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Identification of "True Value" of the Error of Measurement and of the Seasonal Variation in Medical Laboratory

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The quality of results of all medical laboratories will be appreciated at the published limits of total error TEA% of any blood constituents. It was established that the total error may be calculated from all daily (or weekly or monthly) results analyzed with a computerized program "JEG". Results of the analysis may be plotted as a year-course of the analyte. This plot shows some disturbances suggesting that the baseline have some seasonal variations influencing negatively the result of error calculation. A procedure that enables the separation of two components of the total error and calculation of the "true" error connected with the laboratory work (human error) is demonstrated.

K e y w o r d s: error of laboratory results, seasonal variation of serum constituents, medical laboratory

1. Introduction

Remarkable advances in technology, automation, and testing procedures resulted in radical changes in laboratory organization, major precision and accuracy of test results. The most important changes are based on fast progress of the quality connected with the fast development and popularization of the daily work automation. Contemporary analyzers used in medical laboratories are of the highest quality, work fast and very precisely. In addition the widespread use of commercial reagent sets produce further improvement of the quality of laboratory results. Despite of the general progress higher or smaller errors may be observed by the analysis of the results of any, also the best laboratories.

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Great numbers of archival results from very different laboratories were examined. In sets of results of the most popular serum constituents collected for a year in daily, weekly or monthly portions, some instability of the mean values may be observed. Analysis of many sets demonstrates that these variations depend obviously on the origin of the sets and concrete laboratories. More exactly analyses indicate that in the great set of laboratory results two independent sources of errors may be suspected: one of them is the imprecision of the laboratory work (human error) but the other seems not to be connected with the staff error. It suggests, that the observed and measured error may be seen as a sum of these two very different components, one of daily frequency, the other of most longer variation.

2. Material and Method

The aim of this work was to state, if the human errors in the medical laboratory are in fact smaller than errors generally calculated as the "total error". It should be pointed out, that the clinical physicians are generally not interested on correctness of the work inside laboratory but in errors of results released from the laboratory, received by them and used for the diagnosis and control of the course of disease.

On the other side it is also interesting how big are the unavoidable biological changes of the mean level of biochemical serum constituents within a year, created by till now mostly unknown external causes.

To realize this aim the choice of an adequate **methodology** was necessary. As a **material** for the examinations great sets (many thousands of data) of archival laboratory results were used all obtained from colleagues from different laboratories located in different regions of Poland. As principal **method** for analysis of any particular data set the "JEG" computer program were applied. This program has been developed and used in the Institute of Biocybernetics and Biomedical Engineering [1–3] for the statistical analysis of great laboratory data sets. Unfortunately the correlation of the test results with respective clinical diagnoses or patients' personal data other than sex and age was not possible, because this information is not registered in polish laboratories.

The "JEG" computer program [2, 3] enables (Fig. 1): construction of a histogram from a dataset, smoothing this histogram with a kernel density estimation method [1], generation of a scaled Histographic Curve (HC), and finally approximation of an appropriate Gaussian curve [2] to the HC. Statistical features of this Gaussian Curve (MV-2SD=min, MV=opt, MV+2SD=max) are called Gaussian Reference Intervals (GRI min, opt, max).

As the **first step** the analysis of any set of laboratory results with "JEG", a day-, week- (mostly) or month-set must be performed. Results of particular analyses in the form of three features of Gaussian Reference Intervals (GRI min, opt, max) were put on the time-scale, mostly all days or weeks of a year. A three-row figure appeared (Fig. 2).

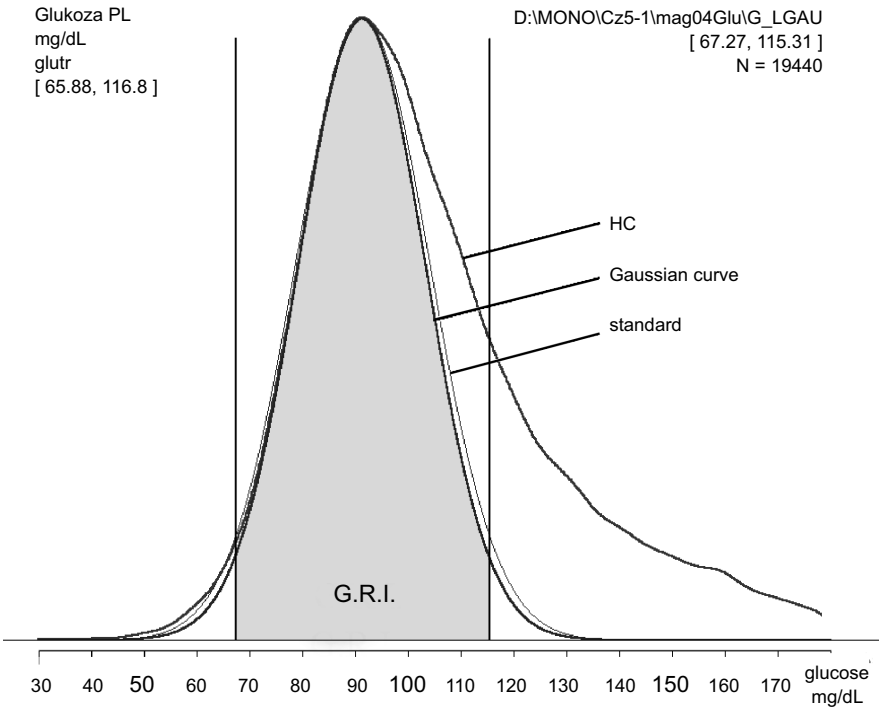

Fig. 1. Computer screen of the full JEG analysis of a set of glucose results: HC (outer curve), Gaussian curve (inner curve), Gaussian Reference Interval (GRI) and own laboratory standard [3] (thin line). Vertical scale in relative %. Upper left corner – name, units, symbol and norm-range of the parameter, upper right corner – computer address of the investigated set, its interval and number of results

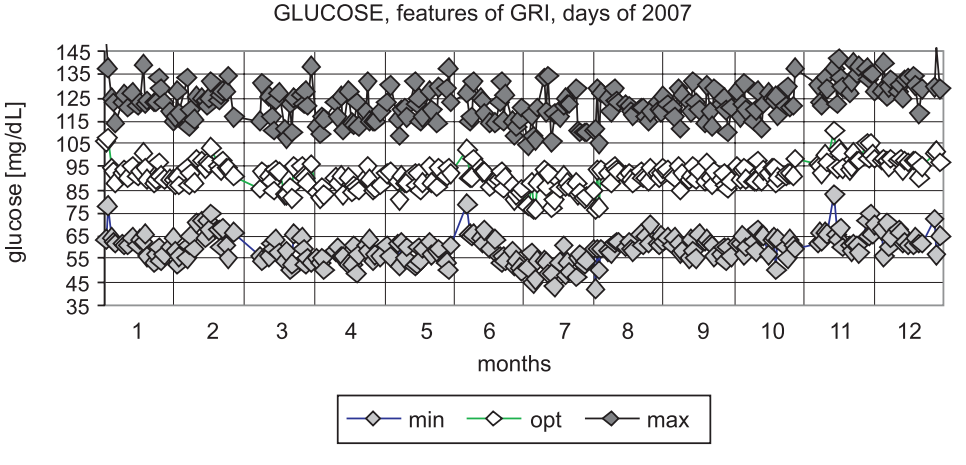

Fig. 2. The basic picture of the analysis of daily sets of glucose results within one year

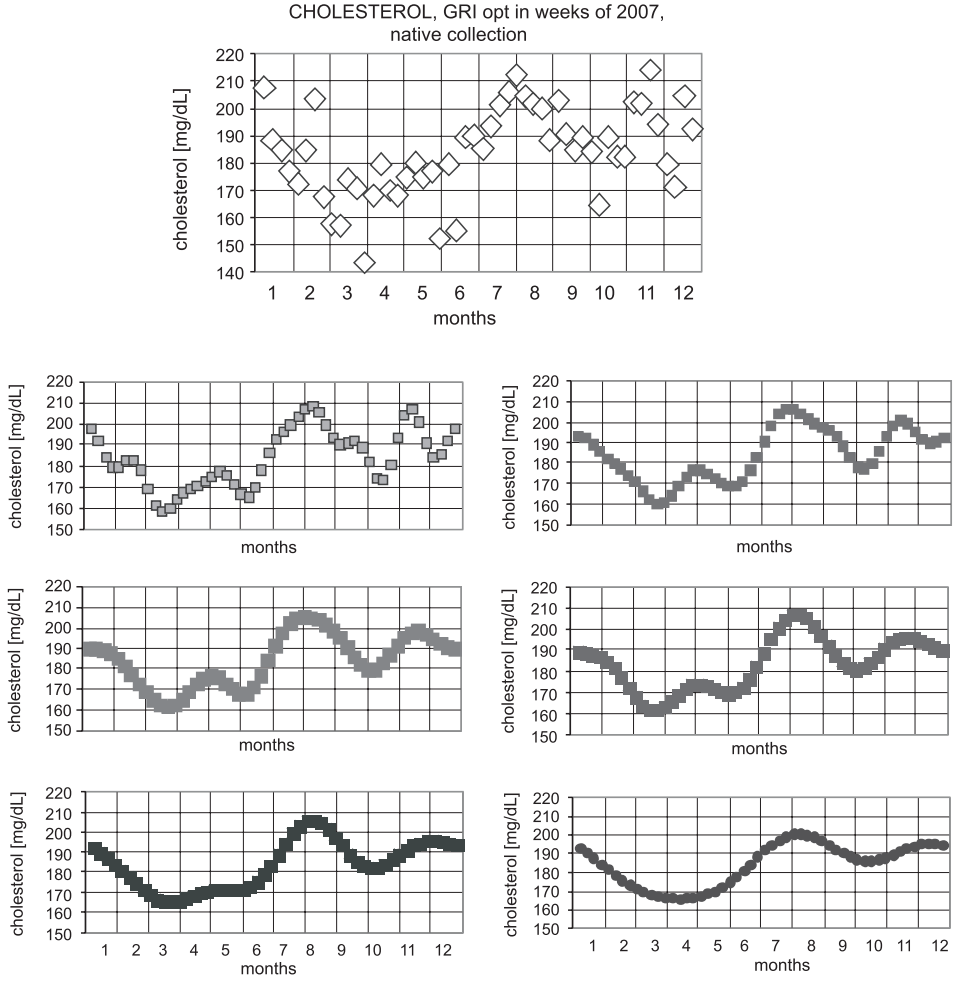

Fig. 3. The picture of the native GRI opt data and their sequential Fourier retransformations with 8–3 components

In the **second step** only one row, mostly the sequence of the mean values (MV=opt) were taken to further calculations. The data of this row were recalculated with the fast Fourier transformation (fft, MATLAB) and retransformed with subsequent numbers of the components with the lowest harmonic frequencies (Fig. 3).

The frequency most suitable for further investigation may be found with help of analysis of the course of differences between the SD's of sequential retransformed and native data. This number of the most suitable frequency lays in the inflexion of the curve, and at the minimum of its derivative (Fig. 4).

In the **third step** the differences between the native data and their appropriate retransformed values should be calculated and statistically analyzed.

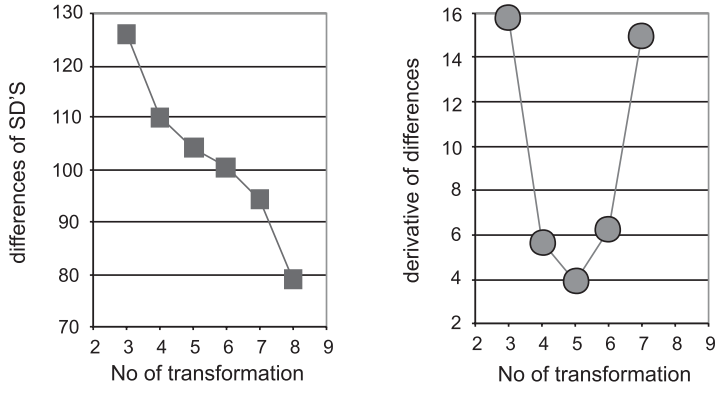

Fig. 4. Differences between the standard deviations (SD) of sequential Fourier retransformations with 3–8 components and native data (left) as well as derivative of these differences (right)

3. Results

Figure 5 shows an example of the result of a concrete analysis of the cholesterol set. The standard deviation SD of the native set was 16.27 with CV= 8.84, and of the set of differences SD = 10.18 with CV = 5.53. The latest number may be seen as a "true error" of cholesterol examination in this laboratory but the first one will be normally calculated as total error. This total error in this example was relative great, laid between the middle and upper tolerance limit [4] for cholesterol assay (TE_A% advisable = 8.5 < CV = 8.84 < TE_A% minimal = 12.6). The "true error" was located much advisable, between the lower and middle limit (TE_A% optimal = 4.1 < CV = 5.53, but < TE_A% advisable = 8.5). It should be pointed out that the error in any laboratory and for any analyte is always estimated at these limits.

Not always the differences were so clear and convincing as in the example above. For the same laboratory and time the analysis of glucose results showed different situation. The CV of native set was 2.35 and this for the differences to the retransformed data ("true error") 1.837 . The difference between these values was not great, because the retransformed curve of the year-profile was very flat, with a minimal influence on the "total error". All values lied under the most convenient tolerance limit for glucose (TE_A% = 3.7).

4. Discussion

The interest in the true error in laboratory work increases in the latest years [5 - 9] but the direction of investigations had changed. The growing quality of results accelerates the evolution of laboratory diagnostics into an independent medical knowledge [10]. In this situation any source of error had to be identified and eliminated.

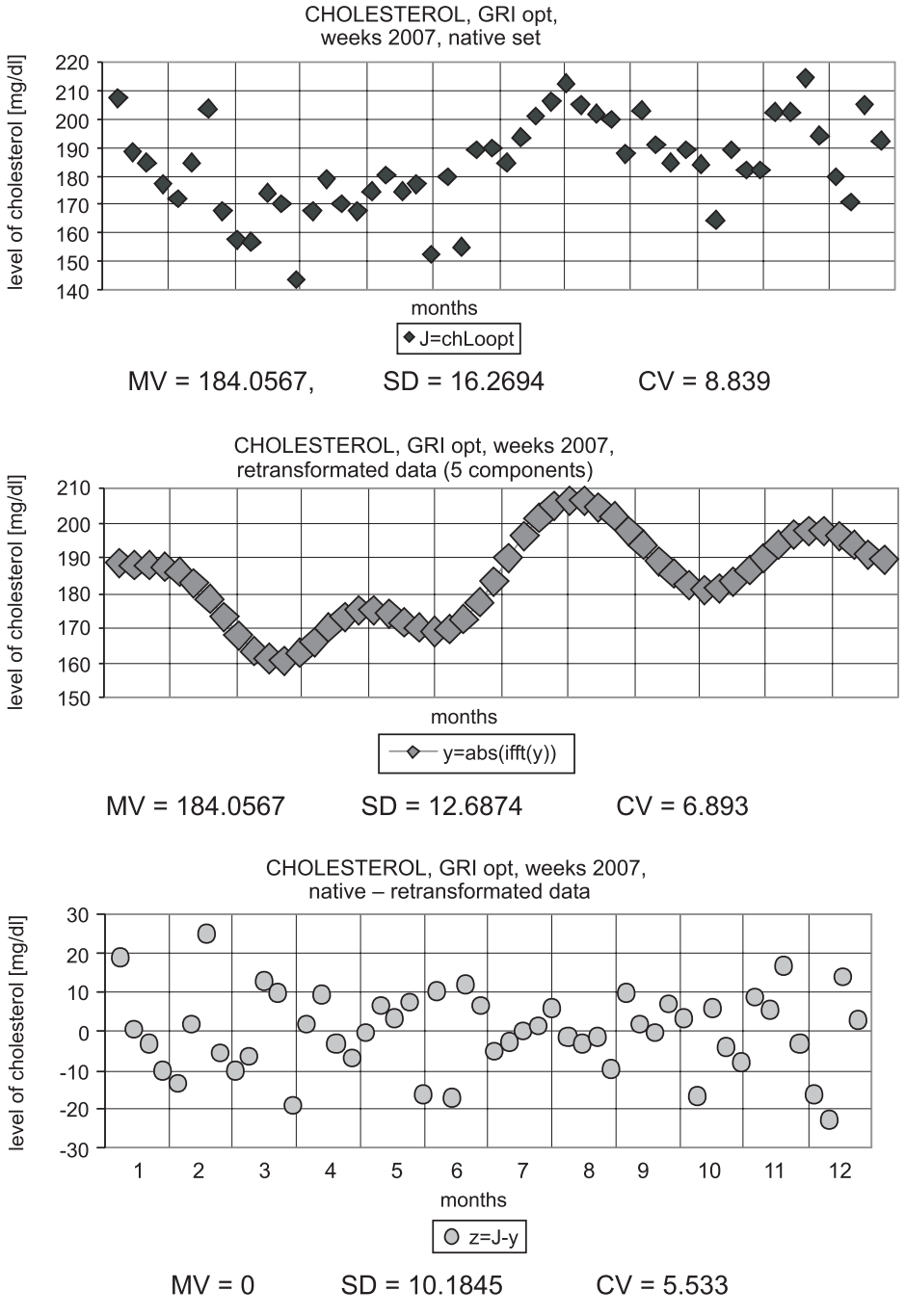

Fig. 5. The picture of the native set of a year cholesterol GRI opt data (up), these data after retransformation with Fourier transform (fft) with 5 components (middle), the results of differences between native and retransformed data (down)

The JEG method [1, 3] was for more than five years developed step by step in the Institute of Biocybernetics and Biomedical Engineering in Warsaw, PL. The procedure described in this paper is fully original and may be hardly compared with any other method from the literature [11, 12]. The attention of clinical physician is less directed at the quality of the laboratory work, but much more at the results appearing in the bed-station. In the literature are many doubts regarding reference-values system [1, 12, 14–17] and look for references in the own stock of archival results. It may be controversial, but the here described method was proved very intensively for last 7 latest years with good results.

In all this years the fast progress in precision of the work of medical laboratories in Poland [18, 19] could be observed On the other side the tendency to base medicine on evidences increases the role as well as the responsibility of the laboratory in the course of medical treatment. The computers can and should support medical diagnostics [20–26] and prognostics [27, 28] but it demands really precise, credible results of investigations.

In this paper is showed that the error calculated in any laboratory may be seen as a sum of two in fact independent components. The high frequency time-curve showing mostly daily changes of the baseline, very good seen in Fig. 2, represent the true failure probably induced by not ideal calibration of analyzers. On the other side the laboratory can not be responsible for any seasonal variation which will not be identified by the Internal Quality Control. The problem is to have an adequate method to identify this source of error. One of such methods is demonstrated in this paper.

It is worth to emphasize, that in the same way the true value of the biological variations of the biochemical data in the population may be easily estimated. The course of variation in the time of some serum constituents, like cholesterol [29] and PSA [30] are of interest for surprisingly many different physicians, health service officers and scientists: in aging [31], dose-calculation of medicaments [32], risk of prostate cancer [33], suicide occurrence [34], reproductive function [35], grow old problems [36], cardiovascular disease risk [27], andropause control [31], bone turnover [37], and many other.

5. Conclusions

The observed and measured laboratory error may be seen as a sum of two very different components. To distinguish these components a suitable methodology is necessary. The "JEG" computer program, developed and used for years in the Institute of Biocybernetics and Biomedical Engineering helps to solve this problem. Relative easy calculation with the help of the MATLAB program differentiate the high-frequency "true error" of laboratory work from the low-frequency seasonal variation, that the laboratory can not be responsible for. The differences may be smaller or greater, but

the “true error” is always smaller then the actual calculated “total error”, which is used to estimate the quality of work of any laboratory.

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