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Investigation and development of methods for automatic search for AUC-diagram-based features of Parkinson's disease and essential tremor

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Abstract: **Methods and optimization algorithms for automatic search for AUC-diagram-based features of Parkinson's disease and essential tremor were studied and developed. AUC diagrams are a new method for statistical analysis of biomedical signals, based on visualizing the parameters of wave train electrical activity in the brain and muscles. The effectiveness of this method has been demonstrated in solving problems of early and differential diagnosis of Parkinson's disease and essential tremor. The disadvantage of this method is the need to construct and analyze a large number of graphic diagrams. In this regard, automation of the analysis of AUC diagrams is an urgent task. The mathematical problem of finding features based on the analysis of AUC diagrams is reduced to an optimization problem in a multidimensional feature space. A distinctive feature of the space constructed using AUC diagrams is the presence of relatively large compact areas containing local maxima and minima. This property of the feature space facilitates the search for solutions to the optimization problem, but at the same time requires the selection of optimization algorithms and fitness functions that increase the likelihood of detecting global extrema. In this work, methods for automatically searching for global extrema in the multidimensional space of features of wave train electrical activity are investigated and developed.**

Keywords: **optimization methods, robustness, AUC diagrams, ROC analysis, wave train, electromyogram, Parkinson's disease, essential tremor, differential diagnosis, neurodegenerative disease features**

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Contents

1. INTRODUCTION

The goal of this work is to further develop the wave train electrical activity analysis method [1-18], designed by the authors for identifying regularities in biomedical signals. The concept behind the analysis of wave train electrical activity is to merge the advantages of conventional spectra and wavelet spectrograms. This involves identifying wave trains (local maxima) on wavelet spectrograms of signals, calculating these wave train characteristics – namely, the central frequency of the wave train, maximum power spectral density (PSD) of the wave train, duration of the wave train in seconds, duration of the wave train in periods at the central frequency, bandwidth of the wave train normalized to the central frequency of the wave train, and instantaneous phase of the wave train. Subsequently, mathematical statistics methods are employed to uncover generalized properties of wave trains (for example, ranges of listed wave train parameters) that are characteristic of the analyzed signal sample or differentiate one signal sample from another. The effectiveness of the proposed method was demonstrated in the early (preclinical) and differential diagnosis of neurodegenerative diseases Parkinson's Disease (PD) and Essential Tremor (ET) [1-3,16,17], as well as in the recognition of so-called immature epileptic discharges in laboratory animals [15,18]. All examples discussed in this paper are based on the analysis of a special type of wave train electrical activity – the so-called cross-wave trains [3], which are local maxima on cross-spectra of electromyographic (EMG) signals of paired antagonist muscles in patients with ET and patients with the first stage of PD.

The primary tool of the wave train electrical activity analysis method is AUC diagrams [1-3]. An AUC diagram is a way to visualize statistical regularities that distinguish two signal samples. Different types of AUC diagrams [2,3] are used to analyze various wave train parameters, but the principle of using any AUC diagram boils down to creating a two-dimensional diagram, with the abscissa axis representing the value of the lower boundary of the investigated wave train parameter, and the ordinate axis representing the upper boundary of this parameter (see example in **Fig. 1**). For each possible combination of lower and upper wave train parameter boundaries, an AUC diagram uses a color scale to show the degree of difference between one signal sample and another. The degree of difference is characterized by the area under the ROC curve (AUC), constructed to compare the average number of wave trains (per second of time) found in the analyzed signal samples, such that the value of the considered wave train parameter falls within the range between the considered

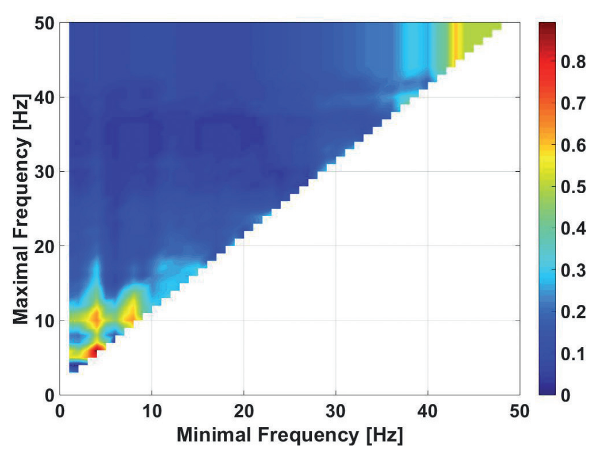

Fig. 1. *An example of a frequency AUC diagram. The comparison involves the EMG signal envelopes in paired antagonist muscles in the left hands in two patient groups. The first group consists of patients with the first stage of PD with onset in the left hand (10 individuals), and the second group consists of patients with ET (13 individuals).*

lower and upper parameter boundaries (indicated on the abscissas and ordinates of the diagram). Historically, a blue-red color scale is used for AUC diagrams, so values of AUC close to 0 correspond to blue areas on the diagram, while values close to 1 correspond to red areas. For researchers, both blue and red areas on the AUC diagram are of interest. Blue areas correspond to wave train parameter ranges in which the number of wave trains in the first sample is less than in the second, while red areas correspond to ranges in which the number of wave trains in the first sample is more than in the second. In this paper, we will adhere to the same terminology. In particular, when automatically searching for features distinguishing signal samples, we will talk about "blue" and "red" solutions to the optimization problem corresponding to blue and red areas discovered on AUC diagrams.

Searching for regularities in signal samples using AUC diagrams manually is a rather laborious process. During data analysis, the researcher creates AUC diagrams of various types. Upon detecting a blue or red area with a good AUC value on one of the diagrams, the researcher decides to further investigate the found area. A constraint corresponding to the selected area on the AUC diagram is imposed on the investigated range of the parameter, after which AUC diagrams of all other types need to be rebuilt and reanalyzed. This described sequence of actions is repeated iteratively until the observed AUC values cease to improve [2]. From the standpoint of mathematical analysis, the mentioned algorithm for finding regularities represents solving an optimization problem in a twelve-dimensional space (six parameters of wave trains, each with a lower and upper bound) by iteratively moving two-dimensional slices of this space (i.e., AUC diagrams). In practice, it may take a week or even a month of manual work to search for signs of neurodegenerative disease in a sample of electroencephalographic (EEG) or electromyographic signals.

Of course, the idea of automatic analysis of AUC diagrams arose from the very beginning of the development of the method for analyzing wave train electrical activity. Analyzing the twelve-dimensional parameter space is not a difficult task for modern optimization algorithms, so we hoped to automate the search for regularities in biomedical signals using standard optimization algorithms [19], such as simulated annealing [20], pattern search [21], and genetic algorithms [22]. However, our experiments quickly showed that this idea was very naive.

The first problem we encountered in the automatic search for blue and red areas on AUC diagrams was that some automatically found wave train parameter ranges that differentiate signal samples with very good AUC values (close to 0 or 1) ceased to "operate" after we rounded the values of these ranges to one or two decimal digits after dot. We termed this issue the "fragile solutions" problem. A careful examination of the fragile solutions problem revealed that in the twelve-dimensional wave train parameter space, indeed, there are very narrow areas with AUC values close to 0 or 1, around which AUC sharply worsens and approaches 0.5 (indicating an inability to distinguish the analyzed signal samples). During manual analysis of AUC diagrams, a person naturally avoids entering such areas of parameter space, focusing mainly on blue and red areas of relatively large sizes. Standard optimization algorithms lack criteria for assessing the robustness (resistance to small parameter changes) of the solutions found and therefore identify formally very good but impractical solutions.

The second problem encountered in the automatic analysis of AUC diagrams was the large number of solutions computed. From the perspective of practical use of wave train parameters for the recognition and differential diagnosis of neurodegenerative diseases, one could simply select several good (in some sense) solutions and disregard the rest. However, if AUC diagrams are used as a research tool, it is necessary to somehow compare and interpret the entire set of found solutions as a whole. For example, when analyzing tremor signals in patients with the first stage of PD, we found that the AUC diagram comparing the group of patients with tremor in the right hand with the group of patients with ET (**Fig. 2**) substantially differs from the AUC diagram comparing the group of patients with PD with tremor in the left hand (Fig. 1) with ET. This raised the question of whether the observed differences are manifestations of fundamentally different neurophysiological mechanisms in the right and left hands of patients, or whether similar regularities are observed in both hands of patients but in a different ratio. The automatic search identified hundreds of solutions on the AUC diagrams, which did not simplify answering the posed question.

Fortunately, automatic methods allow for the implementation of more complex schemes for analyzing the parameter space of wave trains than simply searching for global extrema, and we can take advantage of them for a detailed study

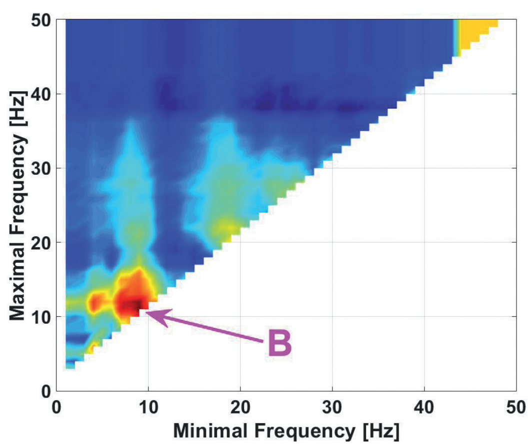

Fig. 2. *An example of a frequency AUC diagram. The diagram compares the envelopes of electromyographic (EMG) signals in paired antagonist muscles in the right hands in two patient groups. The first group consists of patients with the first stage of PD with onset on the right hand (12 individuals), and the second group comprises patients with ET (13 individuals). The arrow points to a large red area absent in Fig. 1.*

of the structure and properties of this space. The second part of the paper discusses the method of so-called "multidimensional drilling of the wave train parameter space", developed by the authors for the search and analysis of local extrema in the wave train parameter space. The third part of the paper considers the problem of assessing the robustness of optimization problem solutions and proposes a criterion for assessing robustness, based on the physical meaning of the wave trains parameter space. The fourth part of the paper discusses the application of developed statistical tools for researching clinical data of patients and developing diagnostic procedures.

2. MULTIDIMENSIONAL DRILLING METHOD OF THE WAVE TRAIN PARAMETER SPACE

The idea of multidimensional drilling of the wave train parameter space aims to enhance the expressive capabilities of conventional AUC diagrams through the application of optimization algorithms. The improved AUC diagrams (referred to as AUC-Drilling diagrams) differ from the standard ones in that, within each cell of the diagram, not just the AUC value is calculated, but the global extremum of the AUC function within the wave train parameter space. In the search for the global extremum, the optimization algorithm is allowed to vary all the boundaries of the wave train parameters, except for the two that correspond to the abscissa and ordinate of the diagram under consideration. These two parameter boundaries must remain within the confines of the considered cell on the diagram.

Fig. 3 illustrates the idea of multidimensional drilling of the wave train parameter space using an analogy with drilling oil wells. The figure shows a three-dimensional cube (a particular case of a twelve-dimensional cube). Each face of this cube can correspond to a certain AUC-Drilling diagram; the top face is chosen for the illustration. The perpendicular edges of the top face correspond to the axes of the abscissa and

Fig. 3. *The concept of multidimensional drilling of the wave train parameter space.*

ordinate of the AUC-Drilling diagram. In each cell of the top face of the cube, a well is drilled through the remaining ten dimensions of the space, to find areas of the space where AUC values are close to 0 or 1. Depending on which specific optimization problem solutions we are looking for, blue or red, two different AUC-Drilling diagrams can be constructed – blue or red.

The initial experiments with multidimensional drilling revealed that the results of EMG signal analysis of patients with PD and ET differ substantially from those shown by conventional AUC diagrams. Continuing the analogy with mineral extraction, the difference between the types of AUC diagrams is akin to that between surface geological surveys and exploratory drilling. Primarily, we observed that in some frequency ranges, both blue and red solutions with AUC close to 0 and 1 exist simultaneously. On conventional AUC diagrams, these solutions may overlap each other, preventing a complete view of the regularities within the wave train parameter space. AUC-Drilling diagrams separate blue and red solutions into different diagrams, allowing us to study them independently.

For example, on the red AUC-Drilling diagram for the left hands of patients, a red

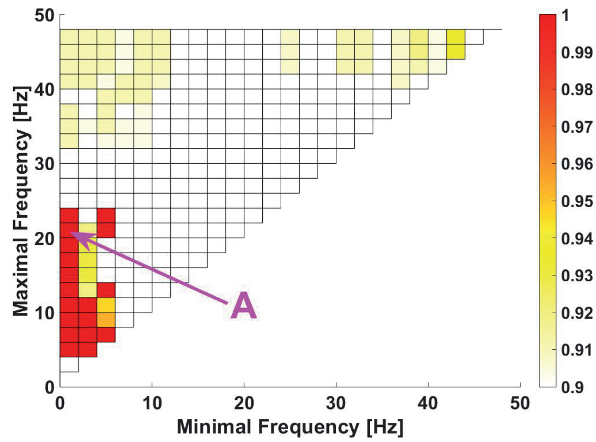

Fig. 4. *An example of a red frequency AUC-Drilling diagram. The envelopes of EMG signals in paired antagonist muscles in the left hands in two patient groups are compared. The patient groups are the same as in Fig. 1. A red area, invisible on the corresponding AUC diagram in Fig. 1 due to its overlap with a certain blue area, is indicated by an arrow. To solve the optimization problem here and in subsequent considerations, a pattern search algorithm is applied* [21].

area was discovered (see **Fig. 4**, area A) that is invisible on the corresponding AUC diagram (Fig. 1) because it is covered by a certain blue area (see **Fig. 5**).

At the same time, it was found that the red areas on the AUC-Drilling diagrams for the right

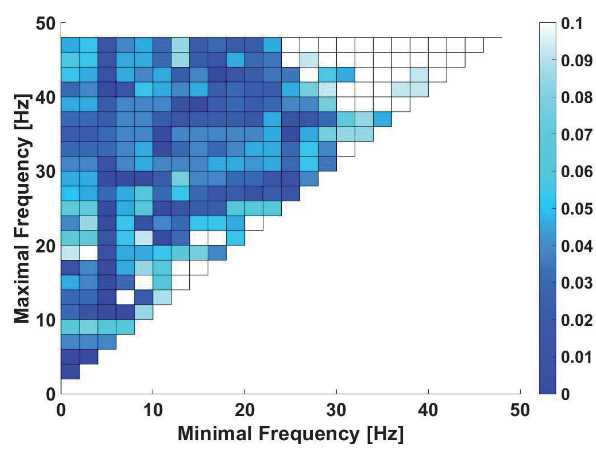

Fig. 5. *An example of a blue frequency AUC-Drilling diagram. The envelopes of EMG signals in paired antagonist muscles in the left hands in two patient groups are compared. The patient groups are the same as in Figs. 1 and 4.*

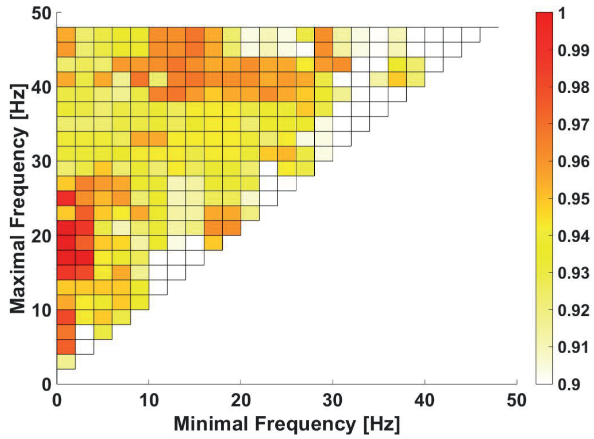

Fig. 6. *An example of a red frequency AUC-Drilling diagram. The envelopes of EMG signals in paired antagonist muscles in the right hands in two patient groups are compared. The patient groups are the same as in Fig. 2.*

(**Fig. 6**) and left (Fig. 4) hands of patients in the frequency range below 25 Hz have roughly the same shape. The difference in the red areas on the corresponding AUC diagrams (see Figs. 1 and 2) turned out to be only apparent. In particular, the large red area on the AUC diagram for the right hands of patients (Fig. 2, area B) stands out only because, in this frequency range, there are no blue solutions (see **Fig. 7,** area C).

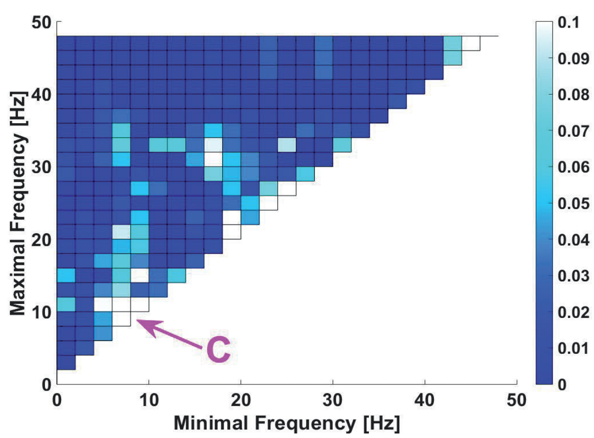

Fig. 7. *An example of a blue frequency AUC-Drilling diagram. The envelopes of EMG signals in paired antagonist muscles in the right hands in two patient groups are compared. The patient groups are the same as in Figs. 2 and 6. An area where blue solutions are absent is indicated by an arrow.*

The examples of AUC-Drilling diagrams discussed above allow us to hypothesize that the tremor in the left and right hands of patients with PD and ET is controlled by the same neurophysiological mechanisms, but the impact of these mechanisms occurs in different ratios, leading to different clinical presentations. This observation supports the conclusion that different algorithms need to be applied for diagnosing patients with PD with left-sided and right-sided onset [3].

3. ROBUSTNESS ASSESSMENT OF OPTIMIZATION PROBLEM SOLUTIONS

Robust solutions of an optimization problem are defined as points in the explored parameter space that possess a certain neighborhood in which the solution remains good in some sense [23-25]. As a quantitative assessment of the robustness of a solution, one can adopt the maximum radius R of a multidimensional ellipsoid (stability radius) surrounding the considered solution, inside which no "bad" solutions exist. In the context of this study, we consider "bad" solutions to be those in which the AUC value, compared to the AUC at the center of the ellipsoid, has approached the value of 0.5 by more than half. For instance, if a blue solution with an AUC value of 0.1 is considered, the quantitative assessment of the robustness of this solution would be the maximum radius of the ellipsoid within which AUC values do not exceed 0.1 + (0.5 - 0.1)/2 = 0.3. If a red solution with an AUC value of 0.9 is considered, the quantitative assessment of the robustness of this solution would be the maximum radius of the ellipsoid within which AUC values are not lower than 0.9 - (0.9 - 0.5)/2 = 0.7. Note that different coordinate axes in the wave train parameter space correspond to different units of measurement, so measuring the radius of the ellipsoid in absolute units does not make sense. We measure the radius of the ellipsoid in percentages of the ellipsoid's center coordinate values.

Unfortunately, the twelve-dimensional wave train parameter space does not have an analytical description, so the only tool available for assessing the robustness of blue and red solutions in the wave train parameter space is a computational experiment. As the neighborhood of the considered solution, models also must be applied.

Currently, we use the following model for the neighborhood of the optimization problem solution. The considered solution S is a point in the twelve-dimensional space and can be described by a vector of twelve coordinates $<S_1, ..., S_{12}>$. The model of the neighborhood (ellipsoid) with radius R of the solution S in the parameter space we call the set of all points P such that each coordinate P_i of the point differs from the corresponding coordinate S_i of the explored solution by a value of R or $-R$ (see **Fig. 8**).

It should be noted that the described ellipsoid model is only a crude approximation of the exact description of the set of points located in the neighborhood of the solution. However, the use of this simplified model allows for a significant reduction in the computational resources needed for conducting computational experiments while still providing a general understanding of the properties of the optimization problem solutions.

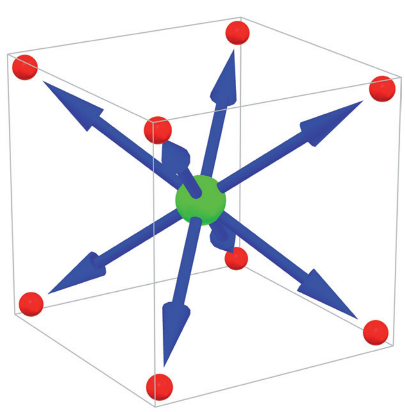

Fig. 8. *The model of the neighborhood (twelve-dimensional ellipsoid) of the optimization problem solution in the wave train parameter space. The figure shows only three dimensions of the ellipsoid.*

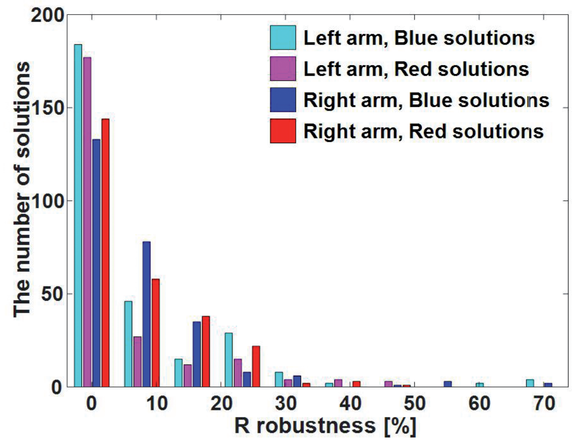

Fig. 9. *Histograms of quantitative R robustness assessments of optimization problem solutions during the construction of frequency AUC-Drilling diagrams comparing the EMG signal envelopes in paired antagonist muscles in patient groups with the first stage of PD and patients with ET.*

Fig. 9 presents histograms of the quantitative robustness assessments of the optimization problem solutions found during the construction of frequency AUC-Drilling diagrams, comparing the EMG signal envelopes in paired antagonist muscles in patient groups with the first stage of PD and patients with ET, as shown in Figs. 4-7. The histograms in Fig. 9 indicate that a significant number of solutions have robustness close to 0. This is even though the model of the multidimensional ellipsoid (Fig. 8) is inclined to overestimate the robustness assessments of solutions since it does not account for every point adjacent to the explored solution in the wave train parameter space. This means that the presence of "fragile" solutions, unfortunately, is one of the inherent properties of the wave train parameter space, and it must be taken into account when solving medical diagnostic problems.

One of the unique properties of the wave train parameter space is that each point in this space has a simple physical meaning, namely, the average number of Q_1 and Q_2 wave trains per second observed in the first and second signal samples respectively, whose parameters fall within the ranges corresponding to the considered point in the space. This opens opportunities for the development of new methods for assessing the robustness of optimization problem solutions, which are not based on the concept of "stability radius" and other geometric analogies.

As a measure of solution robustness, the authors proposed using the maximum average number of wave trains observed in the considered signal samples, $Q = \max(Q_1, Q_2)$. The idea of the Q robustness assessment is based on an empirical observation made while studying the wave train parameter space. It turned out that fragile solutions often arise at points in the space imposing strong restrictions on certain wave train parameters. In such points of the space, the number of observed wave trains decreases to a few wave trains in tens or even hundreds of seconds. As a consequence, the probability increases sharply that at this point in space, the ratio of the number of wave trains observed in the two analyzed signal samples can substantially change due to random fluctuations in the number of wave trains. As a result, we obtain a solution with a very good AUC value, close to 0 or 1, which stops "working" with the slightest change in parameter boundaries.

The study of the correlation between the robustness estimates Q and R based on experimental data confirmed that both assessments yield similar results (see **Fig. 10**). In particular, it was found that the Spearman's rank correlation between the Q and R estimates is 0.6-0.8 with a high level of significance ($p < 0.001$) when comparing both the right and left hands of patients, for both red and blue solutions of the optimization problem. Interestingly, a significant number of the solutions do not fit this regularity and demonstrate high R robustness scores with Q metric values close to zero (points located near the ordinate axis in Fig. 10). This indicates the potential risk of using the stability radius and similar geometric estimates, as they may not always identify potentially fragile solutions.

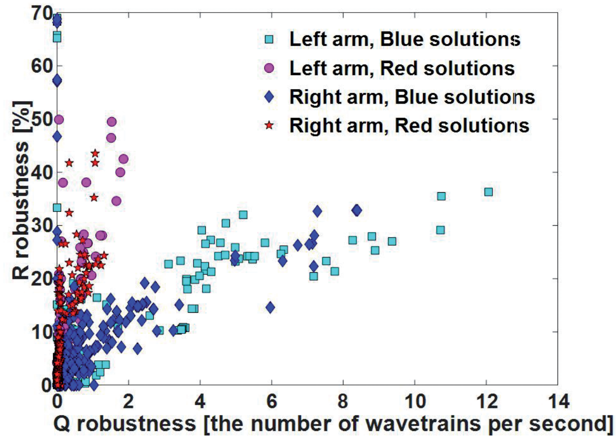

Fig. 10. *Correlation between robustness estimates Q and R for optimization problem solutions during the construction of frequency AUC-Drilling diagrams, comparing the EMG signal envelopes in paired antagonist muscles in patient groups with the first stage of PD and patients with ET.*

A significant advantage of the robustness estimate Q, compared to the R estimate, is its computational simplicity. Estimating the number of wave trains, whose parameter values fall within the considered intervals, is an intermediate step in calculating AUC, so any constraints on the Q value can be added to the optimization algorithm's objective function without additional computational costs. The situation with the robustness estimate R is quite different because an additional check of the solutions' neighborhood, assessed by the optimization algorithm, substantially increases the time to solve the optimization problem.

Currently, we apply a constraint on Q directly in the process of multidimensional drilling of the wave train parameter space, and then we perform an additional check of the robustness of the found solutions using the Q and R metrics. In particular, during the calculation of the AUC-Drilling diagrams presented in Figs. 4-7, an additional condition $Q \geq 0.5$ was applied. In the subsequent verification of the found solutions, restrictions on the AUC, Q, R, and other characteristics of the solutions can be established.

4. DISCUSSION

Experiments with clinical data have shown that using the method of multidimensional drilling of wave train parameter space, it is possible to compute several dozen or even hundreds of optimization solutions with high robustness suitable for clinical diagnostics of patients. A natural question arises: is there any reason to analyze such a large number of solutions? What benefit can be derived from them in studying the neurophysiological mechanisms of neurodegenerative diseases? Should all found solutions be used for clinical diagnostics, and what danger lies in the application of a large number of solutions? These questions are certainly subject to further research, but we can make some observations based on the experience of studying the clinical data of patients.

Typically, the set of solutions computed by the multidimensional drilling method is quite heterogeneous. Fig. 10 shows an example of a correlation matrix of 225 solutions, each characterized by a vector of 12 numbers representing the average number of wave trains per second observed in a patient with ET or a patient with the first stage of PD with onset in the left hand. In this example, only the red solutions are considered. As seen in **Fig. 11**, some solutions yield approximately similar results, while others yield completely different results. This means that combining some solutions can substantially increase the accuracy of patient diagnostics. However, combining solutions that are similar to each other can lead to overfitting of the diagnostic procedure, i.e., a very confident diagnosis of patients included in the training set and poor recognition of new patients.

Comparison of the number of wave trains satisfying different solutions allows researchers to assess the homogeneity of the patient sample, and clinicians to verify the diagnosis of individual patients. Let us consider an example of a correlation matrix of a patient group in **Fig. 12**. The correlation matrix vividly shows that patients diagnosed with PD differ from patients diagnosed with ET. However, in some cases, the EMG parameters of a patient may more closely resemble those of patients with a different diagnosis. Of course, this requires a careful reexamination of the patient's clinical data and possibly further analysis.

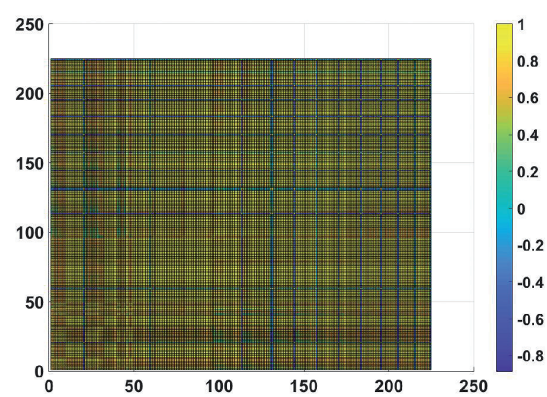

Fig. 11. *Correlation matrix of 225 optimization solutions obtained using the multidimensional drilling method in the wave train parameter space in patients with the first stage of PD with onset in the left hand (5 individuals) and patients with ET (7 individuals). Each solution is characterized by a vector of 12 values representing the average number of wave trains per second observed in the respective patient.*

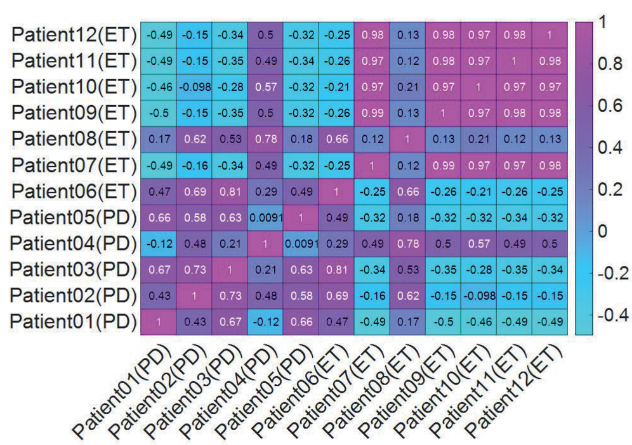

Fig. 12. *Correlation matrix of the patient group with PD and patients with ET, as considered in Figure 11. Each patient is characterized by a vector of 225 values of the average number of wave trains per second, satisfying certain 225 solutions of the optimization problem. The correlation matrix indicates, in particular, that the diagnosis of patient 6 needs to be reevaluated.*

5. CONCLUSIONS

The main idea of the method for analyzing wave train electrical activity lies in the statistical analysis and search for regularities in the parameters of local maxima (wave trains) identified in wavelet spectrograms of signals. The method is versatile and can be applied to investigate biomedical signals of various types, including EEG, EMG, and accelerometer signals.

AUC diagrams serve as the primary working tool of the wave train electrical activity analysis method. The new type of AUC diagrams described in the paper combines visualization tools for wave train parameters and automated search tools for regularities in the wave train parameter space. This statistical tool will be useful both for studying the neurophysiological mechanisms affecting the clinical condition of patients and for solving practical problems related to identifying diagnostic features of neurodegenerative disorders and developing diagnostic algorithms.

The issue of "fragile solutions" discovered during the investigation of clinical patient data has been addressed. Two fundamentally different approaches to assessing the robustness of solutions to the optimization problem, computed during the analysis of wave train parameter space, have been proposed. The first approach is based on calculating the stability radius of the investigated solution. The second approach is based on th physical meaning of the wave train parameter space. A comparison of robustness estimates of solutions to the optimization problem based on these two principles has been conducted.

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