An Application Supporting Gastroesophageal Multichannel Intraluminal Impedance-pH Analysis

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Abstract: Due to a significant rise in the number of patients diagnosed with diseases of the upper gastrointestinal tract and the high cost of treatment, there is a need to further research on one of the most popular diagnostic tests used in this case – esophageal Multichannel Intraluminal Impedance and pH measurement. This may lead to finding new diagnostically relevant information, used to quicken and improve the diagnostic procedure. The paper presents an algorithm used in a new computer application dedicated for researchers and physicians interested in research connected with Gastroesophageal impedance and pH data analysis. A possibility to modify a wide range of the algorithms parameters as well as rich set of the programs functions allows researchers to search for new criteria to assess the pH and impedance data when diagnosing diseases of the upper gastrointestinal tract. This, in turn, may lead to improving the time and accuracy of the MII-pH analysis which will substantially affect the patient's diagnosis time and treatment. Moreover, the diagnosing physician will be able to asses more tests, which is important, due to a significant rise in the number of patients seeking attention when speaking about the diseases of the upper gastrointestinal tract.

1 INTRODUCTION

The mechanism of gastric content regurgitation from the stomach to the esophagus is a physiological phenomenon which occurs naturally in the human circadian cycle (Yamada, 2006a; Porro, 2003). The anti-reflux barrier and the esophagus purification mechanism from hydrochloric acid (the so-called acid clearance) protect against excessive exposure of the esophagus tissues to the gastric material - mainly hydrochloric acid and pepsin. An undesirable situation occurs when, for various reasons, the physiological mechanisms of esophagus protection against acid fail. Given that the hydrochloric acid and pepsin are the most harmful upper gastrointestinal tract secretions and play an important role in the pathogenesis of erosive esophagitis (Porro, 2003), such a situation often leads to the onset and development of reflux disease of the upper GI (gastrointestinal) tract.

Gastroesophageal reflux disease - GERD is one of the most commonly diagnosed diseases of the upper gastrointestinal tract, especially among the inhabitants of developed countries (Yamada, 2006a; Segal et al., 2011; Tutuian et al., 2008). It is estimated that the symptoms occur at least once a month in 44% of adult Americans, approximately 20% of Europeans, 6.6% Japanese and Singaporeans and 3.5% of Koreans, whereas among the inhabitants of Africa and some Asian countries the disease is diagnosed very rarely (Yamada, 2006a). The impact on the occurrence and development of the disease is largely influenced by the lifestyle of people in the developed countries, including: type of diet, the use of stimulants (alcohol, coffee, smoking), or stress. In addition, the symptoms of GERD may increase as a result of misalignment during sleep or during increased physical activity (e.g. during exercise at the gym) (Yamada, 2006b).

Diseases of the upper gastrointestinal tract such as GERD or LPR - (laryngopharyngeal reflux) have troublesome symptoms which, if untreated, can lead to reduced quality of life, tissue lesions of the upper gastrointestinal tract and even, in extreme cases, be the source of neoplastic changes. The most common, troublesome symptom of the diseases is heartburn, often described as a burning sensation behind the breastbone, moving from the xiphoid in the direction of the mouth (Yamada, 2006a) or, in fever cases, the back (Yamada, 2006b). During the early stage of

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diagnosing the cause of the pain, this symptom may be erroneously associated with ischemic heart disease. An additional complication in the case of distinguishing between the diseases is that regurgitation into the esophagus causes, among other things, a reduction in blood flow in the coronary arteries. In addition, patients indicate a bitter or sweet taste in the mouth - a result of activation of the anti-acid defense mechanism in the esophagus - secretion by the salivary a fluid containing salts.

Another important symptom associated with the esophagus reflux diseases is chest pain, often described as tightness or burning occurring behind the sternum and radiating to the back, neck, jaw or arm, which may be incorrectly diagnosed as angina pectoris. Often, the pain intensifies after a meal or while under the influence of stress and often causes awakening from sleep. Typically an episode of pain, caused by a gastroesophageal reflux disease lasts from a few minutes to several hours and disappears spontaneously. Extensive research of the cause of pain did not give clear answers. It is considered that the cause of pain for patients with GERD is multifactorial and related to the concentration of H^+ ions, the volume of the gastric content, the duration of the reflux episodes and secondary spasm of the esophagus. Moreover, GERD is the third most common cause of chronic cough, after the symptoms associated with sinuses and asthma - it is estimated that reflux diseases causes approximately 20% of chronic cough cases. A co-occurrence of GERD in 80% of patients with asthma was observed.

Research also revealed a relationship between the reflux diseases of the upper gastrointestinal tract and diseases of the upper respiratory tract - in particular asthma.

Abnormalities associated with an increased number of reflux episodes may also be the cause of ailments and symptoms of laryngological changes, among which the most common are the reflux inflammation of laryngitis and also inflammation of the ear, nose and throat. It should also be noted that the growing number of patients who are diagnosed with GERD has a significant economic importance. In the U.S. alone, the annual cost of antacid medicine is estimated at 4-5 billion dollars (Yamada, 2006b).

Over the years many different methods for diagnosis of diseases of the upper gastrointestinal tract were developed, including invasive and non-destructive methods, with different values of specificity or accuracy. By far the most frequently used invasive method of diagnosing lesions associated with GERD and LPR is the measurement

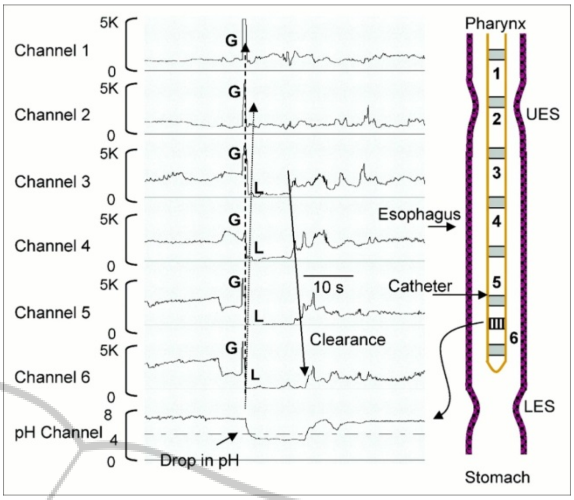

Figure 1: MII-pH exam overview (Tutuian and Castell, 2003).

of esophageal pH and, in recent years, the measurement of the impedance of the esophagus (Yamada, 2006a; Yamada, 2006b; Kahrilas, 2001; Lazarescu and Sifrim, 2008; Pritchett et al., 2009; Shay et al., 2001; Sifrim and Fornari, 2008; Sifrim et al., 2001; Smith et al., 1993; Villa and Vela, 2013). The two tests can be performed at the same time, which not only does not put on the patient any additional unpleasantness associated with the same technique but also allows to observe the recorded pH and impedance under the same conditions and time. An overview of the exam is shown in Figure 1.

The few existing computer programs to assist in diagnosing reflux disease - often being added as software to measuring devices, allow to display the results and perform simple analysis mainly pH and relatively rarely, impedance (Tutuian et al., 2008; Hila et al., 2007). Admittedly, this may affect the reduction of the analysis time, but the data provided by the software is not free from interpretation errors of algorithms, which's task is to search and determine reflux episodes. Thus, there is a need to develop such algorithms to support the analysis of pH - impedance, with the help of which the detection of reflux episodes is not only faster, but more reliable. Moreover, the developed algorithms can be applied in a variety of support systems helpful in diagnostics of the upper gastrointestinal tract, without the need to adapt them to the specificities of the software environment, which will highlight their use and application (e.g. after light modifications they can be used to study diseases of the upper digestive tract of animals).

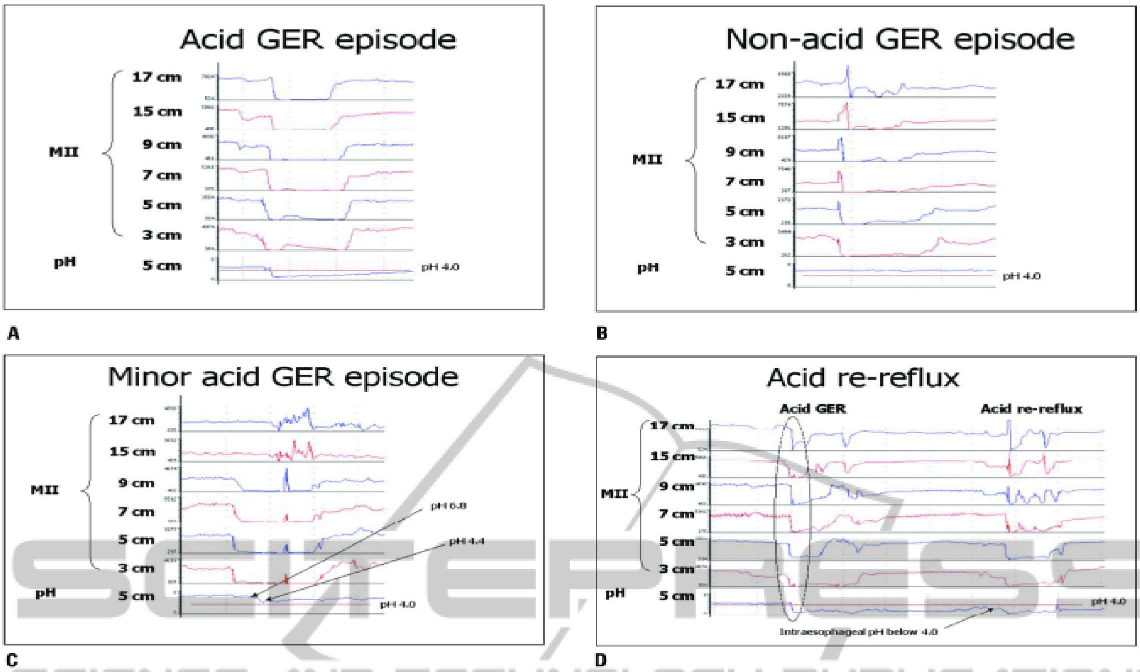

Figure 2: Types of reflux episodes (Tutuian and Castell, 2003).

2 IMPEDANCE ANALYSIS

Checking esophageal impedance changes in relation to pH allows to specify the type of registered reflux. Two types of reflux episodes are defined: due to the pH of content (acid reflux, non- acid, low acid and acid re-reflux) and due to the state of the content aggregation (liquid, gas or mixed reflux) (Tutuian et al., 2008; Tutuian and Castell, 2003). The differences in the recorded impedance courses for each type of the reflux are shown in Figure 2.

In the process of diagnosing GERD the most important is detecting liquid and mixed reflux episodes. The easiest to detect seem purely acidic episodes, in which the pH drops below 4 and a significant (over 50 %) increase in impedance values can be observed. Similarly, in the case of non-acidic episodes, the search includes only checking when the impedance increases significantly, while the pH remains above 4. It would seem that the low-acid episodes would be more difficult to detect, in which a significant increase of the impedance, but only a slight drop in pH (pH of about 1) can be observed. Due to the high degree of interference in the measurement it can prove to be difficult to determine the actual slight decreases in pH, which may cause to omit them during the process of analysis. Equally difficult to detect appears to the reflux episode, wherein not only the registered acid reflux episode can be observed, but also in a short time a drop in pH accompanying an increase in the impedance can also be seen.

The lack of clear mathematic criteria, on which it could be possible to automate the process of analyzing impedance results, forces the medical diagnosticians to rely on their own experience and subjective assessment of changes in the impedance. However, the correct interpretation of the test results may strongly influence the final diagnosis. It is estimated that the specificity of the test using only the pH results compared with the pH-impedance is 68% for pathological pH below 4, 67% for the positive coefficient of symptoms or 58% for both (Hila et al., 2007). Population-based studies suggest that the same pH tests related to the assessment of patients with gastroesophageal reflux disease suspicion is characterized by high sensitivity but relatively low specificity. In about 22% of cases this can lead to a misdiagnosis, qualifying healthy individuals as patients with GERD LPR.

3 MII-PH ANALYSIS ALGORITHM

In light of these facts, it seems appropriate to carry out such actions, tending not only to deepen the knowledge in the field of signal analysis of impedance and pH but also widespread the ability to conduct an analysis of these signals. To fulfill this demand, a computer system supporting the educational issues related to the analysis of pH-impedance signals was designed and developed.

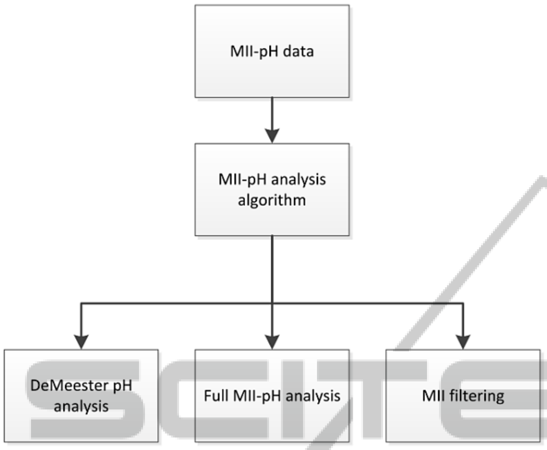

Figure 2: The developed system structure.

The system has a modular design (Figure 3), allowing the user to use only the functions of the program, which currently seem to be relevant for him. The modular structure has several advantages. The individual program modules operate in an independent manner, based solely on data provided by the MII-pH analysis algorithm so that it is possible, if necessary, to add or remove modules in the environment, in accordance with the wishes of the user who wants to use the program for a specific purpose. From the perspective of a programmer, the module design allows for a transparent distribution of the code, due to which the work on the same program may be carried simultaneously by a number of research teams, without the need for time-consuming exchange of data between them.

Each uploaded course is analyzed by the MII-pH algorithm, shown in the Figure 4. Depending on the needs, the user has three modes to his disposal: a simplified pH analysis, a full MII-pH analysis and the MII filtration mode.

A simplified pH analysis is dedicated to teaching and clinical solutions. In this situation the pH analysis is performed by applying the most popular scale for diagnosing GERD based on pH alone–the DeMeester scale shown in Table 1. In this procedure, the pH course is analyzed in reference to a certain pH threshold, a pH value of 4. Of course the user can set a different pH reference value, due to his needs. In this case, the MII-pH analyzing algorithm is used only to a limited extent.

Table 1: The DeMeester pH evaluation parameters.

no	Required Parameter
1	Number of reflux episodes (pH<threshold)
2	Number of long reflux episodes, lasting more than 5 minutes
3	Time of the longest reflux episode [min]
4	Time when pH values was under threshold in supine position [%]
5	Time when pH value was under threshold in upright position [%]
6	Total time when pH was under threshold [%]

As a result, the user receives complete information about the considered pH plot, as well as a preliminary suggestion from the analyzing algorithm whether the plot can be classified as normal or is it showing pathological signs. Additionally, in a legible manner, the pH plot along with the reference scale is shown, so that the user can intuitively verify the automatically generated data set based on his own experience to assess the course. Data obtained from the program in this module can be saved as a convenient-to-read text file type .doc

Another application module is a full MII-pH analysis. The user has the opportunity to explore interesting aspects of his impedance and pH courses having available a full range of the algorithm parameters that set the analyzing MII-pH methods. As a result, the algorithm identifies and selects the type of reflux episodes: Acid, Aon-acid and Acid Minor, according to the set analysis parameters. The test results are displayed on relevant graphical windows. Additionally, the user has the ability to perform statistical analysis of the MII-pH course, check the probabilities distribution of the measurement results, as well as individual episodes of reflux (eg by assigning the approximating function the characteristic values of a single reflux episode).

The last available module is the filtration of the MII-pH courses. In this case the user can check the uploaded course of the Hilbert transform, transformation into the frequency domain or Fourier filtering, both classical methods (filtration digital) and wavelet filtering.

As described above, the most important part of the program is the MII-pH analysis algorithm which is shown in Figure 4. The initialization of the algorithm includes initial upload: Dt - Drop threshold, It -Increase threshold, Pht - pH threshold, I(n) - impedance samples, pH(n) - pH samples. In the first step, the algorithm calculates the change in impedance between subsequent samples - I(k),

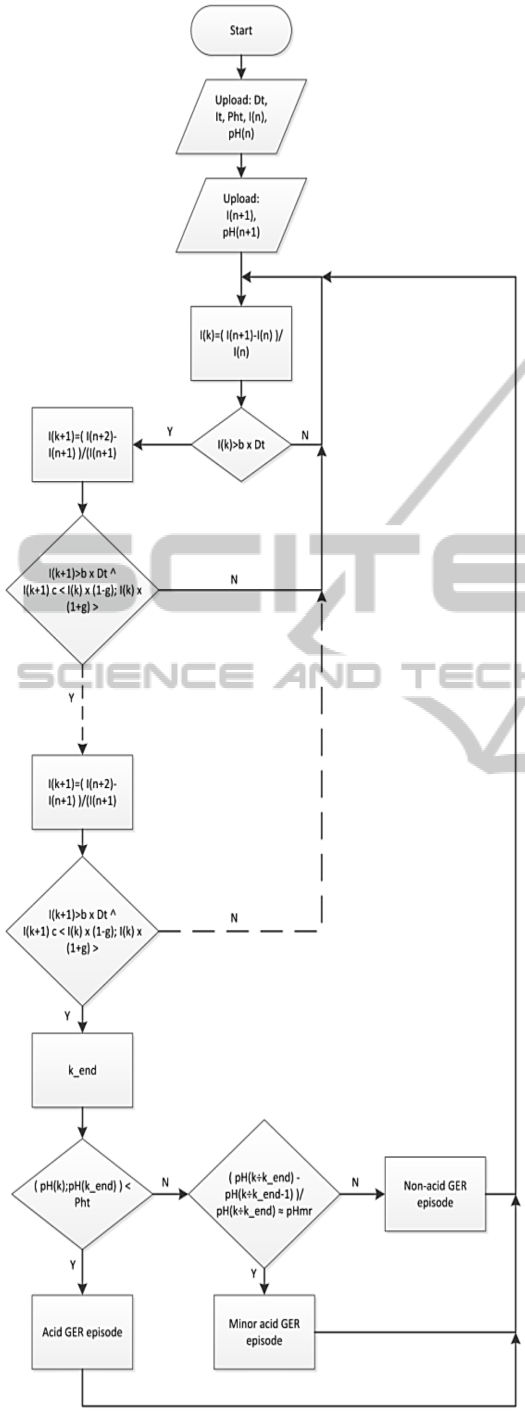

Figure 4: The algorithm simplified structure.

where k is the first sample of a series out of the tested data. The calculated change in relation to subsequent samples is compared with the impedance drop threshold multiplied by a rescaling parameter b. The b parameter specifies the percentage variation of the set threshold. If a threshold is set, for example, for an impedance drop at a 50% level and the b parameter is set to a 10 % level the resulting threshold will be counted as between 45% to 55 %. In the case where the change parameter - I(k) is not within the preset threshold range, the algorithm checks another pair of impedance samples. This situation is repeated until another pair impedances samples meet the set condition for the threshold impedance. In such a case, the k value is stored, the algorithm enters the detection of the impedance drop mode and continues the comparison. In further comparisons the algorithm calculates not only decreases of the impedance values pairs, but also checks whether the calculated decrease is included in the set between the previous I(k) value multiplied by a scaling coefficient g. By analogy as with the b coefficient, the user defining the g coefficient assumes the impedance drops fluctuation rate.

The diagnosis of whether the change of successive samples is indicative of an increase or decrease occurs by checking the sign of the calculated I(k). For a decrease the value is negative. When detecting a positive change, which lasts for a number of samples, the algorithm recognizes increase and a recovery from a reflux episode. In this case, the Dt parameter is replaced by the It parameter.

The algorithm computes the time of detection, the lack of inheritance and the end of growth. Consecutive samples, ranging from k until the last sample k_end which was marked as participating in the episode of reflux, are described as a reflux episode. In the last stage of the algorithm compares the value of pH in the range of k to k_end. Depending on the change in pH (below the threshold, above the threshold, or in the range of pH value decreased by more than 20%), the algorithm suggests the type of reflux, forwards and forgets the value of k to k_end the previous episode and continues to operate after the end of the previous episode. As a result, the algorithm generates the data spaces are found to reflux episode. Calculated data are forwarded in order to display the graph. The analysis takes place in all impedance channels.

The algorithm computes till it cannot detect any drops and when the increase period is over. The detected samples, ranging from k until the last sample which was marked ask_end are described as a reflux episode. In the last stage the algorithm compares the value of pH in the range of k to k_end to the value selected by the user (the default value is pH 4). Depending on the change in pH (whether it is below the threshold, above the threshold, or in the range when the pH value decreased by more than

Figure 5: Marked reflux episodes drops and rises.

20%), the algorithm suggests the type of reflux, forwards the data and forgets the value of k to k_end. This allows the algorithm to prepare itself to continue the search for reflux episodes, starting at the subsequent to the k_endsampe. As a result, the algorithm generates the data spaces in which reflux episodes were found.The calculated data are forwarded in order to display the graph.

4 RESULTS

Figure 5 shows an example of determination of reflux episodes as a threshold for accepting two different values: 50% drop and rise threshold and a situation when the drop threshold is set to 80% and rise threshold remained on a 50% level. The b and g algorithm parameters were set to 90%. As can be seen, in the case of a 50% impedance rise and drop threshold in a predetermined time interval, the implemented algorithm detected four short reflux episodes. Changing the drop threshold to 80% prevented the detection of previously observed episodes. Instead, the implemented algorithm detects only increases in the impedance values, which however, are not treated as reflux episodes. In the shown example in both cases the search algorithm was set to search for acid reflux episodes, and thus only when the pH value drops below 4 (e.g., in accordance with the procedure DeMeester).

Moreover, the analysis of the pH-impedance waveforms containing the denoted by the patient discomfort/painmarkers may lead to the determination of patterns of other phenomena related to diseases of the upper gastrointestinal tract, e.g., associated with the detection of the chest pain cause, as one of the GERD symptoms.

In the Figure 6 a change in the impedance graph along with a pain tag set by the patient can be seen. In two cases, a significant decrease in esophageal impedance, preceding the pain tag registered in all measurement channels can be seen. Comparing this observation with the pH reading it can be concluded that in the short time before the patient's sensation of pain, he experienced a minor acid reflux episode. Using the developed environment on aappropriate amount of data, the user is able to analyze cases of pH and impedance decrease or increasein reference to search for the cause of various types of pain. This in turn can lead to successfully relate to existing or develop new math standards and benchmarks to assist in assessing the disease in patients and to raise awareness of the possible causes of thoracic pain not related to a heart disease.

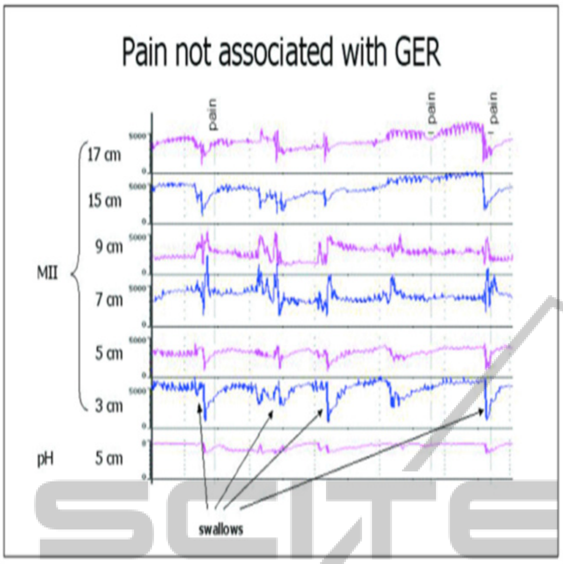

Figure 6: Pain markers in reflux episodes (Tutuian and Castell, 2003).

Examining the other measurement channels in the same time frame, it is also possible to evaluate to what extent of the esophagus the reflux episode took place. The developed system also has the ability to mark reflux episodes. Additionally, the system represents a selected fragment of the found episode according to user requirement (minimal, maximum values, beginning or end of an episode of reflux).

5 CONCLUSIONS

The available in the developed computer system tools allow to conduct research related to finding or modifying existing criteria for determining the types of gastroesophageal or laryngopharyngeal reflux episodes. Thanks to the possibility to determine a significant amount of coefficients and thresholds that characterize the pH and impedance analysis, the user has a wide range of possibilities to customize the research. Through research, experienced physicians and researchers, may try to develop new reference thresholds for esophageal impedance that would prove to be helpful in a more accurate interpretation of the medical diagnosis, relationships between symptoms of diseases of the upper gastrointestinal tract and the values of impedance and pH.

Research shows that the algorithm successfully marks acid reflux episodes, when using the standard DeMeester evaluation parameters. It also successfully enables the user to implement his own algorithm parameters, which in turn leads to establishing new conclusions regarding certain types of parameter values. It is particularly important since no such algorithms are available to use by research interested in improving their functioning. The programs that are used to evaluate MII-pH do not allow access to their computational methods. With the developed system researchers have the unique opportunity not only to use a tool ready for clinical use, but also to undergo research on their own, with the use of the algorithm. This, in turn, can allow to find new approaches to MII-pH data analysis in which previously omitted details will prove diagnostically important.

Further research aims at the extension of pH and impedance analysis capabilities by improving filtration of the waveforms using wavelet transforms. This will enable the possibility to compare the analysis results both in the original and filtered data, which in turn may lead to new discoveries in the regarded field.

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