Software solution to quality assessment in medical analytical laboratories

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Abstract

Quality control and quality assessment in medical analytical laboratory ensures that the various analytical measurements performed have a high degree of accuracy, precision and reproducibility. The most used tools in quality assessment are the Levey-Jennings charts along with Westgard rules. In this paper is presented a software solution that implements the most common Westgard rules and ensures the autoimmunization of routine quality assessment. The basic quality control notions along with corresponding statistical fundaments for the Westgard rules are also presented.

1. Introduction

Quality control is a procedure or set of procedures intended to ensure that a manufactured product or performed service adheres to a defined set of quality criteria or meets the requirements of the client or customer.

Quality assurance is defined as a procedure or set of procedures intended to ensure that a product or service under development (before work is complete, as opposed to afterwards) meets specified requirements. Quality assurance is sometimes expressed together with quality control as a single expression, quality assurance and control (QC) [1].

In medical laboratory these terms are applied to various measurements performed on human fluids. There are a varied range of substances measured, using various methods. Most of the procedures determine the concentration of a solution by measuring the quantity of absorbed light at certain wavelength. Others, measure other properties. However, at some point, every method implies an electric measurement. This measurement is affected by Gaussian noise. In addition to this noise, there are other noises, like thermal noise, impurities in the substances, wrong dilutions of the reactants, etc. Some of these sources of noise can alter the results in a clinically significant amount. Quality control tries to maintain a low level of noise into the analysis process. Ideally it will detect any noise that has other source than implicit Gaussian noise.

In order to perform a quality control, physicians follow a specific procedure: A special designed serum named control serum with known concentration is analyzed using regular procedures (i.e. as if it comes from a patient). Its values are recorded on a special chart, the Levey-Jennings chart. The measured value for the control serum is called the control value.

Using basic statistical tools these values are analyzed. When the recorded values are not in specific bounds, or they violate certain rules, the physician declare the current state of QC as "out-of-control", meaning that the analysis returned by the device are not reliable and actions must be taken in order to correct this problem. After the problem is corrected all the analysis performed on the patients since the last validated control are performed again.

Sometimes it is recommended that several control serums are used for a certain substances (i.e. one control serum is set at a clinically normal concentration and another serum at a clinically abnormal concentration). If for a substance we use two or more control substances of different concentration, we collect a control value for each concentration.

The operation of determining the control values is named a run, or performing a control run.

Some analysis require a very high degree of accuracy and precision because the measured quantities are in range of 10^{-6} g/ml. (i.e. hormone levels or various cancerous markers) A tight quality control is required to maintain accurate and precise results [2].

For each substance that the laboratory can measure a different quality control protocol must be established.

Manual handling of quality control data is cumbersome and error prone. There are several commercial software available, but they lack the flexibility of defining complex quality control rules. In this paper is presented a software system that enables a

high degree of flexibility in defining the control rules and in defining the quality control protocol.

We also give comprehensive statistical notions on which the Westgard rules are based.

The paper is organized as following: in Chapter 2 are presented the most used Westgard rules along with their statistical foundations, in Chapter 3 is presented the proposed software solution and in Chapter 4 conclusions to this paper are drawn.

2. Westgard Rules

Each measurement is subjective to a Gaussian noise. For a series of measurements of the same physical quantity we obtain values that are distributed according to a Gaussian law. A Gaussian distribution is governed by two parameters, the mean and the standard deviation. In Equation 1 is shown the Gaussian distribution law. For an observation, this function gives the probability of measuring a certain value.

$$p(x) = \varphi_{\mu,\sigma^2}(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{(x-\mu)^2}{2\sigma^2}}, \quad (1)$$

where μ is the mean of the distribution and σ is the standard deviation.

Let x_i be a series of N observations that follows a normal distribution. Then,

$$\mu = \frac{1}{N}\sum_{i=1}^{N} x_i, \quad (2)$$

$$\sigma = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(x_i-\mu)^2}. \quad (3)$$

Another important quantity that needs to be defined is the probability of obtaining a measurement less or equal to a certain value, the cumulative distribution function for the normal distribution, *cdf*:

$$p(X \le x) = \Phi_{\mu\sigma^2}(x) = \int_{-\infty}^{x} \varphi_{\mu,\sigma^2}(u)du. \quad (4)$$

The integral in the right part of the Equation 4 doesn't have an analytical solution. The *cdf* is expressed in terms of the error function *erf*:

$$\Phi_{\mu\sigma^2}(x) = \frac{1}{2}\left[1 + erf\left(\frac{x-\mu}{\sigma\sqrt{2}}\right)\right]. \quad (5)$$

By performing consecutive measurements to a process that is affected only by a stable Gaussian noise one should expect that all the measurements follow a normal distribution. The distance of an observation from the mean is expressed in multiple of standard deviations. Let o be the value of an observation. The distance form μ to o is:

$$d_{SD} = \frac{o-\mu}{\sigma}. \quad (6)$$

From Equation 5 one can compute the probability of an observation at certain distance from the mean. Because the observed value can be lower or higher than the mean, one have to count both tails of the Gaussian distribution. In Equation 7 is shown the probability of finding a value at certain distance from the mean, distance expressed in standard distributions.

$$p(X > x) = 2\left(1 - \Phi(d_{SD})\right), \quad (7)$$

where $\Phi(x) = \Phi_{0,1}(x)$.

Westgard rules are based on the assumption that an unperturbed measurement process will follow a normal distribution. For each measurement there are defined a series of rules that will accept the measurement as being unbiased or will reject it because the measurement process is altered. We can define two probabilities. The probability of false rejection p_{fr} is the probability of rejecting a measurement when there are no errors except the inherited Gaussian noise. The probability of error detection p_{ed} is the probability of rejecting a measurement that is affected by other errors except the Gaussian noise [3].

For an analytical laboratory, the observation is the measurement of the same control substance. The repeated controls must follow a Gaussian distribution. If the resulted data do not follow normal distribution it is a sign that there are some errors in the measurement process. These errors can be random or systematic [4].

Quality assessment is based on the theoretical foundations described above. Historically, the basic tool for quality assessment is the Levey-Jennings chart. This chart is built by graphically representation of several serum determinations. Usually this chart is drawn on paper. In Figure 1 is shown such a chart. On the X axis is represented the number of control values, each control value has marked the date and time of measurement (6). On Y axis is represented the value of the measurement. The difference of a simple Cartesian graph is that the origin is marked with the mean value of the control serum, and the measurement units are in standard deviations from the mean. Usually markers are

drawn on Y axis at ±2 standard deviations and ±3 standard deviations (2,4). Each control value is represented by a dot (3). These dots are connected and form a curve (5). The Levey-Jennings chart contains also the name of the substance for which the chart is built (1).

There are five common Westgard [3] rules: 1_{3s} rule, 1_{2s} rule, 2_{2s} rule, R_{4s} rule and 10_x rule. Usually the rules take into consideration the current measurement and n previous values, where $n \geq 0$. There are cases when a rule considers two or more values measured in the same run, but at different concentrations. In the first case the rule is applied horizontally and in the second case the rule is applied vertically. Each rule will be described in the following.

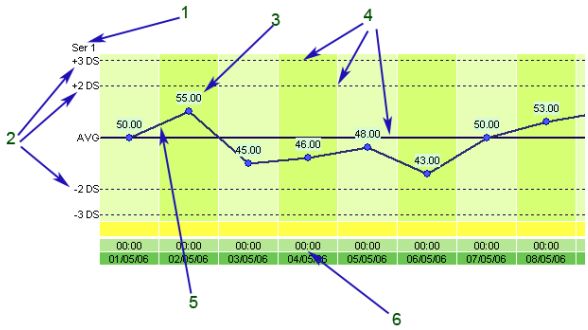

Figure 1. Levey-Jennings chart Elements are described in text.

1_{3s} rule. This rule is broken when one control value is beyond ± 3 standard deviations from the mean.

1_{2s} rule Usually this rule is a warning rule. It is out of control when one measurement is beyond ±2 standard deviations from the mean. Roughly each measurement has a chance of 5% to be farther than 2 standard deviations from the mean. Because of this, 1_{2s} rule has a high false rejection rate. It is usually used in non computerized environments where complex rules cannot be implemented.

2_{2s} rule. This rule is similar to 1_{2s} rule but it requires 2 consecutive measurements to be on the same side of the mean, and a distance greater than 2 standard deviations from the mean. This rule is sensitive to systematic errors in the measurement process. There is a special case of 2_{2s} when we have two or more control levels. The rule is considered out of control if at the same run there are two values beyond 2 standard deviations. Proposed software solution can handle both simple 2_{2s} rule and vertical 2_{2s} rules.

R_{4s} rule. This rule is highly sensitive to errors that affect the precision. This rule is out of control when there is a difference of 4 standard deviations between pervious control value and current control value.

10_x rule. This rule is sensitive to systematic errors. It is out of control when 10 consecutive control values are on the same side of the mean. One should note that each measurement is validated using the mean and standard deviation of the data.

Each rule has its won false rejection and error detection probabilities. As we described above, the errors can be systematic (they affect the mean of the observed distribution) or random (they affect the dispersion of the distribution). We will have two error detection probabilities, one for systematic errors and one for random errors.

Let n be the number of controls that the current rule takes into account and k the standard deviation. For 1_{3S} rule $n=1$ and $k=3$. Let ε_{syst} denote the mean shift (expressed in standard deviations) for a systematic error. For a random error, e_{ran} denote the ratio between current SD and expected SD.

Using Equations 8, 9, 10 one can compute the p_{ed} and p_{fr} for each rule in the implemented quality control routine.

$$p_{fr} = 2(1-\Phi(k))^n, \tag{8}$$

$$p_{ed}^{syst} = (1-\Phi(k-\varepsilon_{syst}))^n, \tag{9}$$

$$p_{ed}^{rand} = \left(1-\Phi\left(\frac{k}{\varepsilon_{ran}}\right)\right)^n. \tag{10}$$

The parameters of the expected distribution are computed using Equations 2 and 3 on the previously "in-control" measurements.

What happens when there is not enough data to obtain a reliable mean and standard deviation? The answer is that each laboratory should perform about 40 determinations for each control serum. Based on these determinations the mean and a standard deviation are computed.

The values that are beyond ±3DS are removed and the whole procedure is repeated until the resulted series doesn't contain values beyond ±3DS.

Resulted mean and standard deviation are used as parameters for expected distribution.

The producer of each control serum marks a mean value and a working interval on each control substance. These numbers should be used as a guideline because they are obtained by taking into consideration the measurements performed at several laboratories.

As a result, usually the producer's standard deviation is considerably higher than the one computed in the laboratory [5].

Another good practice is to compute the mean and standard deviation on all in-control measurements performed in last few months.

3. Proposed software solution

We propose a software system that helps the physician to perform the quality assessment of the analytical measurements. The software performs the following functions: stores and retrieves the quality control measurements, automatically applies the selected control rules to the input data, alerts the physician about out-of-control rules, builds the Levey-Jennings charts according to required specifications and determines the laboratory specific statistical parameters for each control serum.

The software allows the physician to input data about the name of the analyt, the clinical significance levels and the measuring unit, etc. After this step, the GUI displays several important elements like: information about current control, the state of the current control, etc.

The next step is to establish the Westgard rules that will be applied to this analyt. The rules are applied to all control levels. All the rules presented in Chapter 2 are readily available.

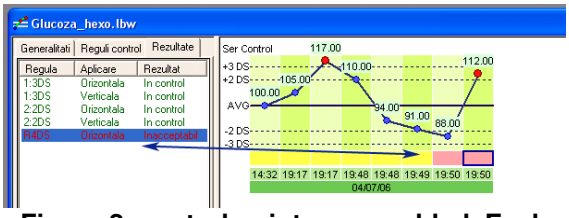

Figure 2. control points were added. Each control is represented by a blue dot. If there are rules out of control, the color of the dot is changed in red. Selecting a rule and a run one can see the control data that rule took into account when taking "out-of-control" decision.

After the rules were selected the physician can start adding the control values for the current run. Each control value represents the result of performing an analysis on the control serum. As the new values are added the software starts building the Levey-Jennings map. In Figure 2 is presented the GUI showing few control runs. The last run has a "out-of-control" status because of a broken R_{4DS} rule.

The physician can construct other rules, by altering the standard deviation threshold, by altering the applicability of a rule (horizontal or vertical), the number of runs that will be considered and the type of rule (warning rule or rejection rule).

The software allows the physician to add rules having almost any combination of controls and standard deviations. The number of controls is limited to a non zero natural number. The standard deviation threshold can be any positive number.

Using Equations 8-10 a physician can build a rule or a set of rules knowing exactly the theoretical operation parameters of each rule in the quality control protocol.

4. Conclusions

The software solution helps implementing the every day requirements of the quality control. Further developments might include a file management unit that will integrate the archiving process and that will make possible to observe at a glance the evolution in time of the control parameters for each analyt. It is important that the quality should be maintained constant over the time.

Building complex rules or a multi rule decision system is the best way to maintain a tight quality control. One of the greatest disadvantages of this approach is that the false rejection rates and false acceptance rates cannot be immediately assessed. This paper presents the analytical expressions for false rejection probabilities and error detection rates. These expressions can be used to precisely determine the global parameters for the implemented quality control procedures. By visualizing the behavior of the system when dealing with specific errors the physician may fine tune the rule system in such a way that it will fit the desired laboratory standards.

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