

Comparison of the capabilities of the frequency domain near infrared spectroscopy and electrical impedance rheography for solving diagnostic problems in surgery

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Among the diagnostic methods used in surgery, we can highlight time-resolved near infrared spectroscopy and electrical impedance rheography. Both methods are effective for local tissue probing at a specified depth. The optical method provides absolute estimates of tissue blood filling and allows the detection of neurovascular inclusions. In rheography, the measured value of the baseline impedance is used to assess blood flow dynamics and contact resistance. The aim of the study is to evaluate the comparability of both methods for analyzing the physiological dynamics of blood flow, for detecting neurovascular inclusions, and assessment of the feasibility of combined use of the methods in surgical diagnostics: in plastic surgery to assess the adequacy of blood supply to tissue flaps intra- and postoperatively, in cardiac surgery to assess the effectiveness of myocardial reperfusion intraoperatively, and in neurosurgery for intraoperative detection and identification of neurovascular inclusions in the volume of the tumor being removed. For experimental studies, a model of a combined small-sized fiber optic probe with a built-in tetrapolar electrode assembly was developed, and a commercial spectrometer and electrical impedance rheograph were used. Simultaneous in vivo measurements were performed on the hands of volunteers, experimental studies were carried out on homogeneous and heterogeneous gelatin phantoms, and numerical modeling of the detection of neurovascular inclusions by the frequency domain near infrared spectroscopy and electrical impedance rheography was performed. The results of preliminary studies revealed the potential of the electrical impedance method for recognizing neurovascular inclusions, as well as the limitations and prospects of the combined use of the methods for diagnosis in surgery.

Keywords: intraoperative diagnostics, time-resolved near infrared spectroscopy, neurovascular structures, electrical impedance rheography, multimodal measurements, numerical modeling.

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1. Introduction

There is a problem in neurosurgery with detection of neurovascular inclusions (NVI) in tumor tissue during tumor resection. Objective control of blood flow in reperfused tissues at intraoperative and/or postoperative stages is equally relevant in cardiosurgery for coronary artery bypass grafting (CABG) and in plastic surgery for skin grafting [1–5]. There are currently no universal approaches allowing for simultaneous detection of vessels and nerves in tissue. Existing techniques (ultrasound, trigger electromyography [6,7]) have limited selectivity and are hardly suitable for small operative field conditions. Standard control methods for CABG rely on ultrasound that provides information about blood flow velocity and volume in large vessels, but not in tissue at the microvascular level. There are no standard approaches and techniques for control of tissue flaps during and after grafting [1]. Tumors in the lower third of the skull can reach 6 cm in diameter [7], myocardial wall thickness varies from 1.5 mm to 17 mm [8], graft thickness is also variable from several millimeters to tens of millimeters [9], which necessitates subsurface probing.

Red and near infrared time-resolved spectroscopy in ranges from 650 nm to 900 nm (NIRS) holds promise for subsurface probing of biological tissues to a depth from several millimeters to several centimeters [10–14]. Frequency-domain (FD) NIRS or time-domain (TD) NIRS allows for measuring molar concentrations of oxyhemoglobin, deoxyhemoglobin and total hemoglobin, and local tissue oxygenation correlating to blood volume, blood flow velocity and oxygen consumption level in the test tissue volume. The characteristics of back-scattered within the tissue radiation are affected by both a molecular composition and structural features of tissues, including the presence of NVIs that differ in optical properties from the surrounding tissue. Possibility of detecting such NVI using the FD NIRS method has been confirmed theoretically and experimentally in previous studies [15], consideration of optical background properties of tissue is critical for identifying NVI. Important benefits of FD NIRS include the possibility of fabricating miniaturized flexible fiber-optical probes for specific applications [16], compatibility with various physical test methods.

For subsurface study of tissue composition and tissue blood flow, there are known electrical impedance spectroscopy methods (EIS) and electrical impedance rheography (EIR) methods [17]. EIR involves the measurement of

tissue's electrical impedance sensitive to tissue structure and blood content [18], which justifies the comparison between EIR and FD NIRS and study of combined use of EIR and FD NIRS for NVI detection and local tissue blood flow control. There are known examples of successful use of electrical impedance and optical approaches to assess the degree of postoperative brain edema [19], muscle mass in sarcopenia [20], quantitative differences in properties of normal and malignant cells [21] for biotissue composition analysis [22].

Regardless of the demonstrated capabilities of FD NIRS for detecting NVI, sensitivity to NVI of the EIR base impedance hasn't been studied before. Blood flow dynamics estimates obtained via FD NIRS and EIR haven't been compared as yet. Feasibility of adding electrical impedance measurements to FD NIRS during intraoperative and post-operative monitoring of tissues hasn't been studied.

The purpose of the study is to compare the capabilities of FD NIRS and EIR approaches for analyzing the physiological dynamics of blood flow on the basis on preliminary experimental studies and for detecting neurovascular inclusions, based on theoretical modeling and measurements on phantoms, as well as to evaluate the feasibility of their combined use.

Objectives of the study include the development of a combined fiber-optic probe with tetrapolar electrode assembly, preliminary in vivo measurements on biotissues for testing FD NIRS and EIR signal consistency during functional changes of functional changes in tissue blood supply, comparison of FD NIRS and EIR sensitivity to inclusions on prepared phantoms, evaluation of sensitivity to NVI on the basis of numerical simulation, feasibility study of using EIR together with FD NIRS.

2. Materials and methods

2.1. Experimental study

2.1.1. Equipment used Minimum hardware sets were chosen for the methods at the preliminary study stage. For EIR, one measurement channel with one probing current frequency and tetrapolar electrode assembly with a small electrode contact area was used. For FD NIRS, a measuring transducer with two wavelengths and a fiber-optic probe with two source–detector distances (SDD) were chosen. RheoCardioMonitor, a system used for clinical applications in the Russian Federation, was used to record impedance. 100 kHz AC current (with 0.5% accuracy) with an amplitude of 2.8 mA (with 20% accuracy) is applied to the external current electrodes. Base impedance (Z_b) and variable impedance component (ΔZ) with a sampling frequency of 200 Hz are measured simultaneously between the internal potential electrodes. The measurement range of Z_b is from 1 to 240 Ω with $\pm 0.2 \Omega$ accuracy. The measurement range of ΔZ is from 0.01 to 0.5 Ω , and the sensitivity is at least 0.5 m Ω . Optical measurements were performed using the OxiplexTS spectrometer (ISS, Inc., USA). The instrument

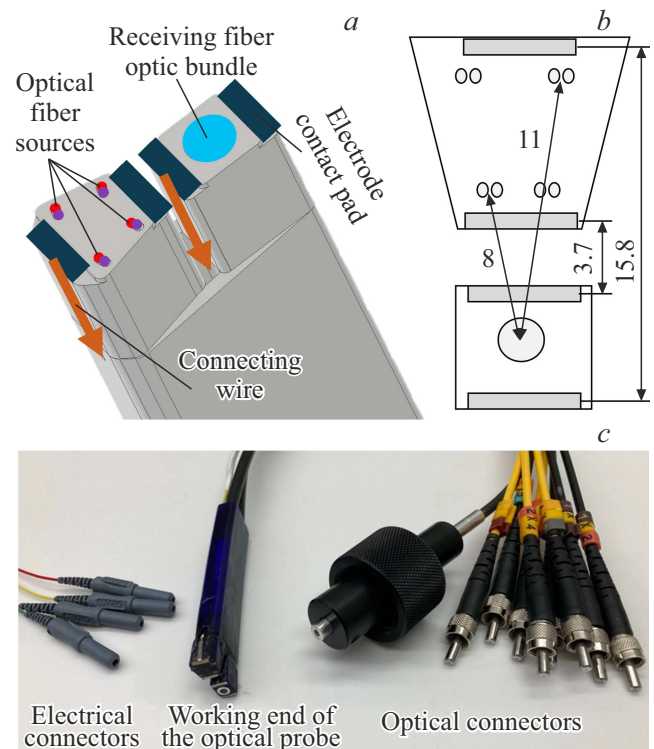


Figure 1. Combined probe for joint FD NIRS and EIR measurements: (a) combined probe assembly and optical fiber and electrode layout, (b) probe prototype dimensions, (c) combined probe prototype view.

employs a multi-distance frequency-domain approach, enabling the measurement of absolute values of optical and physiological parameters within the volume of biological tissue under study. The spectrometer has the following specifications. Probing radiation intensity modulation frequency is 110 MHz. Laser diodes with wavelengths of 684 nm and 828 nm are used as radiation sources and are combined in groups of two (one diode for each wavelength) at each distance from the detector. A photomultiplier tube (PMT) is used as a detector. Relative measurement error of the radiation intensity modulation amplitude (AC) and mean intensity level (DC) is $\pm 1\%$, and phase measurement error (Ph) is $\pm 0.1^\circ$. The instrument was calibrated on a standard ISS calibration block mimicking the optical properties of muscle tissue at 684 nm and 828 nm: $\mu_a(684 \text{ nm}) = 0.162 \text{ cm}^{-1}$, $\mu'_s(684 \text{ nm}) = 6.29 \text{ cm}^{-1}$, $\mu_a(828 \text{ nm}) = 0.163 \text{ cm}^{-1}$, $\mu'_s(828 \text{ nm}) = 5.70 \text{ cm}^{-1}$, where μ'_s is the reduced scattering coefficient.

To combine optical and electrical impedance measurements, the authors have developed a prototype of a compact optical probe. Configuration and dimensions of the probe are shown in Figure 1, a and 1, b. Combined probe (Figure 1, c) for optical and electrical measurements contains the following parts: a housing made from photopolymer resin on a 3D printer; stainless steel electrodes with a 3 mm² contact pad cut from a 0.3 mm steel sheet

using a laser cutting machine; multimode optical fibers (400/426/560A, NA=0.22) with the SMA905 optical connectors for connection to the spectrometer and radiation supply from the sources; 2 mm receiving glass fiber bundle (NA=0.5±0.005) in an aluminum sleeve of 4.8 mm in diameter and 75 mm in length in a special connector for connection to the spectrometer.

2.1.2. Test objects Preliminary experimental *in vivo* study involved transcutaneous measurements on right hands of two healthy volunteers in the radial artery projection area (Figure 2, *a*).

Gelatin-based phantoms were made to mimic simultaneously optical and electrical properties of biotissues; these included both homogeneous phantoms (Figure 2, *b*) and those with inclusions (Figure 2, *d, e*). Optical characteristics were formed by introducing milk powder and ink [14], while electrical properties were simulated by adding NaCl [23]. For the base mixture, mass concentrations of components relative to water were: 15% gelatin and 6.4% milk powder with a fat content of 26%. The mass concentrations of NaCl and ink relative to the mass of the mixture are given below. For the purpose of development and to evaluate whether combined phantoms can be formed, concentrations of ink and NaCl varied in a wide range. This made it possible to implement both background properties of biotissue and local vascular inclusions characterized by increased μ_a [15] and decreased resistivity ρ [24] compared to the surrounding medium. Figure 2, *c* shows dependences of ρ on NaCl concentration calculated [24] as follows

$$\rho = \frac{\pi}{2} \frac{Z_b}{\frac{1}{|L-s|} - \frac{1}{|L+s|}}, \quad (1)$$

where L is the distance between the current electrodes (mm), s is the distance between potential electrodes (mm), and dependences of μ'_s on ink concentration are presented on the same figure. Z_b , μ_a and μ'_s were measured using the chosen equipment.

Experimental data confirms that targeted and independent control of optical and electrical properties of phantoms is possible through composition variation. To mimic nonuniform cylindrical inclusion with different diameters (d) and depths (h), phantom molds had holes for bars with appropriate diameters to form cavities to be filled with the inclusion material, representing either vascular or neural tissue. To avoid the salt diffusion effect, the inclusions were filled with a material immediately before EIR measurements. The main mixture mimicking the background properties of biotissue was formed by adding 0.35% of NaCl and 0.015% of ink to the base mixture. Mixtures mimicking two different types of inclusions were formed as follows: 0.005% of ink was added to the base mixture and milk powder concentration was doubled to mimic a nerve, or 1% of NaCl and 0.4% of ink were added to mimic a vessel [15,24]. A total of 19 phantoms were prepared, including three homogeneous samples with optical and electrical properties corresponding

to the background, inclusion type 1 (I_1) and inclusion type 2 (I_2), four phantoms each with the variable diameter d and four phantoms each with the variable depth h for each of two types of inclusions. h was experimentally measured as a distance from the sample surface to the upper boundary of the inclusion.

2.1.3. Experimental test procedure For testing the sensitivity of FD NIRS and EIR to blood flow dynamics, *in vivo* measurements were performed on the right hand near the wrist in the radial artery projection region in two participants (Figure 2, *a*). Measurements were performed at rest, with arterial (40 s, 200 mmHg in the cuff) and venous occlusion (40 s, 100 mmHg in the cuff) followed by blood flow recovery. The probe was held by the participant's other hand. Measurements were synchronized through the auxiliary block of the OxiplexTS spectrometer and the rheograph's second channel.

To evaluate FD NIRS and EIR sensitivity to NVI, two measurements were performed for each of 16 phantoms with the inclusions, for which the probe was oriented parallel ($\parallel$) and perpendicular ($\perp$) to the inclusion axis. Three repeated measurements were performed for each of the homogeneous phantoms. Three repeated measurements were performed for each of the homogeneous phantoms characterized by the background properties and properties of inclusions I_1 and I_2 . There are two optical SDD lines in the combined probe. For further evaluation of inclusion detectability measurements shall be performed with one of the lines strictly parallel or perpendicular to the inclusion axis. Taking into account that the EIR mathematical model shall be verified using the measured data, it was decided to first perform electrical impedance measurements and then optical measurements on the fabricated test objects. For all experiments on phantoms, the probe was fixed on a laboratory stand to ensure repeatability of the measurements.

2.1.4. Measured data processing Based on impedance measurements, increase in blood volume ΔV_r (ml) within the probed tissue volume is determined [25] using the main rheographic equation as follows

$$\Delta V_r = -k \frac{\Delta Z \rho s^2}{Z_b^2}. \quad (2)$$

Here, k is the dimensionless correction factor which takes into account that the test region contains bone tissues with a constant volume and/or takes into account the characteristics of the shape of the probed tissue volume, $k = 0.80 \dots 0.95$ [25]; Z_b is the base impedance of the test tissue volume (Ω); ΔZ is the impedance variation relative to Z_b due to the difference between blood inflow and outflow to/from the test segment (Ω); ρ is the resistivity of blood ($\Omega \cdot \text{cm}$). ΔZ is calculated as $\Delta Z(t) = Z_b(t) - Z_b(t_0)$, where t is the time from the initial time t_0 . In further

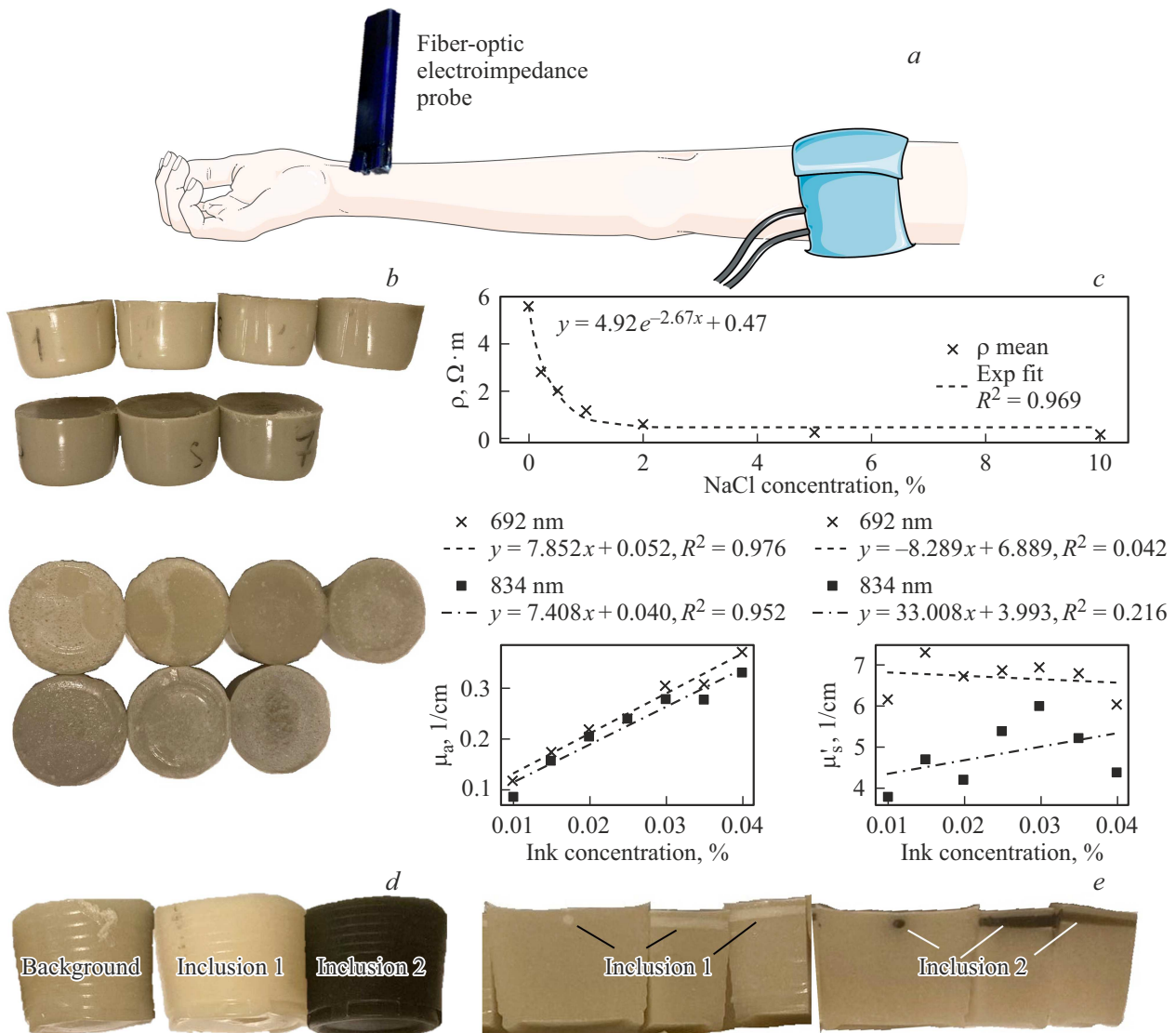


Figure 2. Experimental test objects: (a) *in vivo* measurements on a hand (graphical images in (a) are provided by Servier Medical Art (<https://smart.servier.com>), license CC BY 4.0), (b) homogeneous phantoms for analysis and selection of properties, (c) measured electrical and optical properties of uniform phantoms, (d) homogeneous phantoms with selected properties, (e) phantoms with inclusions.

calculations, k varied in the specified range to avoid the bias, $\rho = 135 \Omega \cdot cm$ [26].

According to the FD NIRS data, increase in blood volume ΔV_s (ml) is calculated [27] as

$$\Delta V_s = \frac{\Delta[HbT] \times MWHb}{HGB \times F} V_{pr}. \quad (3)$$

Here, $\Delta[HbT] = [HbT](t) - [HbT](t_0)$ is the time variation of the total hemoglobin concentration in the probed tissue volume relative to the concentration at t_0 ($\mu M = \mu mol/l$), $MWHb$ is the molecular weight of hemoglobin ($g/\mu mol$), HGB is the hemoglobin concentration in large vessel blood (g/l), F is the Fahraeus factor defined as the ratio of hematocrit in small vessels to hematocrit in large vessels, V_{pr} is the tissue volume probed by FD NIRS (ml). For further evaluations, the following values were taken:

$MWHb = 0.0645 g/\mu mol$, the HGB concentration took on values from the physiological range from 120 to 160 g/l to avoid the bias, F was taken equal to 1 because experimental measurements were performed in a large artery projection region. Probed tissue volume V_{pr} was estimated using numerical simulation of photon distribution in medium with optical properties detected on the wrist during preliminary measurements: $\mu_a(684 nm) = 0.183 cm^{-1}$, $\mu'_s(684 nm) = 11.81 cm^{-1}$, $\mu_a(828 nm) = 0.228 cm^{-1}$, $\mu'_s(828 nm) = 9.25 cm^{-1}$. MATLAB NIRFASTER software package was used for evaluation [28,29]. Probe dimensions are shown in Figure 1, b , $SDD=8 mm$, which corresponds to the minimum SDD of the combined probe. Threshold for Jacobian ($\ln(AC)/\mu_a$) was taken equal to 1%, which is defined by the relative measurement error of OxiplexTS.

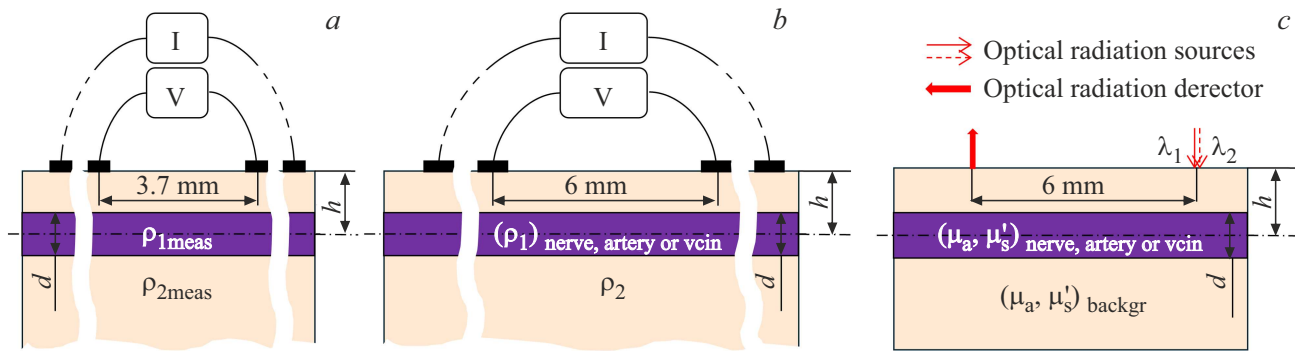


Figure 3. Configurations for mathematical simulation: (a) for comparison with measurements by the combined probe, (b) for simulation of EIR sensitivity to NVI, (c) for simulation of FD NIRS sensitivity to NVI.

Calculated probed volume for hand tissues in the wrist was $V_{pr} = 1.38$ ml.

To evaluate $\Delta[HbT]$ and calculate ΔV_s by (3), the modified Bouguer-Lambert-Beer (BLB) law was used [14]. Calculations were performed only for smaller SDD = 8 mm for higher comparability with the EIR measurements at $s = 3.7$ mm. Mean dimensionless differential pathlength factors (DPF) [14] of photons in high-scattering medium for each of two probing radiation wavelengths were evaluated [30] for the initial period of optical signal detection at rest as $\frac{1}{2} \sqrt{\frac{3\mu_s'}{\mu_a}}$, using the measured absolute values of μ_a and μ_s' . Calculated values for the first participant were $DPF(684 \text{ nm}) = 8.0$, $DPF(828 \text{ nm}) = 7.0$; calculated values for the second participant were $DPF(684 \text{ nm}) = 8.8$, $DPF(828 \text{ nm}) = 8.0$. For calculations of $\Delta[HbT]$ with respect to $\Delta\mu_a$, the following molar extinction coefficients were taken at 684 nm and 828 nm, respectively: for oxyhemoglobin — 0.9560 and $2.33 \mu\text{M}/\text{cm}$, for deoxyhemoglobin — 4.9 and $1.79 \mu\text{M}/\text{cm}$.

2.2. Mathematical simulation

The study used numerical simulation to compare the ability of each of the two methods, EIR and FD NIRS, to detect NVI independently. Simulation made it possible to study a wide range of combinations of optical and electrical properties of tissues and NVI, their sizes and depths, which is substantially hindered when physical phantoms and biotissues are used. Configuration of models was chosen for intraoperative detection of neurovascular structures in endoscopic endonasal surgery for skull base tumors such as pituitary adenoma and other chiasm-sellar tumors [7]. Tumor tissue in this case generally has a glandular or adenomatous structure consisting of repetitive functional units and can be treated as quasi-homogeneous. Semi-infinite medium assumption for the model is justified, as tumor dimensions of several centimeters [7] are much greater than the effective probing depth. NVI are the subjects for detection when they are included in the

investigated tissue volume under the probe for layer-by-layer tumor removal.

Rheographic approach used a mathematical model of semi-infinite conducting medium mimicking the soft tissues of limb with NVI in the form of a cylinder (Figure 3, a, b) corresponding to a nerve, artery or vein [26]. Such model was used to determine the effect of NVI on the measured impedance.

Measured impedance of a medium volume with NVI [26] was evaluated as follows:

$$Z = Z_b \left(1 + 8 \sum_{n=1}^{\infty} \frac{\beta^n \gamma^{2n}}{(1 + \gamma^{2n})^2} \frac{1 - \left(\frac{r}{h}\right)^2}{1 - \left(\frac{r}{h}\right)^2 + \left(\frac{1 - \gamma^{2n}}{1 + \gamma^{2n}}\right) \left(\frac{l}{h}\right)^2} \right). \quad (4)$$

Here, Z_b is the measured base impedance at distance between the potential electrodes s and between the current electrodes L ; r is the NVI radius; h is the NVI depth (Figure 3); γ is the vessel radius function defined by

$$\gamma = \frac{h}{r} - \sqrt{\left(\frac{h}{r}\right)^2 - 1},$$

β is a function of tissue resistivity according to the relationship to $\beta = \frac{\rho_1 - \rho_2}{\rho_1 + \rho_2}$, where ρ_1 is the resistivity of NVI; ρ_2 is the resistivity of soft tissues calculated using equation (1); $\Delta Z(t) = Z_b(t) - Z_b(t_0)$, t is the time from t_0 . Mean $Z_b = 47.5 \Omega$ was previously measured on the wrist with $s = 3.7$ mm and $L = 15.8$ mm. $\rho_2 = 2379 \Omega \cdot \text{mm}$ calculated using equation (1) for soft tissues. Then, $Z_b = 85.1 \Omega$ with $s = 6.0$ mm and $L = 15.8$ mm according to equation (1). NVI properties for calculation were taken as follows: $\rho = 10000 \Omega \cdot \text{mm}$ for a nerve (as for the specific resistivity of brain tissues [24]), $\rho_1 = 1000 \Omega \cdot \text{mm}$ for an artery and $\rho_1 = 1350 \Omega \cdot \text{mm}$ for a vein [26]. Lower resistance of an artery compared with a vein is due to orientation effects of erythrocytes in blood flow [26].

This model used for the first time to detect NVI in tissue requires validation of the used assumptions. For model verification, numerical simulation (Figure 3, a) was

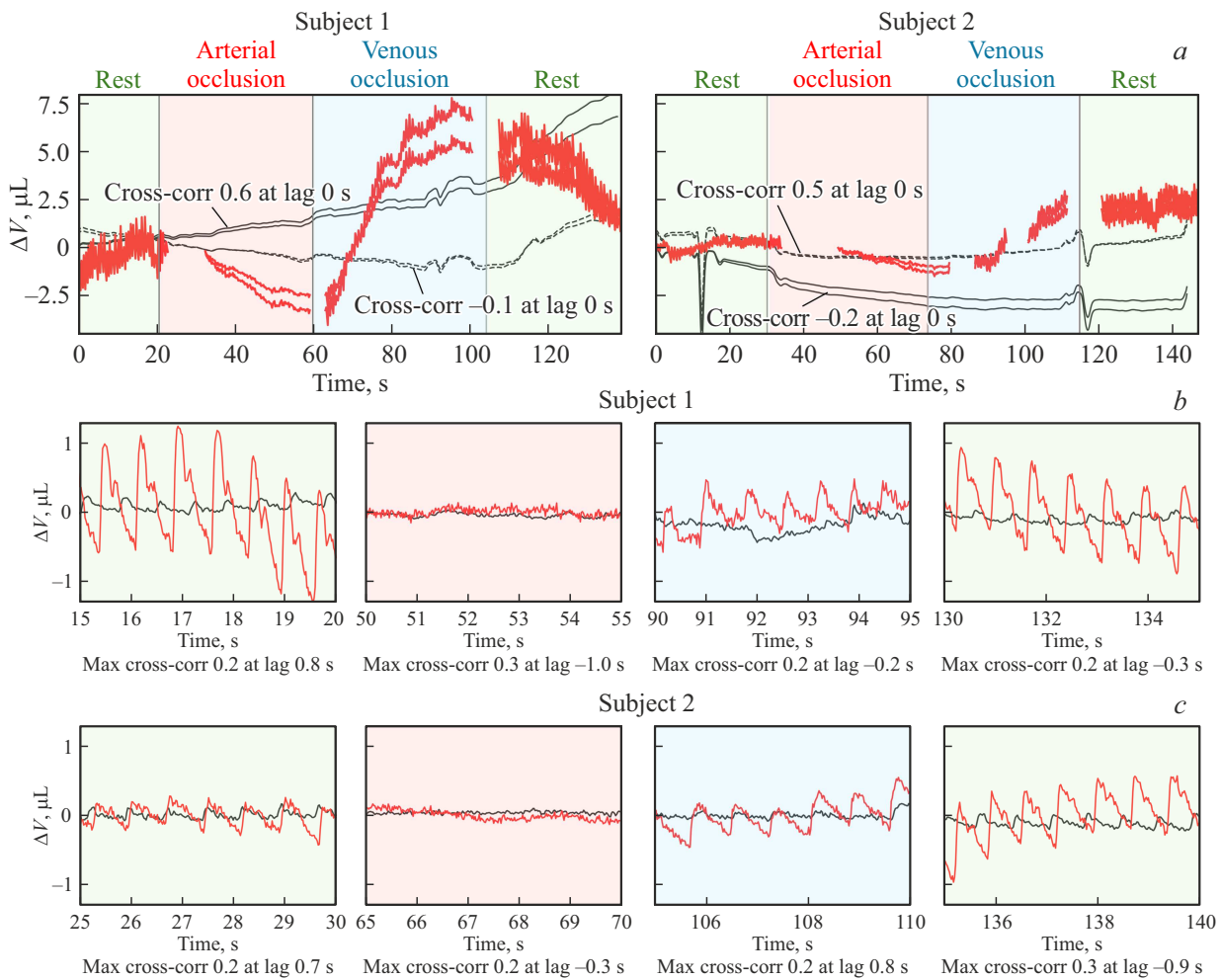


Figure 4. *In vivo* measurements (two healthy participants) with arterial and venous occlusions: (a) occlusive changes in blood volume at $k = 0.8$ and 0.95 , $HGB = 120$ and 160 g/l ; (b) pulse changes in blood volume at $k = 1$, $HGB = 150 \text{ g/l}$. ΔV_s are marked in red, ΔV_r are marked in black (thin solid line — recorded data with trend, dashed line — recorded data without trend).

performed using combined probe dimensions (Figure 2, b) and optical and electrical properties of the gelatin phantoms (Figure 1, c, d), which allowed for direct comparison between the simulation data and experimental measurements. For correct comparison between FD NIRS (Figure 3, c) and EIR (Figure 3, b), identical dimensions of the measuring system were used: SDD — for FD NIRS and s — for EIR, which is critical for intraoperative applications with endonasal access where probe dimensions are strictly limited. Tetrapolar electrode assembly, two wavelength radiation sources and optical radiation detector were placed above and along NVI (Figure 3). The distance set to 6 mm corresponds to small dimensions of the operative field and it is a compromise between minimization of the probe dimensions and FD NIRS applicability restrictions [31].

FD NIRS simulation was conducted using NIRFASTER as described in [15]. AC and Ph components of signals at wavelengths of 684 nm and 828 nm corresponding to the specifications of the OxiplexTS spectrometer employed

for measurements were calculated. DC wasn't evaluated because intraoperative application was impossible due to the sensitivity of the parameter to ambient light. The model used optical properties of the participant's wrist tissues detected experimentally, rather than optical properties of an unknown tumor: $\mu_a(684\text{nm}) = 0.183 \text{ cm}^{-1}$, $\mu'_s(684\text{nm}) = 11.81 \text{ cm}^{-1}$, $\mu_a(828\text{nm}) = 0.228 \text{ cm}^{-1}$, $\mu'_s(828\text{nm}) = 9.25 \text{ cm}^{-1}$, which wouldn't affect the community of conclusions. Optical properties of NVI corresponded to the properties for a nerve CN1, artery A1 and vein V1 from [15].

Threshold of sensitivity to inclusions of each of the methods was evaluated by the signal difference between cases with and without NVI (no inclusion, NoI). Signal difference ($|\Delta Z|$, $|\Delta AC|$, $|\Delta Ph|$) exceeding the resolution of measuring transducers was used as a criterion. For $|\Delta Z|$, the threshold is 0.2Ω . For $|\Delta AC|$, the threshold was chosen equal to 0.0001, assuming that an avalanche photodiode was used as a radiation detector [15]. For $|\Delta Ph|$, a threshold was set to 0.1° . The proposed approach to NVI simulation and

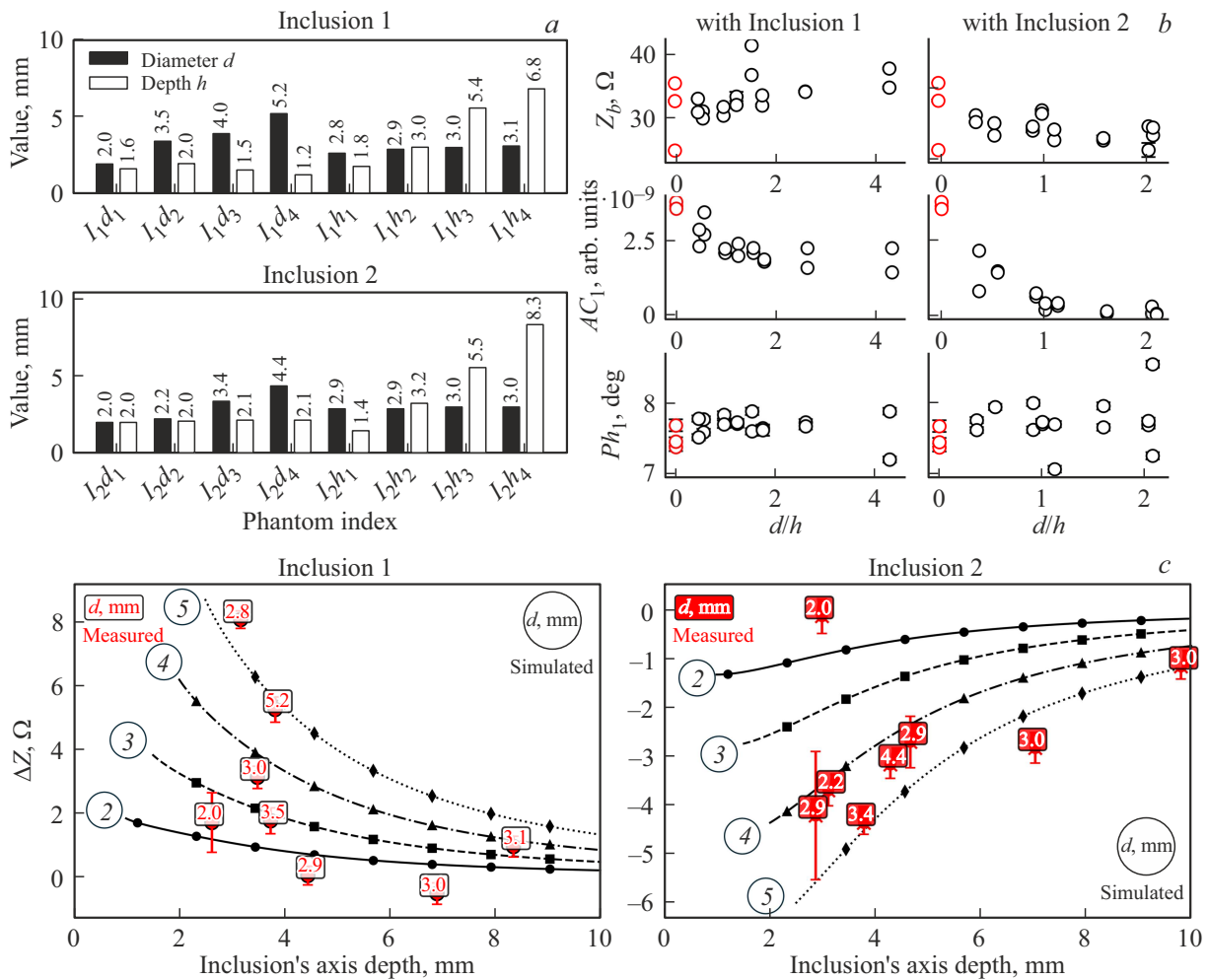


Figure 5. Measured and simulated data for gelatin phantoms: (a) geometric parameters of inhomogeneous phantoms, (b) measured Z_b , AC and Ph , (c) comparison of simulated and measured data for phantoms with inclusions I_1 , I_2 .

identification in tissue makes it possible to determine the minimum sizes and depth of NVI with which both methods can reliably detect NVI.

3. Results

3.1. Experimental study

Figure 4, *a, b* shows ΔV_r , ΔV_s calculated for blood volume changes caused by occlusions and pulsatile blood filling in the projection area of the radial artery of two healthy subjects. Influence of slow polarization in EIR was eliminated by removal of a linear trend from base impedance signals. FD NIRS signal segments with „spike“ type motion artefacts [32] were removed, to remove the „step“ type artefacts [32] a part of signal was transferred to the corresponding spike value. Computer-assisted approaches to artefact removal are described in [32]. Analysis used a signal cross-correlation coefficient normalized to the length and standard deviation, while maximum cross-correlation

was considered for short segments due to the absence of reliable signal synchronization.

Figure 5, *a* shows phantom geometric parameters. For 19 phantoms described in Section 2.1, Z_b , AC and Ph were measured at two distances and two wavelengths: AC_1 and Ph_1 at $r = 0.8$ cm, $\lambda = 684$ nm; AC_2 and Ph_2 at $r = 0.8$ cm, $\lambda = 828$ nm; AC_3 and Ph_3 at $r = 1.1$ cm, $\lambda = 684$ nm; AC_4 and Ph_4 at $r = 1.1$ cm, $\lambda = 828$ nm (Figure 5, *b*). Optical properties ($\pm$ RMS error) of gelatin phantoms:

– (background mixture)

$$\begin{aligned}\mu_a(684 \text{ nm}) &= 0.094 \pm 0.005 \text{ cm}^{-1}, \\ \mu'_s(684 \text{ nm}) &= 2.17 \pm 0.07 \text{ cm}^{-1}, \\ \mu_a(828 \text{ nm}) &= 0.078 \pm 0.005 \text{ cm}^{-1}, \\ \mu'_s(828 \text{ nm}) &= 1.37 \pm 0.09 \text{ cm}^{-1};\end{aligned}$$

– (inclusion I_1)

$$\begin{aligned}\mu_a(684 \text{ nm}) &= 0.070 \pm 0.003 \text{ cm}^{-1}, \\ \mu'_s(684 \text{ nm}) &= 5.23 \pm 0.27 \text{ cm}^{-1}, \\ \mu_a(828 \text{ nm}) &= 0.068 \pm 0.006 \text{ cm}^{-1}, \\ \mu'_s(828 \text{ nm}) &= 3.76 \pm 0.30 \text{ cm}^{-1};\end{aligned}$$

– (inclusion I_2) cannot be measured using the OxiplexTS due to strong absorption of phantom, because μ_a is comparable with μ'_s , the main condition of diffusion approximation $\mu_a \ll \mu'_s$ underlying the measurements is not met [14].

Figure 5, *c* shows comparison between phantom measurements and numerical simulation performed using combined probe dimensions and electrical properties of gelatin phantoms.

Shapiro–Wilk test (SWT) showed that Z_b distributions of homogeneous phantoms (background) and inhomogeneous phantoms with inclusions I_1 and I_2 were not normal ($p < 0.001$). Kruskal–Wallis test (KWT) identified statistically significant differences between groups ($p < 0.001$), and Mann–Whitney test (MWT) confirmed the significance of differences ($p < 0.001$) in all pairwise comparisons (NoI vs I_1 ; NoI vs I_2 ; I_1 vs I_2) [33]. For all AC and half of Ph , SWT showed departure from normality ($p < 0.05$). KWT identified significant differences in AC ($p < 0.001$) between the groups, which was confirmed by MWT for all pairwise comparisons ($p < 0.05$). For Ph_1 and Ph_3 , KWT didn't identify any significant differences between ($p > 0.1$), while for Ph_2 and Ph_4 , significant differences between groups were identified ($p < 0.001$) and confirmed by the MWT pairwise comparisons ($p < 0.05$).

For practical testing of EIR and FD NIRS detection of inclusion in tissue, three learning samples were prepared where the attribute vector consisted of Z_b , AC and Ph ; Z_b , AC and Ph . Each training set included 35 phantom measurements, Data standardization (StandardScaler) was used for feature scaling. To avoid data leak, the Leave-One-Object-Out cross-validation was used where all timing cycles assigned to a single experiment were completely excluded from the training set and were used only for testing; due to class disbalance, a priori probabilities of classes (Figure 6 shows the best results) were set during learning the quadratic discriminant analysis (QDA) algorithm. QDA procedure was considered only for the purpose of classification because it showed the best results of binary classification of inclusions in tissue [15,34]. Figure 6 and the table contain the QDA results.

3.2. Mathematical simulation

Numerical simulation results are shown in Figures 7 and 8. Figure 7, *a* reflects theoretical evaluation of whether EIR is possible to detect a nerve, artery and vein with the model parameters specified in Section 2.2. The measurement „dead“ zone is indicated in gray on the graphs.

Figure 7, *b* shows the dependence of $|\Delta Z|$ on h with various β from (4). Model curves were calculated for a fixed NVI diameter of 0.5 mm. Example of simulation of FD NIRS parameter sensitivity to NVI is shown in Figure 7, *c* for 828 nm. Due to insignificant differences in optical properties of both a vein and nerve for 684 nm and 828 nm, any significant difference in FD NIRS sensitivity to these NVIs isn't observed. For arterial NVI, absorption at 684 nm is much lower than at 828 nm, which results in a

higher sensitivity of FD NIRS at 828 nm. The findings are summarized in Figure 8.

4. Discussion

4.1. Experimental study

During occlusion testing, typical behavior is observed in signals ΔV_r , ΔV_s in the radial artery projection region. For example, after the start of arterial occlusion, the blood volume in the arterial compartment decreases, while during venous occlusion the blood volume increases due to arterial inflow with hindered venous blood outflow (Figure 4, *a*). Behavior of the curves is in agreement for two methods (cross-correlation coefficient 0.591 and 0.467 for the first and second participants, respectively). Signal amplitude changes for optical data is higher than for impedance measurements. Differences in ΔV_r and ΔV_s can be caused by different probing volumes for the methods with the combined probe prototype configuration and by different sensitivity to small blood volume fluctuations in tissue of measuring transducers used in the FD NIRS and EIR hardware systems. Thus, FD NIRS and EIR capabilities for physiological blood flow dynamics analysis are comparable.

Phantom testing results don't contradict the numerical simulation data (Figure 5, *c*), differences can be explained by inaccurate positioning of measuring channels parallel to the inclusion axis. According to the statistical analysis of measured data, for FD NIRS, AC demonstrates higher sensitivity to NVI than Ph , which agrees with a lower intensity measurement error and small SDD (small Ph).

Results of experimental detection of NVI on inhomogeneous phantoms as shown in Figure 6 and in the table demonstrate differences in the efficiency of EIR and FD NIRS, and of their combined use. When using only EIR, the *accuracy* appeared to be relatively low 66%. In particular, NoI were systematically classified as I_1 and I_2 , leading to zero *precision* and *recall* for NoI, while inclusion I_2 was detected more correctly. FD NIRS provided much better results: *precision* and *recall* of detection of all inclusions appeared to be high, which provided a *accuracy* at a level of 94%. As expected, the combined approach, including EIR and FD NIRS, didn't provide any improvement compared with FD NIRS for the test phantoms.

Constraints The *in vivo* study and combined measurements have shown the following:

- FD NIRS and EIR measuring transducers shall be modified for small test tissue volumes;
- combined probe shall be improved to ensure conformity of tissue volumes tested by different methods;
- the amount of experimental data is very small (2 participants) for statistically significant conclusions about the consistency of blood filling dynamics detected by EIR and FD NIRS;

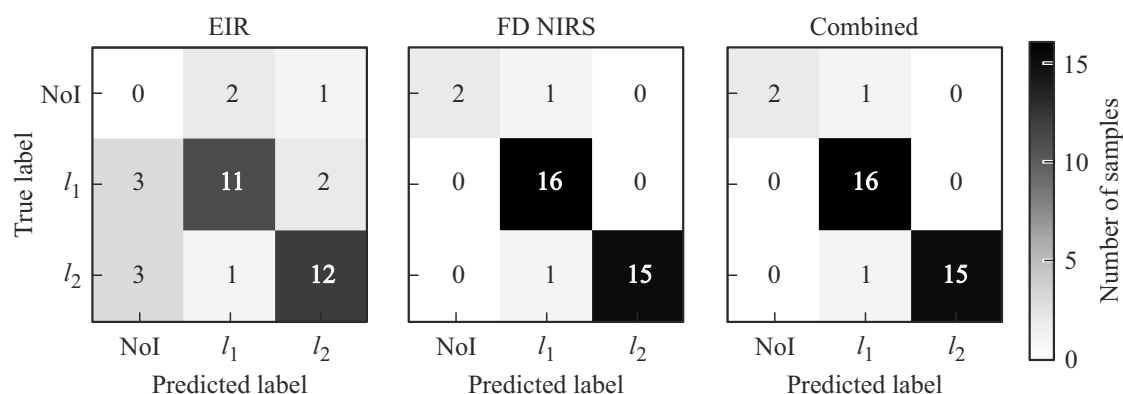


Figure 6. Confusion matrices for NVI detection by the QDA method.

QDA results with an attribute vector based on EIR, FD NIRS, and combination thereof

Attribute vector	Metric value			Mean	Weighted average
	NoI	I_1	I_2		
Precision					
EIR	0.00	0.69	0.75	0.53	0.72
FD NIRS	1.00	0.89	1.00	0.96	0.95
Combination of methods	1.00	0.89	1.00	0.96	0.95
Recall					
EIR	0.00	0.79	0.80	0.48	0.66
FD NIRS	0.67	1.00	0.94	0.87	0.94
Combination of methods	0.67	1.00	0.94	0.87	0.94
F-score					
EIR	0.00	0.73	0.77	0.50	0.69
FD NIRS	0.80	0.94	0.97	0.90	0.94
Combination of methods	0.80	0.94	0.97	0.90	0.94
Sample size	3	16	16	35	35
Accuracy					
EIR	0.66				
FD NIRS	0.94				
Combination of methods	0.94				
Sample size	35				

— synchronization of EIR and FD NIRS measurements shall be improved;

— position-force control of the combined probe shall be implemented during measurements;

— slow polarization effects during percutaneous EIR probing shall be controlled and adjusted; shift of the EIR signal center line due to polarization effects hinders

data interpretation, for example, during tissue flap control; this factor plays a much smaller role during intraoperative application in the wound.

Note the boundedness of properties of the prepared gelatin phantoms, mainly, in electrical properties. It is difficult to provide the required contrast between the background and simulated nerve using the NaCl concentration

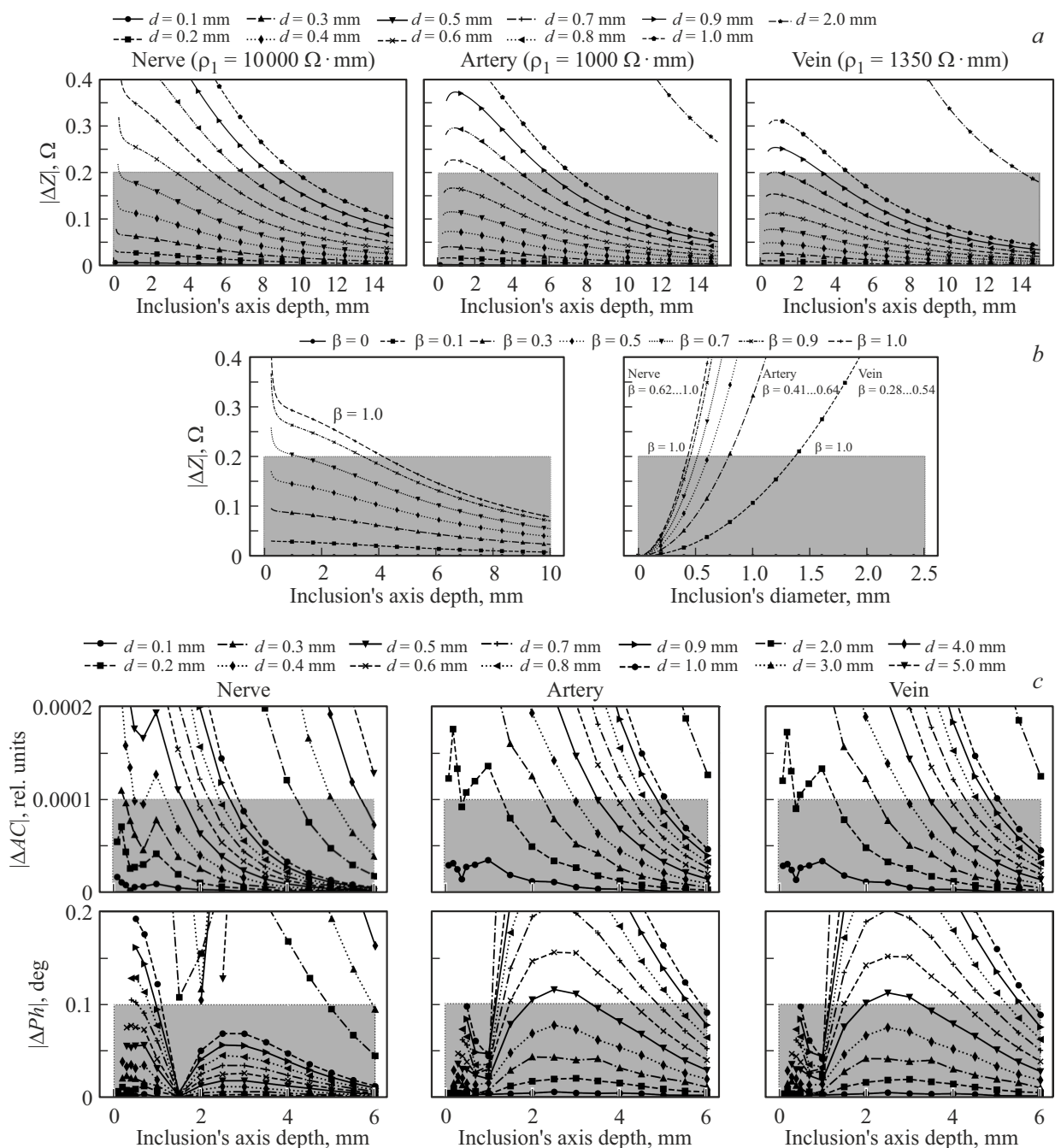


Figure 7. Dependences of simulated differences in Z_b ($|\Delta Z|$), AC ($|\Delta AC|$) and Ph ($|\Delta Ph|$) with and without NVI for different types, diameters and subsurface depths of NVI: (a) dependence of ($|\Delta Z|$) for different types, d and h of NVI; (b) influence of β on the sensitivity to NVI; (c) dependences of $|\Delta AC|$ and $|\Delta Ph|$ for 834 nm.

in the base mixture. Addition of fat to the base material might be required for mimicking the nerve's resistivity. Electrical impedance depends on temperature, but phantom temperature was not monitored in the experiments.

4.2. Mathematical simulation

For nerve simulation, the lowest resistivity $10000 \Omega \cdot \text{mm}$ was selected from the literature to ensure the minimized

contrast with the background, surrounding tissue. Higher values, for example, $166000 \Omega \cdot \text{mm}$ [24], will provide a greater contrast with background and high detection probability.

It should be noted that rheography shows a higher sensitivity to nervous structures than to arterial or venous vessels (Figure 7, a). This is explained by the fact that the electrical properties of nerves are much different from those of surrounding soft tissues, while the electrical properties

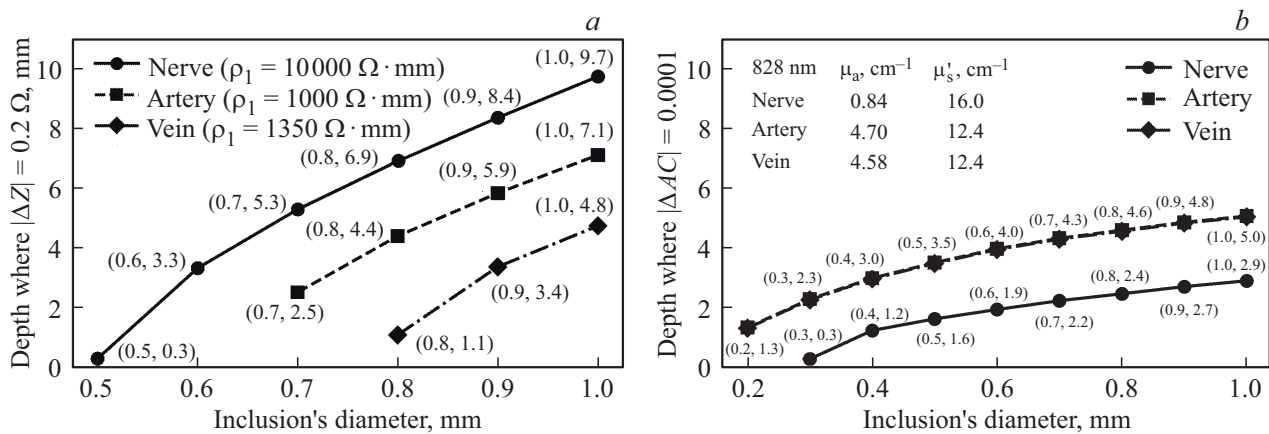


Figure 8. NVI diameter and depth resolution for EIR (a) and FD NIRS (b).

of blood are less different from those of „background“ tissues. Sensitivity of FD NIRS in $|\Delta AC|$ is higher to vascular inclusions, because light absorption by blood is much higher than by nervous tissue (Figure 7, c), and the contrast of blood relative to surrounding tissue is higher. A nerve of 0.7 mm in diameter is theoretically detectable by the FD NIRS method at a depth of 2.2 mm, and by the EIR method at a larger depth of 5.3 mm (Figure 8). For an artery of 0.7 mm in diameter, the relation is opposite. FD NIRS is sensitive to such inclusion at a depth of 4.3 mm, and EIR is sensitive only at 2.5 mm.

As it follows from the simulation results, combination of FD NIRS and EIR is applicable to detecting neurovascular inclusions because EIR is preferable for detecting nervous inclusions, and FD NIRS is more effective for detecting arteries and veins.

5. Conclusion

The study investigated two physical methods: FD NIRS and EIR applicable to detection of NVI in biological tissues and control of tissue blood flow, which is relevant for modern surgery. To compare the capabilities of the methods, a combined probe prototype was developed and fabricated for optical and electroimpedance measurements, experimental *in vivo* measurements were performed on hands of two healthy participants percutaneously and on a set of gelatin phantoms, homogeneous and with inclusions, and mathematical simulation was performed.

Results identified constraints in the experimental investigations which are less effective than mathematical simulation. Removal of the identified technical constraints: improvement of phantom properties, modification of transducers, improvement of the combined probe design, is necessary for further testing of feasibility and efficiency of combining FD NIRS and EIR. Experimental studies on living animal tissues are also necessary, with the support of medical co-investigators of this project and a research protocol approved by the local Ethics Committee.

When the EIR transducer is modified for smaller probing volumes, the methods can supplement each other: the optical method provides high sensitivity in surface layers and for vascular inclusions, and the impedance method allows for examination of deeper structures and nerve trunks, control of electrical contact between the probe and tissue, and pulse waveform analysis.

Further investigations involve provision of synchronization of optical and electroimpedance measurements, positional control of verified tissue structures, for example, using ultrasound scanning data, force control of contact between the probe and experimental surface, and much larger amount of test data for analysis of combined use of FD NIRS and EIR. The employed single-frequency EIR approach makes it possible to detect only blood volume dynamics, whether pulse, respiratory or slow functional, but not the absolute values of local blood volume in tissue which are available in the FD NIRS approach. To evaluate the absolute values of blood volume in the test tissue volume, EIS is required at least at two probing current frequencies.

Compliance with ethical standards

All procedures included in the human study were performed in accordance with the ethical standards established by the institutional and/or national committee on ethics in research and the Declaration of Helsinki (1964) as amended or comparable ethical standards.

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Conflict of interest

The authors declare no conflict of interest.

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