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Monitoring of arterial blood saturation with oxygen (oxygenation) has gained special significance as a result of the COVID-19 pandemic. A new method for computer processing of saturation records (so-called SaO_2 signals), based on the study of differentials (increments) from signals, was proposed. Finding a differential for a time series involves calculating the difference between the pairs of its adjacent elements. The differential is non-zero only if the elements in a pair are different. The study of differentials together with primary signals for a set of records (20 subjects) shows that the spectrum of observed levels of blood saturation is discrete and limited (from 2 to 10 levels). In addition, changes in saturation levels (switches) occur only between the nearest levels.

New indicators of the variability of blood saturation were proposed. These are the frequencies of saturation level switches (event intensities) and the intervals between them. It was established that these indicators are described by statistical distributions of Poisson and Erlang, respectively. Comparison of new variability indicators with the most reliable statistical – inter-quartile range – indicates that the new indicators also provide for the division of the data set into three subgroups according to the magnitude of variability. This division is statistically significant at a confidence level of 0.99 in both approaches, however, the division into sub-groups is slightly different in these methods.

It was shown that the proposed indicators of the variability of SaO_2 signals are scale-invariant, that is, they do not depend on the length of observation interval. This is a consequence of the fractality of the positions of differentials in the observation interval. The established switch frequencies for subgroups in order of increasing variability are (0.06, 0.11, and 0.20) Hz. These frequencies are manifested on Fourier spectra of differentials of SaO_2

Keywords: arterial blood oxygenation, variability, differential analysis, Poisson and Erlang distributions, COVID-19

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DEVELOPMENT OF A METHOD FOR DIFFERENTIAL ANALYSIS OF DATA ON THE ARTERIAL BLOOD OXYGENATION IN HEALTHY ADULTS

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1. Introduction

Studies of the levels of blood oxygenation (saturation), that is, the percentage of oxygen saturation of hemoglobin, became increasingly active as a result of the coronavirus pandemic (COVID-19). The first stage of this viral disease is characterized by «latent hypoxia» due to insufficient oxygenation of the patient's blood [1–3]. Hypoxia, or lack of oxygen, can be almost unnoticeable for saturation levels close to 90 % and below. The range of the oxygenation norm for healthy adults is (95–100) % [4].

The clinical practice mainly uses pulse oximetry – an indirect, but non-invasive, inexpensive, and convenient method for monitoring the oxygen level in the blood. Pulse oximeters are small devices that are fixed on fingers or on ear lobes. In this way, the so-called peripheral oxygenation (SpO_2) is measured [5, 6].

Much more expensive, invasive, and more complex devices, called blood gas analyzers, or CO-oximeters, allow direct, reliable, and more accurate studies [7] They specifically measure the so-called arterial oxygenation (SaO_2) and are used in equipped medical laboratories by qualified personnel. These devices are also the standards for calibrating pulse oximeters, usually based on the data for healthy patients.

There are certain differences in the results between these two methods, which depend both on the diagnosis of a patient and on the measurement range [8]. In particular, at Manchester University Hospital, for patients with

COVID-19 and pneumonia, it was observed that the readings of CO-oximetry (SaO_2) systematically exceeded the data that were recorded by pulse oximeters (SpO_2): SaO_2>SpO_2. The average difference was 5.3 % at the confidence interval equal to 0.95 [9]. Recommendations [10] to maintain oxygen saturation, controlled by pulse oximeters, in patients with COVID-19 close to the upper limit of the range (92–96) % take into consideration this factor.

The growing mass character of measurements of arterial blood saturation with oxygen requires new methods for computer processing of their results, which causes the relevance of the presented paper.

2. Literature review and problem statement

The variability of medical signals is a well-known fact that reflects the complex dynamic balance of living organisms with unstable environments, the so-called homeostasis, which was pointed out in general for metabolic processes in paper [11], and in particular, for electromyography signals, in paper [12].

Pulse oximetry signals (SpO_2 and SaO_2) given in [5, 6] as time sequences are no exceptions to this pattern. Research [5] shows the possibility of determining hyperoxemia using pulse oximetry. The variability of pulse oximetry signals is mentioned but is not studied in detail. Paper [6] explores the principles of pulse oximetry, its accuracy, and its capabilities to determine diseases, the variability is mentioned but is not considered in detail either. Understanding variability gives an idea of the adaptive capabilities of a particular life support system of the body in a healthy state, or in a state of pathology. Variability of the daily heart rate, in particular, can be a useful indicator of the pathological conditions of living beings [13].

However, as noted in [14], the variability of blood saturation with oxygen in the SpO_2 method was studied little and mostly with the use of the less reliable methods than mentioned heart rate variability. Note, by the way, that the variability of time series within the SaO_2 method was studied even less.

The authors of [14] studied entropy and multi-scale entropy of time series, analyzed detrended fluctuations using simultaneously the known statistical methods. The general conclusion is as follows: variability is predominantly long-term with some signs of fractality. There is no clear relation between the variability and the age of the subject. In addition, the signs of fractality were not named specifically and their origin was not disclosed.

Well-known statistical characteristics of variability are standard deviations (dispersions), interquartile ranges, and total data spreads [15]. However, direct application of these methods, as well as variability descriptors from Poincaré graphs [12], faces certain difficulties that are analyzed in [16]. The difference in distributions of probability of real data from the normal Gauss distribution (multimodality, large share of emissions, asymmetry, etc.), makes us look for new, unconventional ways to assess the variability of blood oxygenation data for both SpO_2 [14, 16], and for SaO_2 [17].

Specifically, work [16] offers new variability indicators, such as the number of observed levels of blood saturation, or the probability of top (most likely) levels. The authors of paper [17] applied the technique of differential analysis of primary blood oxygenation records and proposed the mixed Poisson distribution to describe the number of switches between observed levels of saturation. Both works divide the data sets they work with into three constituent parts (subgroups) with significantly different variability.

Practice requires that new ways of describing variability, alternative to traditional statistical methods [15], should be reliable enough and easy for clinicians to understand and apply. In addition, such methods, of course, can be purely empirical, as in [14, 16]. However, it is better if they have certain statistical justification, as in [17], although this research outlines only the contours of such a description.

3. The aim and objectives of the study

The purpose of the research is to apply and improve the differential (incremental) analysis of the SaO_2 time series [17] and its mathematics and statistical justification for the correct description of the variability of these signals. The new, reliable indicators of the variability of arterial blood saturation with oxygen, proposed based on such an analysis, can be useful in clinical practice, in particular, during the COVID-19 pandemic.

To accomplish the aim, the following tasks have been set:

– to create a randomized small-volume set of artifact-cleared data for research, using available medical databases, and to explore the interquartile ranges of the SaO_2 series of the dataset as the most reliable statistical indicator of variability;

– to perform computer differential analysis for differentials in relation to the series of the set, to establish the number and the position of switches (changes) of the observed levels of saturation and establish a statistical distribution for the number of switches in the series;

– to determine the distance between the positions of switches (changes) in each series of the set and establish the statistical distribution of probabilities that describes the distance between them.

4. The study materials and methods

4. 1. The study dataset

The data from the portal of medical databases PhysioNet were used [18]. In detail, these data were described in source [19]. About two thousand (1985) records of arterial oxygenation (SaO_2) lasting one hour at a sampling rate of 200 Hz were provided by the laboratories of the Massachusetts Central Hospital (USA).

Initially, 25 records, each three minutes long, were randomly selected from this database. Thus, each series (a record) had a length of 36,000 countdowns. The set was checked for artifacts and three records were removed due to their presence.

Two more records showed zero variability (one of these appears in the data set [17]). These records had the same saturation value throughout their length. They, too, were excluded from the set as a kind of artifact, due to the limited length of the series. Thus, a total of 20 records that made up the dataset for the study of SaO_2 variability remained. Note that the datasets for this work and the ones for [17] overlap but are not identical.

4. 2. Computer processing of the dataset series

Randomized selection of records (series) of measurements was implemented by the program from the «RandomTools» package, which is part of the system of computer mathematics Maple 2020 (Canada) [20]. The dataset was imported from

the database [18, 19] by the terminal «Cygwin64», which is freely available on the PhysioNet portal [18]. Terminal commands allow, in particular, configuring the desired recording length, since the PhysioNet portal limits this parameter for obvious reasons. The terminal also makes it possible to choose a convenient text format for an imported file.

The search for artifacts in the originally selected records was carried out by programs from the «Statistics» software package. In particular, giant data emissions were found (we are talking about several hundred values of blood saturation with oxygen below 1 %, which is physiologically unreal, at least for alive people) in three records.

The computer processing of the dataset described above was also carried out using Maple 2020 software packages. Various packages of the system of computer mathematics were used: «LinearAlgebra», «Statistics», «SignalProcessing», and «plots». Only to complete tasks 3 and 4 from Section 3, it was necessary to write a separate program in the Maple programming language (the so-called procedure [20]).

5. Results of studying the SaO_2 time series

5. 1. Inter-quartile ranges as the most reliable statistical indicator of variability

The so-called box-and-whisker plots, box plots are a convenient way to visualize the variability of datasets. They rely on the statistical distribution of data on the quartile, showing the interquartile range in the form of the boxes' height, and the full data spread in the form of vertical lines with dashes («whiskers»). Emissions can be shown at separate points [15, 16]. Fig. 1 shows the box plots (charts) for the SaO_2 data set described above.

A box-and-whisker plot convinces that there are at least three subgroups in the dataset. This is a subgroup with a small (formally even zero) variability, which consists of 6 subjects (IDs 1, 2, 5, 10, 15, 16). A subgroup with a relatively large variability (approximately 2 %), which has 6 subjects (IDs 3, 6, 11, 12, 13, 14). An intermediate subgroup with an average (approximately 1 %) variability that has 8 subjects (IDs 4, 7, 8, 9, 17, 18, 19, 20). The difference in typical variabilities between the subgroups is statistically significant at a confidence level of 0.99.

The zero interquartile range for the first subgroup looks a bit strange at first sight. However, it is worth taking into consideration the number of observed saturation levels in the records for this subgroup (from 2 to 4 levels). Then the impossibility of distributing two or three observed levels to four quartiles becomes clear.

5. 2. Differentials of SaO_2 records (series) and their statistical distribution

The operation of finding a first-order differential (increment) for a time series involves calculating the difference between adjacent pairs of elements of a series (a record), starting with the second and first elements, the third and second ones, and so on. The differential is non-zero if the next element of the series is different from the previous one. Non-zero differentials indicate the positions where there is a change in the elements of the time series (series, record).

Fig. 2 shows three series (records) of SaO_2 measurements for three typical subjects from the three different subgroups described above in order of variability increase from left to right. There are also the plots of differentials of these three series in the same order. The number of non-zero differentials is as follows: 10, 22, and 37, respectively.

First of all, note the same amplitudes for all differentials, which are approximately equal to 1 %. This means that a change (switch according to the terminology of [17]) of the observed saturation level is possible only in the nearest higher or lower level from a certain limited spectrum of such levels (from 2 to 10 for the subjects of the selected dataset). Thus, the spectrum of possible levels of oxygen saturation of arterial blood may be limited and discrete.

We consider any change (switch) of the possible level of blood saturation is an event. Then plots of differentials illustrate the flows of such discrete events in the same time interval (t=3 minutes), or countdowns (N=36000). The number of such events (10–40) is small compared to the number of tests (N), so these are rare events.

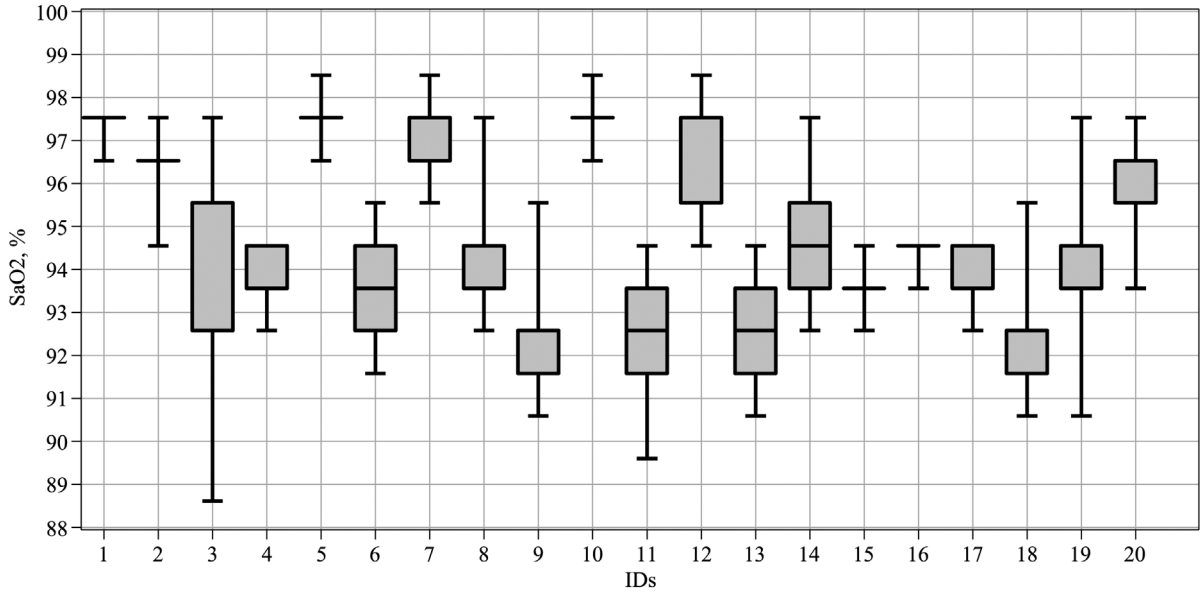

Fig. 1. Box-and-whisker plot (chart) of the dataset of oxygen saturation of arterial blood (SaO_2). The horizontal axis shows identification codes (IDs) of subjects (records), vertical axis — saturation in percentage

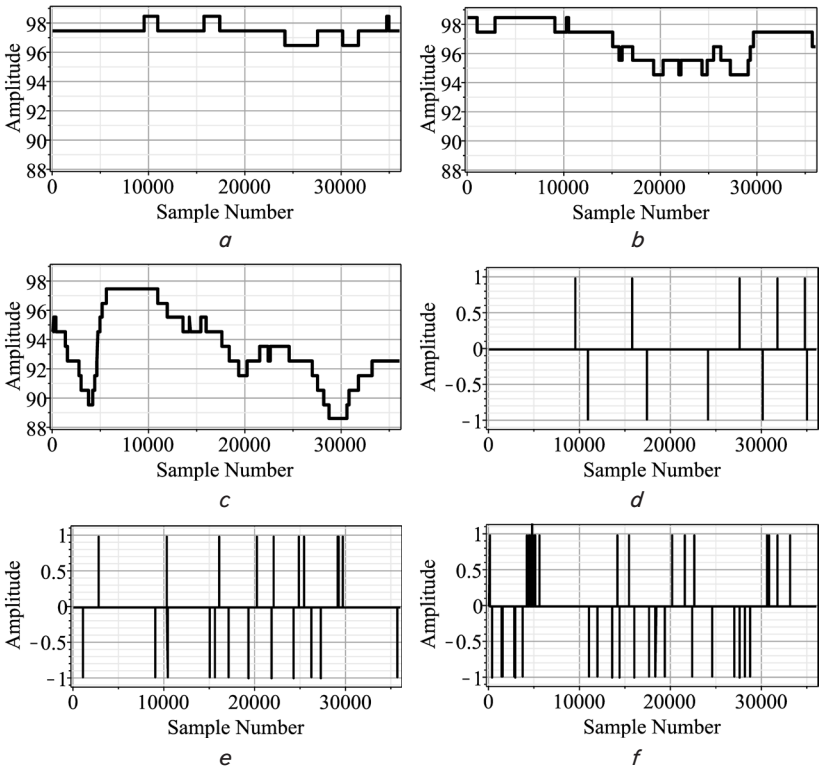

Fig. 2. SaO_2 records and their differentials for three typical subjects of three different subgroups: *a* — SaO_2 record for a typical subject of the subgroup with ID 5; *b* — SaO_2 record for a typical subject of the subgroup with ID 3; *c* — differentials of the records for a subject of the group with ID 5; *d* — differentials of the records for a subject of the group with ID 12; *e* — differentials of records for a subject of the group with ID 3; amplitudes are given as a percentage

Each such event (switch) is independent of the others, that is, it has no aftermath, influence on subsequent events. Each event takes place separately from the others, not in pairs, triples, etc., that is the flow of events is ordinary. Finally, the probability of an event number getting into a small time interval $d \subseteq t$ depends only on the length of the interval dt and does not depend on where exactly on the time axis it is located. Thus, the flow is stationary.

The stationary and single flow of events without the aftermath is described by Poisson distribution for the number of events in any arbitrarily fixed interval (time, or tests) [15, 17]. It is clear that flow intensity, the main parameter of Poisson distribution, is preserved only within a subgroup. It should vary from subgroup to subgroup, as is seen in Fig. 2.

Thus, subgroups can be formed based on the switch flow intensity, that is, selecting subjects with similar event numbers to a subgroup. In this way, three subgroups were separated:

– a subgroup of low-intensity switches with an average intensity of 11 events per series. It includes seven subjects (IDs 1, 2, 5, 7, 10, 15, 16). This group intersects but is not completely identical to the one described above in chapter 5.1 with low variability;

– the subgroup of the intermediate intensity of switches with an average intensity of 21 events. This group includes 9 subjects (with IDs 4, 6, 8, 11, 12, 14, 17, 19, 20);

– the subgroup of higher intensity: 37 events on average. It includes four subjects (IDs 3, 9, 13, 18).

The difference in average intensity of events between subgroups is statistically significant at a confidence level of 0.99.

The Poisson distribution gives the probability of observing x events at a fixed interval if the intensity of events is equal to λ:

$$Pois(x,\lambda)=\frac{\exp(-\lambda)\cdot\lambda^{x}}{x!}. \quad (1)$$

The probability of observing x events in mixed Poisson distribution [21]: for a heterogeneous dataset, which in our case consists of three subgroups with different event intensity, can be recorded as:

$$P(x)=\sum_{i=1}^{3}\left(\frac{n_i}{n}\right)\cdot Pois(x,\lambda_i), \quad (2)$$

where n_i is the number of subjects in the i-th subgroup, $n=20$ is the total number of subjects in the dataset.

Histograms are a useful statistical data mapping tool, making it possible to represent actual probability distributions. To create valid histograms, two parameters are important: the width of the so-called «basket» (or «band») of the regular histogram interval and the starting point of such first interval [22]. Regarding the width of the «basket», there are certain empirical evaluation rules, depending on variability and the amount of data [23]. The ambiguity of the choice of selection of the starting point can be eliminated by averaging the histograms that were shifted several ($m \le 10$) times, or the so-called «averaged shifted histograms, ASH» [22].

Fig. 3 shows an ordinary and the ASH-histogram for the studied dataset and the curves of the complex (mixed) Poisson distribution against their background. The three-modality of the actual probability distribution and the heterogeneity of the data set are evident.

The correspondence between the histograms and the curve of the complex (mixed) Poisson distribution looks quite satisfactory. The curve qualitatively correctly conveys the ratio of modes and minimums of histograms. It should be noted that the ASH histogram is better consistent with the theoretical distribution than the ordinary one, which was emphasized in [22]. It also more accurately gives the position of modes and minimums.

5. 3. The length of intervals between switches and their statistical distribution

Mathematical statistics state that the intervals between events of Poisson flow are described by Erlang distribution [15]:

$$Erl(x,\lambda,n)=\frac{\lambda^{n}x^{n-1}}{(n-1)!}\cdot\exp(-\lambda x), \quad (3)$$

where x is the length of the interval between consecutive switches; n is the number of tests ($n=36{,}000$); λ has the same sense as the Poisson distribution (1).

Fig. 4 shows the ASH-histogram ($m=3$) and the plot of the complex (mixed) Erlang distribution, obtained similarly to the complex Poisson distribution. According to the central boundary theorem of probability theory for such a large value of the $n \gg 1$ parameter, Erlang distribution is well approximated by a normal distribution with the mean value of n/λ and dispersion n/λ^2.

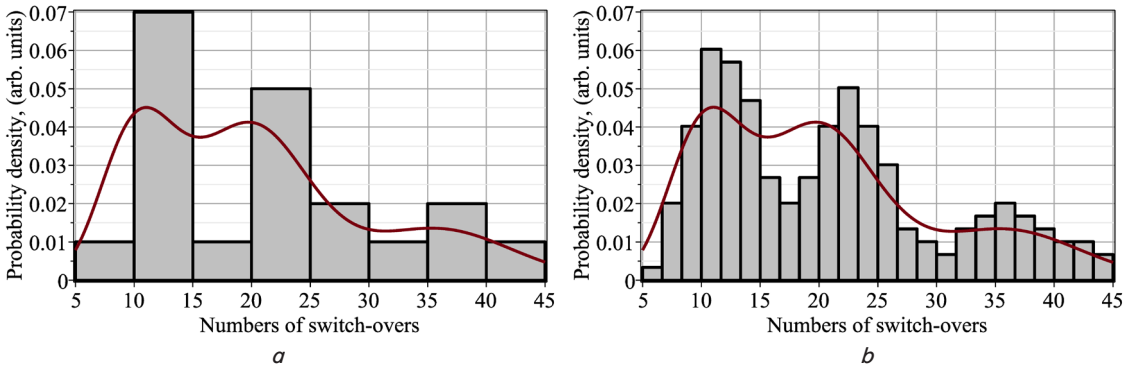

Fig. 3. Histograms and Poisson distribution for the studied dataset:
a – ordinary; *b* – ASH (m=3); horizontal axis shows the number of switches in the series, vertical – probabilities; the curves show probabilities calculated by (2) for mixed Poisson distribution

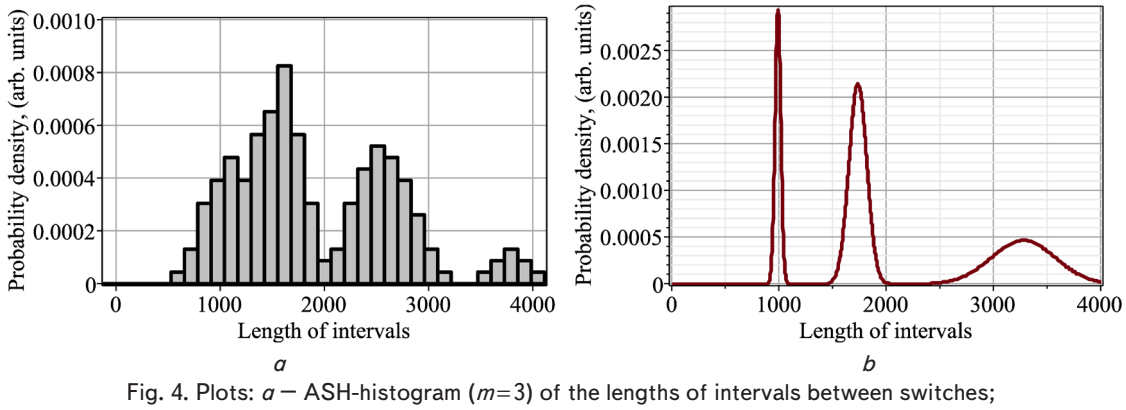

Fig. 4. Plots: *a* – ASH-histogram (m=3) of the lengths of intervals between switches; *b* – plot of mixed Erlang distribution for heterogeneous dataset

Agreement of the histogram and complex Erlang distribution looks satisfactory, at least from a qualitative point of view. Both the histogram and theoretical distribution confirm the heterogeneity of the dataset and the existence of subgroups in it.

The mathematical expectation (mean value) for Erlang distribution is equal to relation n/λ and standard deviation $n^{0.5}/\lambda$. In Table 1, these theoretical indicators are compared with averaged experimental ones in each of the three subgroups.

It can be stated that average lengths of intervals between switches are satisfactorily consistent with their theoretical estimates. However, standard deviations differ by order and more. The reason is the small number of subjects in the subgroups, so the magnitudes averaged within subgroups (bottom row in Table 1) have rather large variances. Thus, refining these magnitudes, as well as the average intensities of switches, requires an increase in the number of records (subjects) in the dataset.

Table 1

Comparison of theoretical and actual estimates for average lengths of intervals between switches and their standard deviations for three subgroups; interval lengths and their standard deviations are given in the countdowns

Type of value	Subgroup of low variability	Intermediate subgroup	Subgroup of higher variability
Theory	3273±17	1732±9	986±5
Actually	2806±504	1758±454	982±105

If the intensities of switches obtained above for each of the three subgroups (11, 21, and 37 switches in the 3-minute observation interval, respectively), are recalculated in frequencies, one can get (0.06, 0.11, and 0.20) Hz, respectively. These frequencies lie in bands F1–F2 of the frequency classification [24]. Fig. 5 presents periodograms of three functions of the lower row of Fig. 2 in these frequency bands.

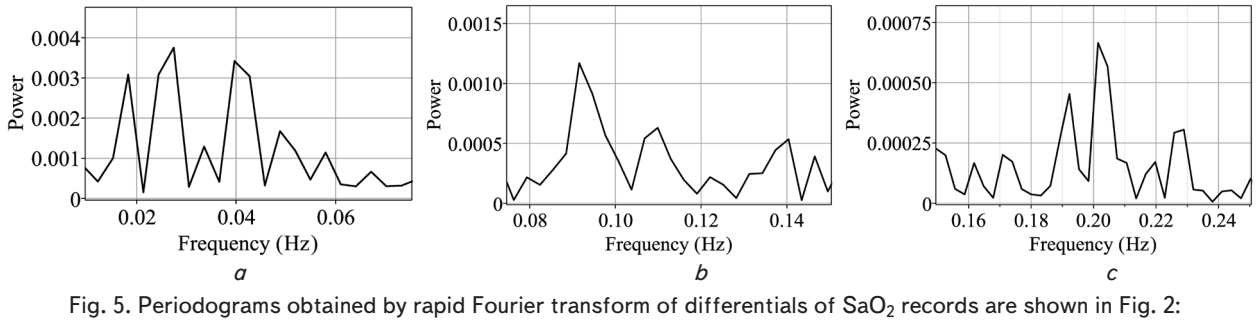

Fig. 5. Periodograms obtained by rapid Fourier transform of differentials of SaO_2 records are shown in Fig. 2: *a* – of a typical subject of the subgroup with ID 5; *b* – of a typical subject of the subgroup with ID 12; *c* – of a typical subject of the subgroup with ID 3; Fourier amplitude squares (vertical axis) are assigned in relative units

Characteristic structures were found: a duplicate of peaks in the range (0.04–0.05) Hz in the left plot, a duplicate in the range (0.095–0.11) Hz in the middle plot, a duplicate in the range (0.18–0.20) Hz in the right plot. The widths of these ranges are comparable to the theoretical resolution capacity at the frequency (0.006 Hz), which is determined by discretization frequency (200 Hz) and the number of points for rapid Fourier transform ($215<n$). Frequency ranges can be considered close enough to the above estimates: (0.06, 0.11, and 0.20) Hz, taking into consideration the magnitude of resolution.

6. Discussion of results of studying data on the oxygen saturation of arterial blood

The functions shown in Fig. 2 have interesting features: their first derivatives by argument (number of countdowns, or time) are equal to zero almost everywhere in the observation interval. «Almost» in this sentence means «except for a discrete set of points (positions) of zero measure» [25]. This discrete set of points is the positions of switches shown in the same Fig. 2 in the bottom row. By itself, this set of points (positions) is asymptotic, an infinitely small particle of the entire signal and has a distinctly heterogeneous structure, that is, it is a fractal of a certain Hausdorff dimensionality in itself [25, 26]. The fractal nature of the SpO_2 series was pointed out earlier in [14], and that of SaO_2 – in paper [17].

Fractal nature means that a fragment of such a set, say, those positions that belong to the left half of the observation interval, is statistically equivalent to the whole set. Thus, it has the same intensity of events (switches between levels of saturation), or the average interval between them, as well as the full set. Thus, scaling (decreasing or, on the contrary, increasing) the length of the observation interval cannot significantly change the intensity of switches, or the average interval between them for the subgroups determined above. They are scaling invariants, at least in the interval of scales, which obey the law of step-by-step scaling [26]. Thus, it is the fractality of the moments of switches of the level of blood saturation with oxygen that is the key to understanding the obtained results.

It is worth emphasizing the agreement of variability indicators proposed in this work (frequency of switches and intervals of time between them) both with each other and with interquartile ranges, the most reliable statistical indicator of variability. There is a predictable strong and negative correlation between the number of switches and the average intervals between them. The linear correlation coefficient is –0.888 and it is statistically significant at the confidence level of 0.99. Thus, the higher one indicator is, the lower is the other, and vice versa.

The periodograms in Fig. 5 indicate that characteristic frequencies of switches between possible levels of blood saturation with oxygen are small (first frequency bands of classification [24]). On the one hand, this proves the statistical rarity of such events. On the other hand, it makes it possible to work with much lower discretization frequencies than those that are commonly used, without losing significant information about the processes of switches in oxygenation levels. The findings are consistent with the results in [16] regarding the division of datasets into three subgroups, although a different dataset was considered in that paper and SpO_2 measurements were analyzed. However, the specific weight of subgroups in the sets is slightly different: (35, 45, and 20) % for the SaO_2 data set against (22.5, 55, and 22.5) % for the SpO_2 data set [16]. The specific weight of the subgroup with the higher variability is approximately the same, but the specific weight of the subgroup with the lower variability is noticeably lower in favor of the intermediate subgroup in the results [16]. Small volumes of the sets (20, or 36 [16] of subjects) are a limitation of the accuracy of assessments of existing studies.

Based on the results of this study, as well as the findings reported in [2, 3, 14, 16, 17], two important problems can be outlined for further solution:

– whether (and how exactly) the spectrum of observed levels of saturation and/or variability of saturation at pathologies, in particular severe forms of COVID-19, changes;

– whether the risk of severe forms of COVID-19 is evenly distributed in the subgroups with different variability. Perhaps there is a more vulnerable subgroup, in particular, a subgroup with maximum variability of blood oxygenation.

7. Conclusions

1. A dataset for studies of oxygenation of arterial blood was generated. It turned out that the open-access database [18, 19] contains a certain amount of data with artifacts (3 cases out of 25). The dataset is heterogeneous, as already seen in the box-and-whisker statistical plot. Healthy adults are divided into three different subgroups by the magnitude of variability of arterial blood oxygenation, and this distribution is statistically significant at a confidence level of 0.99.

2. The spectrum of observed oxygenation levels is limited and discrete, and a change (switch) of the levels can occur only between the nearest ones. The number of switches in the observation interval is described by complex (mixed) Poisson distribution. The variability of arterial blood oxygenation can be characterized by large-scale invariant (independent of the length of the observation interval) indicators, in particular, frequencies (intensities, number) of switches between saturation levels.

3. The intervals of time between switches are subject to Erlang's complex statistical distribution. They can also be scale-invariant indicators of the variability of the blood oxygenation process. Both proposed new variability indicators are well coordinated with the traditional ones (interquartile ranges).

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