its name – Westgard rules – from the name of its main author. The algorithm of this method is shown in Fig. 2. In order to evaluate the reliability of measurements, some experiments were carried out with the use of the Levey-Jennings control chart. According to recommendations, the research was conducted for 20 days, with Sysmex XS-1000i analyser, using thrombocythes as the analyte. Examples of research results are presented in the form of control chart in Fig. 3. The mean value as well as the limits of allowable variation interval determined according to rule12.5S was marked in the figure. As it can be noticed, one of the measurements exceeds the limits of the assumed variation range, which allows us to formulate the conclusion that the measurement method applied is out-of-control. Applying for the same series of results the complex Westgard rule, we should conclude that this measurement method is correct. A variety of possible methods of interpreting measurement results evokes a fundamental question: Which option will be the most suitable? Which rule should we choose, a simple or a complex one? In the authors'

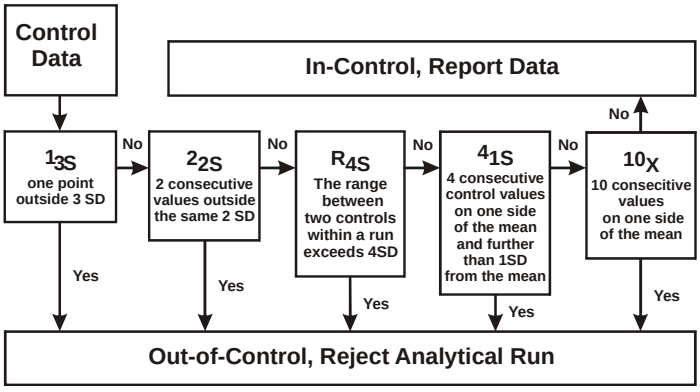

Fig. 2. The modern Westgard Rules $1_{3S}/2_{2S}/R_{4S}/4_{1S}/10_X$

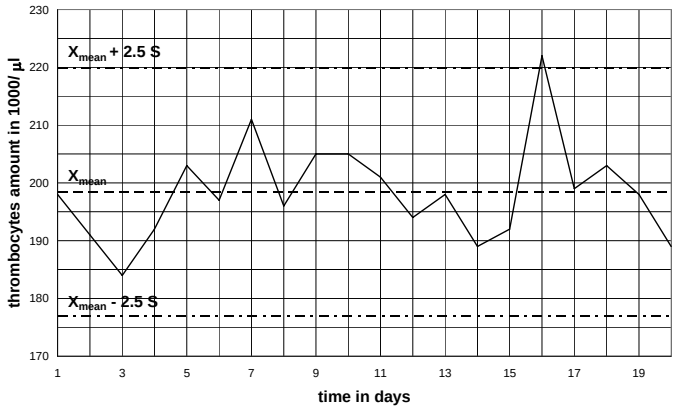

Fig. 3. Levey – Jennings control charts with an example of thrombocytes analysis

opinion, there is no unequivocal answer to such question. An extremely significant part in this situation is played by an experienced person who supervises the research and interprets the obtained measurement results.

4. Conclusions

The paper presents selected problems of the evaluation of the reliability of measurement methods applied in diagnostic laboratories. The authors discussed the applied measurement methods developed to measure blood cells as well as main sources of measuring errors in these methods. They also pointed to the specific approach to evaluating the accuracy of any measurement method applied in such laboratory, as compared with the classical approach and mathematical formal solutions, known from the measurement theory. The present paper indicates only a modest fragment of a whole area of problems relating to the statistical estimation of the results of measuring difficult objects, such as biological objects. One of the purposes of this work is to bring attention to the fact that measuring practice in diagnostic laboratory develops for its own needs specific principles of the estimation of measurement results. These principles on the one hand prove to be quite suitable in practice, and on the other hand they not necessarily correspond precisely with standards recommended in metrology.

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