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Multiparameter optical methods and instruments for the diagnostics of human body microcirculatory-tissue systems

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ABSTRACT

Multiparameter optical non-invasive diagnostics (mOND) combining several methods in a single device is one of the most promising technologies for studying human microcirculatory-tissue systems (MTS). This allows one to obtain highly efficient diagnostic tools for rheumatology, endocrinology, surgery, oncology, neurology, and other areas of medicine, as it is necessary to determine the parameters of the perfusion-metabolic status of tissues. However, there are a number of limitations related to its insufficient methodological and instrumental support. This work is devoted to systematizing of the relationship between the main parameters and states of MTS in various diseases and OND methods, as well as developing a formalized scheme for the synthesis of mOND methods. The aim was to substantiate and develop a methodology for mOND to assess the functional state of the MTS of the human body, and to demonstrate an example of mOND implementation in minimally invasive surgery. The results can be extended to other areas of medicine, for example, to improve these methods in rheumatology, endocrinology, otolaryngology, dermatology, neurology, etc.

Keywords: optical non-invasive diagnostics, multiparameter diagnostics, microcirculatory-tissue systems, laser Doppler flowmetry, fluorescence spectroscopy, diffuse reflectance spectroscopy, minimally invasive surgery

1. INTRODUCTION

In recent decades, the knowledge about tissue optical properties in healthy and pathological state has reached a sufficient level to develop and implement the methods of optical non-invasive diagnostics (OND) in clinical practice[1,2]. The most promising direction is the development of instruments based on the principles of multiparameter OND (mOND) and combining several methods in a single device[3,4]. Currently, the most widely used optical methods in clinical practice are laser Doppler flowmetry (LDF), fluorescence spectroscopy (FS), and diffuse reflectance spectroscopy (DRS), which are often applied together to improve diagnostic efficiency. The multiparameter approach allows clinicians to obtain *in vivo* values of individual physiological and biochemical parameters, as well as to conduct a comprehensive assessment of the viability of tissues in various organ systems, for example, microcirculatory-tissue systems (MTS)[5,6]. However, mOND methods have a number of unsolved problems. In particular, they have low reliability and methodological limitations associated with insufficient elaboration of instrumental and metrological support, which leads to the less efficiency of these technologies in clinical practice[7,8]. One of the possible ways to solve these problems may be to improve the methodological and instrumental support of this technology and, first of all, to develop a formalized scheme for the synthesis of mOND methods.

Thus, the aim of this work was to systematize the relationship between the main parameters and states of MTS in various diseases and the most widely used OND methods, to develop a formalized scheme for the synthesis of mOND methods, and to consider the example of this approach in minimally invasive surgery.

2. SYNTHESIS OF THE FORMALIZED SCHEME FOR MULTIPARAMETER OPTICAL DIAGNOSTICS

Based on extensive analysis of published data (e.g. [9–11]) the scheme (Fig. 1) was developed. It includes interrelations of the main parameters and conditions of the MTS (appropriate parameter changes are increase ↑, decrease ↓, or possible bidirectional changes ↑↓) in various diseases measured with widely used OND methods, allowing one to comprehensively diagnose several conditions by several jointly applied techniques.

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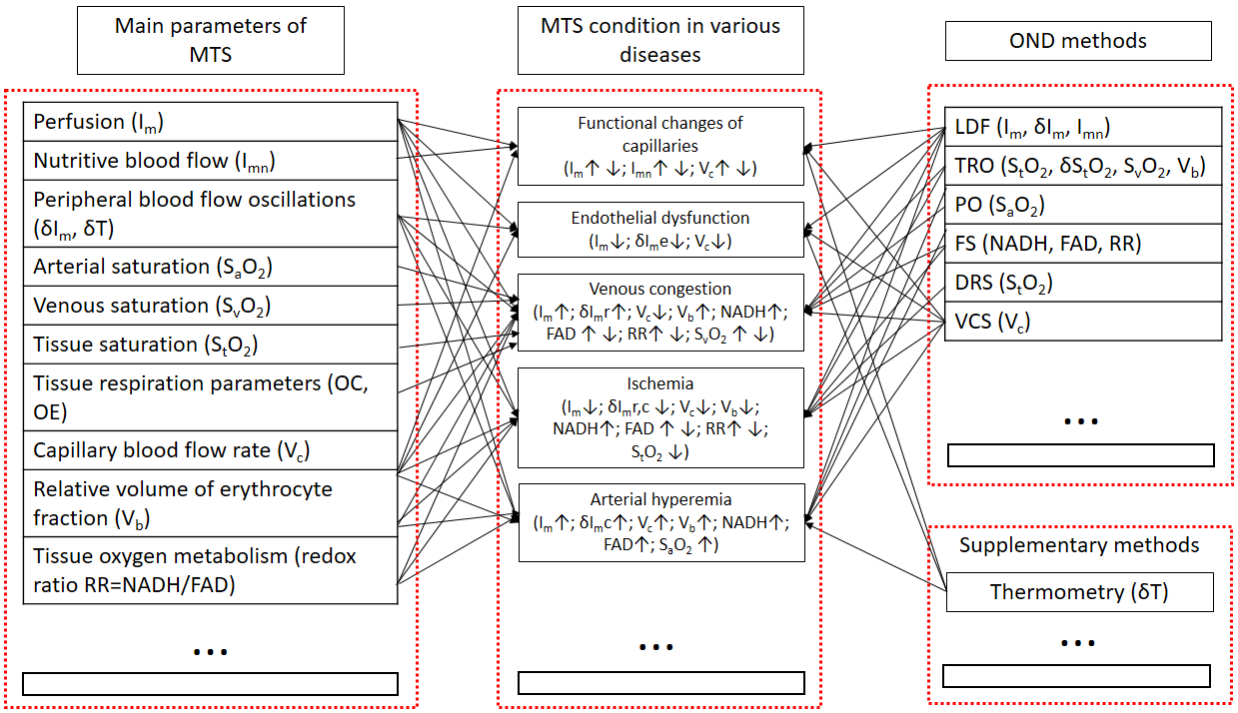

Figure 1. The scheme of relationships between the main parameters and states of MTS in various diseases and OND methods

LDF allows one to noninvasively study the hemodynamic parameters of peripheral blood flow. The application of FS and DRS methods complements the diagnosis with information about morphological and biochemical changes in tissues. DRS is also necessary for correcting fluorescence spectra in order to reduce the effect of absorption and scattering by tissue chromophores. Tissue reflectance oximetry (TRO) method evaluates the saturation of mixed blood to evaluate the dynamics of transport and oxygen consumption in MTS. This method also estimates the relative volume of the red blood cell fraction in the area of interest. The combined application of TRO and pulse oximetry (to assess arterial saturation) makes it possible to calculate the complex parameters of tissue respiration. The combined application of LDF and TRO methods with wavelet analysis of recorded signals makes it possible to evaluate the spectrum of rhythmic processes in the microcirculatory bed, as well as the dynamics and values of blood oxygen saturation. In addition, an approach based on a combination of OND and supplementary non-optical methods has been successfully applied recently. It allows one to systematically assess the functional state of MTS in various diseases, as well as to increase the informative value of diagnostic procedures by increasing sensitivity and specificity.

Thus, according to the developed scheme (Fig. 1), it is proposed to use the combinations of corresponding OND and non-optical methods depending on the research tasks. This approach allows one to register the necessary set of parameters to comprehensively assess the functional state of MTS.

To increase the informative value and accuracy and improve the methodology of mOND is the use of functional tests (FT) (for example, occlusion, cold, local heating and cold pressor tests). Thus, the combination of several complementary OND methods with simultaneous FT provides more valuable and reproducible diagnostic information for assessing the functional state of the MTS. In addition, the combined use of several OND methods provides the development of a composite diagnostic criterion (decision rule – DR) to classify the presence or absence of MTS violations with higher statistical indicators (sensitivity/specificity) compared to the separate OND methods.

Based on the analysis of relationships between the main parameters and states of MTS in various diseases and OND methods and the theory of system analysis in medical and biological practice, it is possible to synthesize a formalized scheme of mOND process. Widely used approaches to biotechnical systems synthesis [12] can serve as a theoretical basis for developing a methodology for the synthesis of mOND to assess the functional state of MTS. As a result, the

formalized scheme for the synthesis of mOND methods for evaluating the functional state of MTS (Fig. 2) was developed.

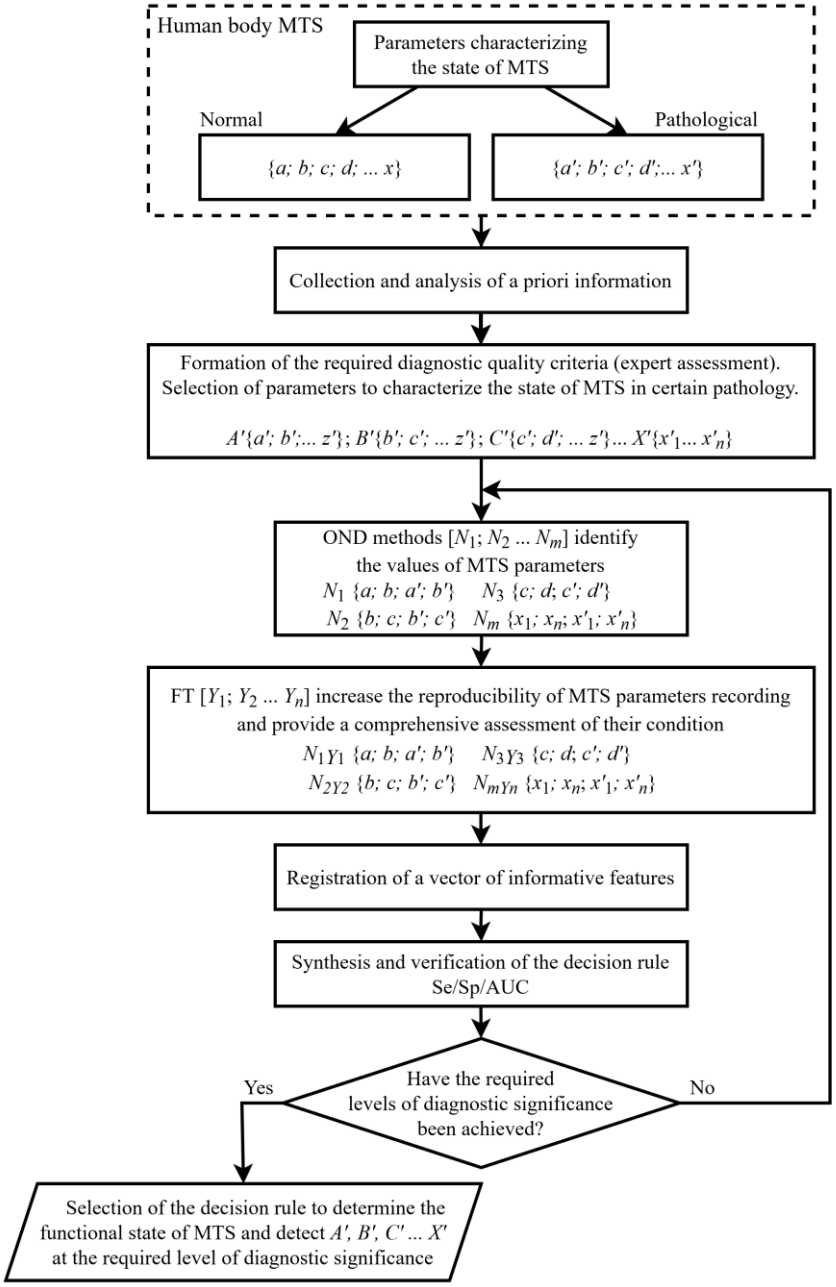

Figure 2. Formalized scheme for the synthesis of mOND methods for evaluating the functional state of MTS

Normally, human MTS are characterized by a number of parameters *{a;b;c;d;...x}* such as perfusion, saturation, nutritive blood flow, etc. The development of various pathologies leads to disorders of peripheral blood circulation and microcirculation (ischemia, venous stasis, etc.) described by a set of changed parameters *{a';b';c';d';...x'}*. Since each pathology is characterized by its own type of MTS disorders, after collecting and analyzing a priori information, the operator (doctor, researcher) selects several possible parameters that characterize MTS state in this particular pathology *A'{a';b';...z'}; B'{b';c';...z'}; C'{c';d';... z'}...X'{x'1...x'n}* and sets the required level of diagnostic quality. Based on the knowledge of the relationship between the main parameters of MTS and OND methods, a set of methods is selected *[N1;N2 ... Nm]* to provide the necessary diagnostic information *N1Y1{a;b;a';b'}; N2Y2{b';c';b';c'}; N3Y3{c;d;c';d'};*

$N_mY_n\{x_1;x_n;x'_1;x'_n\}$. In order to increase the reproducibility, the selection of FT $[Y_1;Y_2...Y_n]$ is made to ensure a comprehensive assessment of MTS state using OND methods: $N_1Y_1\{a;b;a';b'\}$; $N_2Y_2\{b';c';b';c'\}$; $N_3Y_3\{c;d;c';d'\}$; $N_mY_n\{x_1;x_n;x'_1;x'_n\}$.

After registering the vector of informative features for patients with the studied pathology and the control group of conditionally healthy volunteers, the synthesis and verification of the DR is performed with an assessment of the prognostic capabilities of the selected multiparametric approach: sensitivity (*Se*), specificity (*Sp*), area under the ROC curve (AUC). If the levels of diagnostic significance required by the expert are reached, then the DR to determine the MTS state in a specific pathology is considered satisfactory to be applied in clinical practice. Otherwise, it is necessary to select other combinations of OND methods to achieve the required level of diagnostic quality.

Thus, the developed methodology of the synthesis of mOND methods allows one to perform a comprehensive assessment of MTS functional state taking into account the specifics of medicine area (rheumatology, endocrinology, functional diagnostics, etc.) and the required level of diagnostic significance, which ultimately extends the application of OND in various fields of clinical practice and increases its reliability.

3. MULTIPARAMETER DIAGNOSTICS IMPLEMENTATION IN MINIMALLY INVASIVE SURGERY

One of the promising areas of mOND, which has been actively developed recently, is the assessment of perfusion and metabolic disorders of the hepatopancreatoduodenal organs[13]. Figure 3 shows an example of the developed functional diagram of a mOND device for evaluating perfusion and metabolic disorders in the tissues of abdominal organs, based on the methods of FS and LDF.

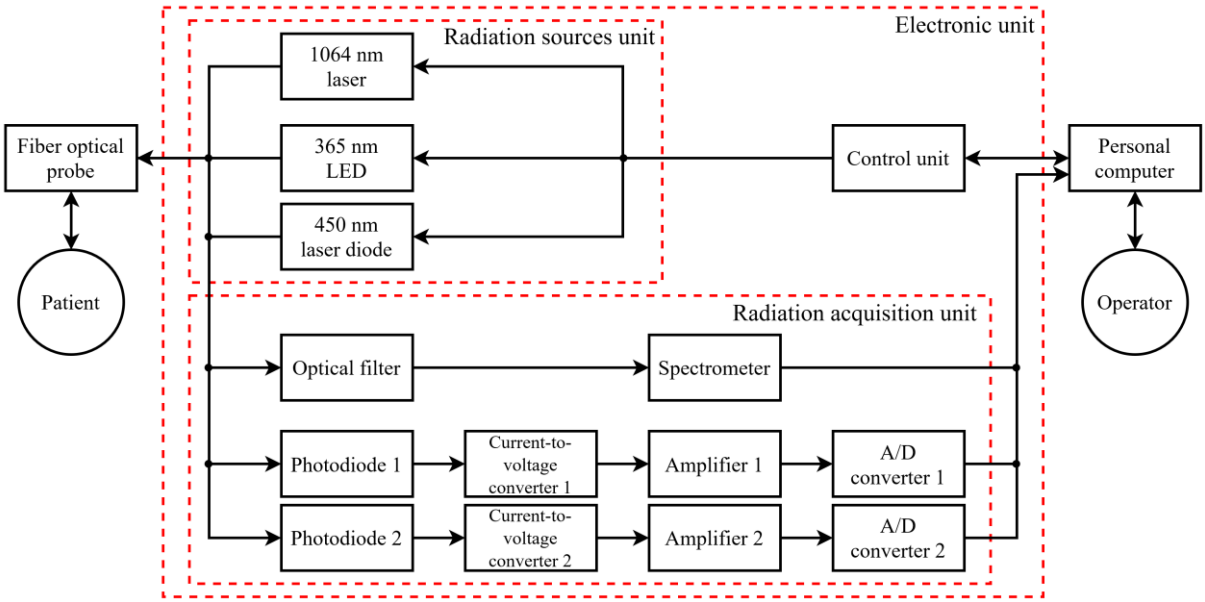

Figure 3. Functional diagram of the mOND device for assessment of perfusion-metabolic disorders in abdominal organs tissues

The LDF channel uses 1064 nm laser as the radiation source. Two identical channels are used to record LDF signal. They include photodiodes 1 and 2 as secondary optical radiation receivers, current-to-voltage converters 1 and 2, amplifiers 1 and 2, analog-digital converters 1 and 2 that transform an analog signal into a discrete one for further data transmission and processing. FS channel includes 365 nm LED and 450 nm laser diode to excite the fluorescence of NADH and FAD target fluorophores. To register the secondary radiation spectra, optical filters are used to attenuate the backscattered radiation of sources. The radiation is transmitted to the spectrometer with a CCD photodetector, the voltage from which is also amplified and converted into a digital signal using the built-in A/D converter.

An important feature of the proposed device is 30 cm laparoscopic fiber-optic probe (Fig. 4) with a diameter of 3 mm, specially designed to provide access to tissues through standard instruments for minimally invasive surgery. The probe

contains 6 optical fibers: 2 transmitting fibers (400 μm) for 365 and 450 nm sources, 1 transmitting fiber (6 μm) for 1064 nm laser, and 3 receiving fibers (400 μm) for the spectrometer and the photodiodes. The fibers' numerical aperture is NA=0.22. During measurements, light from the LDF and FS channel sources is transmitted along the corresponding optical fibers to the area of interest. Secondary radiation containing Doppler and fluorescence signals is transmitted along the receiving fibers to the corresponding photodetectors, converted into an electrical signal, amplified and digitized. The measurement channels are controlled by a field-programmable gate array connected via USB interface to the operator's PC, on which the recorded data is visualized and processed.

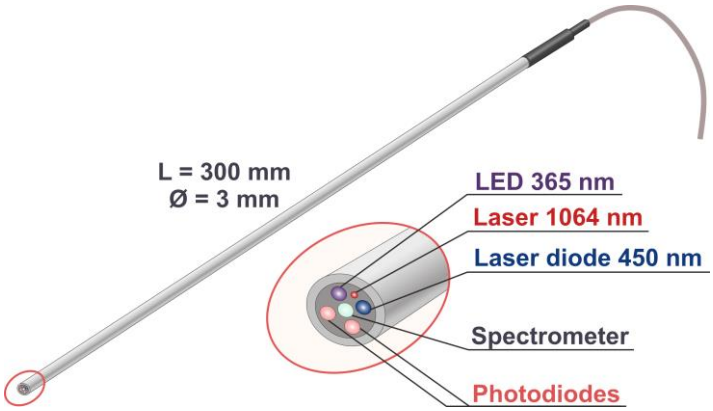

Figure 4. Fiber optic probe for multiparameter assessment of perfusion-metabolic disorders in abdominal organs tissues

Based on previous studies[13,14], a formalized scheme for evaluating the perfusion and metabolic status of tissues for intraoperative analysis in minimally invasive surgery was developed (Fig. 5). The developed method of mOND, based on the analysis of perfusion levels and fluorescence intensities, proves itself to be informative for detecting and localizing pathological changes in tissues, since it is very sensitive to the properties of the studied area and the nature of violations. The study of the parameters of MTS state and tissue viability (Fig. 1) simultaneously recorded with LDF and FS can be used for various abdominal diseases associated with inflammatory, malignant, necrotic, and other processes.

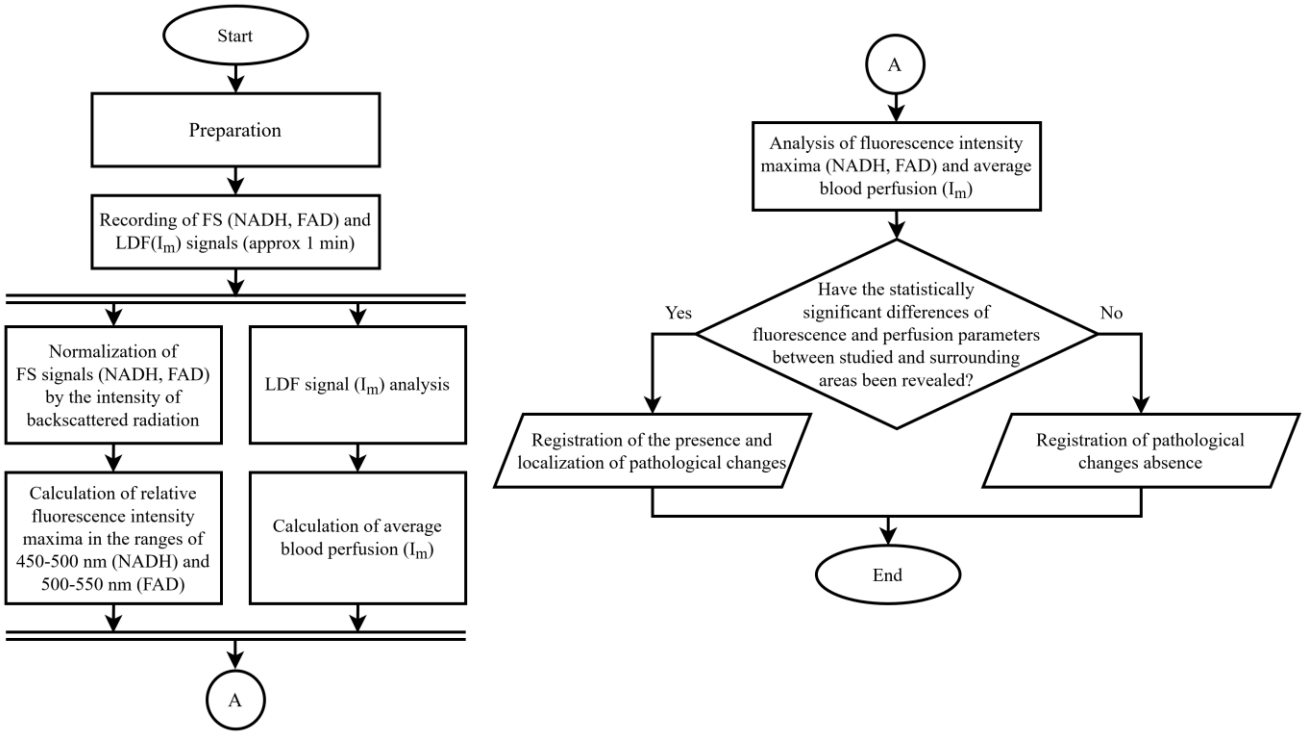

Figure 5. Formalized scheme for detecting the presence of pathological changes in the MTS of abdominal organs tissues

The proposed principle of mOND for minimally invasive surgery and the algorithm for detecting the presence of pathological changes in MTS are promising for evaluating perfusion and metabolic disorders in abdominal organs tissues.

4. CONCLUSION

Thus, the presented results demonstrate the relevance of improving the methodology and technical means of mOND for assessing the functional state of MTS. The proposed formalized scheme for the synthesis of mOND methods for assessing the functional state of MTS, as well as the example of implementing the device for minimally invasive surgery, based on the most common biophotonics methods of LDF and FS, increases the level of methodological and instrumental support for OND and, thereby, brings it closer to standardized diagnostic technologies for modern healthcare.

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