

https://doi.org/10.1070/QEL16284

Method of measuring blood oxygenation based on spectroscopy of diffusely scattered light

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Abstract. **A new approach to the measurement of blood oxygenation is developed and implemented, based on an original two-step algorithm reconstructing the relative concentration of biological chromophores (haemoglobin, water, lipids) from the measured spectra of diffusely scattered light at different distances from the radiation source. The numerical experiments and approbation of the proposed approach using a biological phantom have shown the high accuracy of the reconstruction of optical properties of the object in question, as well as the possibility of correct calculation of the haemoglobin oxygenation in the presence of additive noises without calibration of the measuring device. The results of the experimental studies in animals agree with the previously published results obtained by other research groups and demonstrate the possibility of applying the developed method to the monitoring of blood oxygenation in tumour tissues.**

Keywords: *diffuse optical spectroscopy, blood oxygenation, diffuse reflection, reconstruction of tissue composition.*

1. Introduction

The problems of timely diagnostics and correct treatment of oncological diseases are of primary importance in modern medicine, and to date numerous papers in many fields of science have been published, concerning the solution of these problems. From the biological point of view, the oncological neoplasm (tumour) is a complex system of cancerous cells in the microenvironment that determines the tumour development (growth, invasions, metastasising) [1, 2]. The specific features of the blood flow in the tumour (angiogenesis, microcirculation, blood oxygenation) are among the basic characteristics of its microenvironment [2, 3]. For example, malignant neoplasms possess broadened, curvy, and elongated vessels of capillary type, which leads to the deceleration of the blood flow in the region of the tumour. The vascular bed inferiority in combination with a high metabolic activity of cancerous cells results in disbalance between the supply and consumption of oxygen in the tumour and the formation of hypoxic microenvironment [4]. The presence of hypoxia determines the prognosis of the disease development and the sensitivity to therapeutic treatment [5]. Thus, the search for new and the development of existing methods for measuring blood oxygenation in a tumour tissue is one of the urgent problems of oncology.

The golden standard of determining the biotissue oxygenation is the polarographic measurement of the oxygen partial pressure [6, 7]. However, its application is restricted due to a number of drawbacks (invasiveness, long duration of the procedure, error of electrode introduction). The immunohistochemical methods allow the investigation of only *ex vivo* samples and are inapplicable to dynamic observations [7]. The EPR oximetry method allows blood oxygenation dynamics to be monitored, but it is characterised by a small depth of penetration into the studied tissue [8]. The most efficient method of observing the tissue oxygenation status is the positron-emission tomography, which, however, is characterised by high cost and technical complexity of the procedure [9]. To execute the dynamic observation of blood oxygenation, use is also made of optical methods [10], which are noninvasive, low-cost, and capable of deep (up to 10 cm) penetration. The most widely used methods are those based on the diffusion optical spectroscopy (DOS) that allow the tissue composition to be assessed [10–16].

The DOS method consists in probing a biotissue with optical radiation and detecting diffusely scattered light. The reconstruction of the object optical properties is based on the mathematical model of light propagation, the role of which is usually played by the diffusion approximation of the radiation transport equation (RTE) [11]. Within the frameworks of this model, the optical properties of the biotissue are determined by the transport scattering coefficient and the light absorption coefficient [11, 12]. The spectrum of the light transport scattering coefficient characterises the features of the tissue cellular structure, and the spectrum of the absorption coefficient allows the estimation of concentrations of biological chromophores (oxyhaemoglobin, deoxyhaemoglobin, water, lipids, collagen, etc.) [12, 13]. The oxygenation of blood in the tissue is determined by the ratio of the found concentrations of oxy- and deoxyhaemoglobin [13]. In this case, the reconstructed concentrations of chromophores, as well as the spectra of light absorption and scattering coefficients, describe the average values of these characteristics in the studied volume, where the biotissue is considered to be uniform.

The simplest and most commercially available DOS method for the calculation of the biotissue oxygenation status is based on the separate reconstruction of the absorption and scattering coefficients in the biotissue using the intensity of diffusely scattered light, measured at different distances from the light source (the use of spatial measurements) [14].

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Received 30 December 2016; revision received 21 February 2017
Kvantovaya Elektronika **47** (4) 355–360 (2017)
Translated by V.L. Derbov

However, this approach requires the device calibration and the correct consideration of the external factors (background illumination, gain coefficient of the receiving path, quality of optical contact with the tissue, etc.). The use of the amplitude modulation of the probe radiation [15] or short light pulses [16] allows separate reconstruction of the absorption coefficient and the transport scattering coefficient of a biotissue from the temporal characteristics of the recorded radiation (the shape of the diffusely scattered pulse or the phase shift of the measured signal) at a fixed distance between the light source and the receiver. The method also simplified the calibration of the DOS system. However, the use of special light sources and time-correlated photon counters or high-frequency receiving paths leads to a significant complication of the DOS system and increases its cost.

In this paper, we present a new approach to the calculation of blood oxygenation in a biotissue using the spatial variation of diffusely scattered light spectra, recorded at two different distances from the radiation source. The measurements are carried out in the the geometry of diffuse reflection using the continuous-wave and non-modulated probe radiation, which provides the simplicity of technical implementation and high commercial availability of the proposed approach, as well as the possibility of using the DOS method in different biomedical applications. To assay the tissue composition we propose an original two-step algorithm using analytical models of light propagation in tissue based on the RTE diffusion approximation. We present the results of numerical experiments and approbation of the developed method in a biological phantom, which demonstrate high accuracy of the reconstruction of absorption and scattering coefficients and the measurement of blood oxygenation in the studied object. We also present the results of experimental studies, performed in laboratory animals and aimed at the monitoring of blood oxygenation in tumour tissue.

2. Materials and methods

2.1. Reconstruction of biotissue optical properties

The calculation of blood oxygenation in a biotissue can be implemented in two stages. First, from the measured spectral intensity $I(\lambda)$ of diffusely scattered light it is necessary to reconstruct the spectra of the absorption coefficient $\mu_a(\lambda)$ and the transport scattering coefficient $\mu_s'(\lambda)$ of the biotissue. Then in the reconstructed spectrum of the absorption coefficient one has to determine the partial contribution of absorption by the basic biological chromophores, namely, oxyhaemoglobin, deoxyhaemoglobin, water, and lipids.

Within the frameworks of the RTE diffusion approximation, the spectral intensity of light in a turbid medium at the given distance r from the point isotropic source of radiation can be described by the expression [17, 18]

$$I(\lambda,r) = AI_0(\lambda)\frac{\mu_a(\lambda)+\mu_s'(\lambda)}{r} \times \exp\left(-\sqrt{3\mu_a(\lambda)[\mu_a(\lambda)+\mu_s'(\lambda)]}\right), \quad (1)$$

where λ is the wavelength; $I_0(\lambda)$ is the spectral intensity of probe radiation; and A is the multiplicative factor determined by the light source and receiver parameters (aperture, quantum yield, quality of contact with tissue, etc.) and found by the calibration of the DOS system. With the boundary conditions at the air–tissue interface [18] taken into account, the fraction of intensity (1) of light diffusely reflected from the biotissue is described by the expression for the coefficient of diffuse light reflection from a turbid medium $R(\lambda,r)$ [11, 19, 20]:

$$R = \frac{A\mu_s'}{\mu_t'}\left[\frac{1}{\mu_t'\rho_1^2}\left(\mu_{eff}+\frac{1}{\rho_1}\right)\exp(-\mu_{eff}\rho_1) + \frac{1}{\rho_2^2}\left(\frac{1}{\mu_t'}+2z_b\right)\left(\mu_{eff}+\frac{1}{\rho_2}\right)\exp(-\mu_{eff}\rho_2)\right],$$

$$\rho_1 = \sqrt{r^2+\frac{1}{\mu_t'^2}},\ \ \rho_2 = \sqrt{r^2+\left(\frac{1}{\mu_t'}+2z_b\right)^2}, \quad (2)$$

$$z_b = \frac{2(1+d)}{3\mu_t'(1-d)},\ \ \mu_{eff} = \sqrt{3\mu_a\mu_t'},\ \ \mu_t' = \mu_a+\mu_s',$$

$$d = -\frac{1.44}{n^2}+\frac{0.71}{n}+0.67+0.06n,\ \ n = 1.4.$$

Here n is the index of light refraction at the biotissue–air interface, and z_b is the extrapolated Milne length. The spectrum of the light transport scattering coefficient in the tissue can be approximated by the power function of wavelength, and the spectral dependence of the total absorption coefficient is conveniently presented as a sum of the known spectra of oxyhaemoglobin $\mu_a^{HbO_2}(\lambda)$, deoxyhaemoglobin $\mu_a^{HHb}(\lambda)$, water $\mu_a^{H_2O}(\lambda)$, and lipids $\mu_a^{lip}(\lambda)$, multiplied by the partial concentrations of these chromophores C_{HbO_2}, C_{HHb}, C_{H_2O} and C_{lip} [21, 22]:

$$\mu_s'(\lambda) = C_s\lambda^{-b},\ \ \mu_a(\lambda) = C_{HbO_2}\mu_a^{HbO_2}(\lambda)+C_{HHb}\mu_a^{HHb}(\lambda) + C_{H_2O}\mu_a^{H_2O}(\lambda)+C_{lip}\mu_a^{lip}(\lambda). \quad (3)$$

The numerical solution of Eqn (2) with respect to the unknown parameters of approximation (3) allows the reconstruction of the composition of the studied object and the calculation of the oxygenation (oxygen saturation) StO_2 in the volume of measurement [22, 23]:

$$StO_2 = C_{HbO_2}(C_{HbO_2}+C_{HHb})^{-1}. \quad (4)$$

Besides that approximation (3) for the desired absorption and transport scattering coefficients essentially reduces the dimensionality of the problem of reconstructing the biotissue composition, which enhances the stability of its solution.

In the present paper, for the numerical solution of Eqn (2) with approximation (3) we used the Levenberg–Marquardt algorithm [24], and the spectra of light absorption for the biological chromophores were adopted from the literature data [25]. This approach allows rapid determination of the local solution to the inverse problem near the initial point of the algorithm. However, the presence of the measurement error and the absence of *a priori* data on the composition of a particular biotissue sample do not allow the use of the literature data as the initial point. Therefore, to determine the initial concentrations of the biological chromophores it is convenient to use the approximation parameters (3) for the coefficients of absorption and transport scattering of light in the

studied object, the spectra of which can be estimated using the iteration procedure:

$$\mu_s'^{(i+1)} = \frac{I_1 r_1}{A I_0}\exp\left(\sqrt{3\mu_a^{(i)}\left[\mu_a^{(i)} + \mu_s'^{(i)}\right]}\, r_1\right) - \mu_a^{(i)},$$

$$\mu_a^{(i+1)} = \frac{1}{3(r_2 - r_1)^2\left[\mu_a^{(i)} + \mu_s'^{(i+1)}\right]}\left[\ln\left(\frac{I_1 r_1}{I_2 r_2}\right)\right]^2, \qquad (5)$$

$$\mu_a^{(0)} = 0,\ \ \mu_s'^{(0)} = 0,\ \ i = 0, 1, 2, 3, \ldots .$$

The iteration scheme (5) was obtained from expression (1) for the spectral intensities of diffusely scattered light, I_1 and I_2, recorded at distances r_1 and r_2 from the light source, taking into account one of the conditions of RTE diffusion approximation validity

$$\mu_s'(\lambda) \gg \mu_a(\lambda). \qquad (6)$$

2.2. Numerical experiment

For the primary approbation of the proposed method for calculating the blood oxygenation, we performed the numerical experiments, in which the measured spectral intensity of diffusely scattered light was simulated by means of Eqn (2) with the addition of uniformly distributed noise, corresponding to the noise of the light receiver. Then the simulated measurements for different concentrations of biological chromophores and signal-to-noise ratios were used to reconstruct the initial spectra of the absorption coefficient and transport scattering coefficient, as well as for the calculation of the composition of the studied object. It is important to note that due to the dependence of the measured spectral intensity on the wavelength and the distance between the source and the receiver of light, the signal-to-noise ratio (SNR) here and below is defined as the ratio of the minimal value of $R(\lambda, r)$ within the considered spectral region and the square root of the noise variance σ_{ns}:

$$\mathrm{SNR} = 10\lg[\sigma_n^{-1}\min_{\lambda, r} R(\lambda, r)]. \qquad (7)$$

The simulated measurements of the diffusely scattered light spectral intensity were also used to estimate the effect of the DOS system calibration error on the accuracy of reconstruction of the biotissue optical parameters and calculation of its composition. In this case, the relative error of the calibration ξ was determined by the difference between the measured multiplicative factor A^{rec} and its real value A^{or} in expression (1):

$$A^{rec} = (1 + \xi)A^{or}. \qquad (8)$$

We also simulated the measurements of the diffusely scattered light spectral intensity in the presence of an external interference radiation source contributing to the recorded signal. The simulated measurements for the external sources themselves were used to estimate the accuracy of the biotissue optical properties reconstruction and the calculation of its composition in the presence of additive non-noise interference in the recorded signal.

The simulation of all measurements, as well as the computational algorithm for the proposed DOS method were implemented in the programming environment MATLAB (MathWorks Inc., USA).

2.3. Experimental prototype of the DOS system

To implement the proposed method of DOS measurements, we constructed the experimental setup, schematically presented in Fig. 1. As a source of probe radiation we used an LS-1-LL halogen lamp (ocean Optics Inc., USA), while the diffusely scattered light was recorded simultaneously by means of two S2000 spectrometers (Ocean Optics, USA) at distances 1.5 and 3 mm from the point of the probe radiation incidence. The light was transported from the lamp to the tissue and from the tissue to the spectrometers through optical fibres having a diameter 200 μm ('Polironik' Ltd., Russia), and for displaying the measured spectra of diffusely scattered light intensity a personal computer was used.

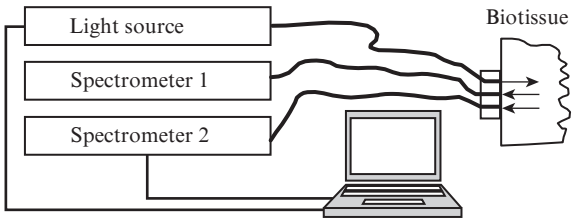

Figure 1. Schematic of the experimental setup for reconstructing the optical characteristics of biological tissues (absorption coefficient and transport scattering coefficient) and calculating blood oxygenation.

2.4. Biological phantom studies

The experimental setup was tested using a biological phantom, a cuvette filled with a solution that consisted of 600 mL of sodium-phosphate buffer, 87 mL of MCT/LCT lipofundin with a concentration 10%, and 2 mL of blood with the haemoglobin concentration of 155 g L^{-1}. To vary the blood oxygenation, a tube with porous disperser was connected to the cuvette, through which oxygen or nitrogen was supplied to the solution. The partial pressure of oxygen p_{O_2} in the solution was controlled by polarographic measurements using a Clark-type OX-N microelectrode (Unisense A/S, Denmark). The phantom temperature was kept equal to 37°C using a thermostatic element merged into the solution.

In the course of the model experiment, the probe optical fibre of the experimental setup was merged in the solution, and the measurements of the intensity spectrum of diffusely scattered light at different partial pressures of oxygen in the solution were carried out. Then, the recorded spectra were used to reconstruct the curve of oxyhaemoglobin dissociation in the biological phantom. In this case, only partial calibration of the experimental setup was executed, in which the zero level of the signal was determined in the absence of the probing radiation.

2.5. Studies in laboratory animals

The developed method of blood oxygenation measurement was additionally approbated in laboratory animals *in vivo*, where the haemoglobin oxygenation in a tumour tissue was monitored. In this study, we recorded the spectral intensity of light diffusely scattered in the developed tumour (human

mammary gland carcinoma SKBR-3) on the body of an animal (female mouse balb/c-nude). The measurements were repeated daily during a week, starting from the 12th day after the subinoculation of the tumour, when the size of the latter exceeded 5 mm. The experimental data were used to estimate the changes of blood oxygenation in the tumour in the process of its growth. All experimental studies were executed in correspondence with the International Guiding Principles for Biomedical Research Involving Animals (1985), developed by the Council for International Organisations of Medical Sciences (CIOMS).

3. 3. Results and discussion

3.1. Results of the numerical experiment

Figure 2a presents the example of the calculated ratio of spectral intensities of light, diffusely scattered in the biotissue, recorded at different distances from the source of probe radiation in the presence of uniformly distributed additive noise. As shown in Fig. 2b, for this spectral dependence the implementation of the iterative scheme (5) leads to the erroneous calculation of the absorption coefficient, but the use of approximation (3) for the optical parameters of the biotissue allows the selection of a smooth function in the reconstructed spectrum. In the numerical experiment, it was found that the signal-to-noise ratio, calculated using Eqn (7), affects only the number of iterations in the developed algorithm, which are required to achieve the given error of the biotissue absorption coefficient reconstruction and to calculate the content of its components. However, it is important that in the present work we did not study the case, when the signal-to-noise ratio would be less than 1 dB, since in real experiments, as a rule, it is always possible to select a region of the measured intensity spectrum of the diffusely scattered light, in which the signal-to-noise ratio exceeds this value.

Figure 3 shows that in contrast to the noise with a zero mean value, the non-noise interference, caused by an external light source leads to a shift of the absolute values of the reconstructed absorption spectrum with respect to the original one. The shift is determined by the ratio of spectral intensities of the external source and the diffusely scattered light and depends on the wavelength. However, in the course of the numerical experiment it was revealed that the relative error ε in the calculation of biological chromophores concentrations does not exceed the ratio of the maximal fraction of the external signal $J(\lambda)$ in the recorded radiation and the minimal value of $R(\lambda, r)$:

$$\varepsilon = \frac{C_{\mathrm{bc}}^{\mathrm{or}} - C_{\mathrm{bc}}^{\mathrm{rec}}}{C_{\mathrm{bc}}^{\mathrm{or}}} < \max_{\lambda} J(\lambda) \Big[\min_{\lambda, r} R(\lambda, r)\Big]^{-1}, \qquad (9)$$

where $C_{\mathrm{bc}}^{\mathrm{rec}}$ and $C_{\mathrm{bc}}^{\mathrm{or}}$ are the reconstructed and the original concentration of any of the biological chromophores. In this case, inequality (9) was also true for the relative error of oxygenation calculation; however, as a rule, the latter was a few times smaller than the error of the composition reconstruction.

The performed numerical experiments have also shown that the relative error of DOS system calibration ξ in expression (8) gives rise to a multiplicative error in reconstructing the coefficients of absorption and transport scattering of light in the biotissue:

$$\mu_{\mathrm{a}}^{\mathrm{rec}}(\lambda) \approx (1-\xi)^{-1}\mu_{\mathrm{a}}^{\mathrm{or}}(\lambda), \;\; \mu_{\mathrm{s}}'^{\mathrm{rec}}(\lambda) \approx (1-\xi)\mu_{\mathrm{s}}'^{\mathrm{or}}(\lambda), \quad (10)$$

where $\mu_{\mathrm{a,s}}^{\mathrm{rec}}(\lambda)$ and $\mu_{\mathrm{a,s}}^{\mathrm{or}}(\lambda)$ are the reconstructed and the original spectra of the optical parameters of the studied object. Thus, according to expression (10), the calibration error leads

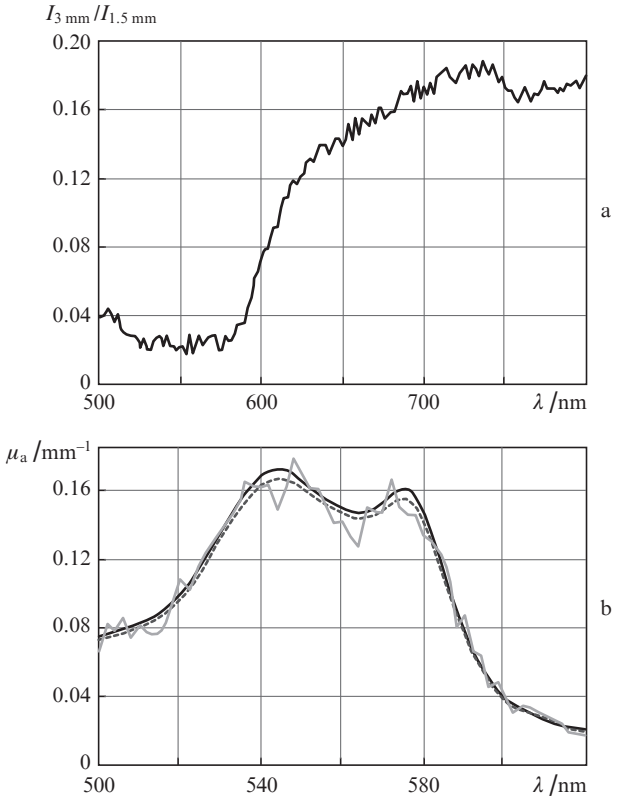

Figure 2. (a) Ratio of spectral intensities of diffusely scattered light in the numerical biotissue model, recorded for the distances 1.5 and 3 mm between the probe radiation source and receiver fibres for the signal-to-noise ratio 1 dB as well as (b) original (solid black line) and reconstructed spectra of absorption coefficient in the biotissue model before (solid grey line) and after (dashed line) their approximation by the linear combination of individual absorption coefficient spectra of biological chromophores.

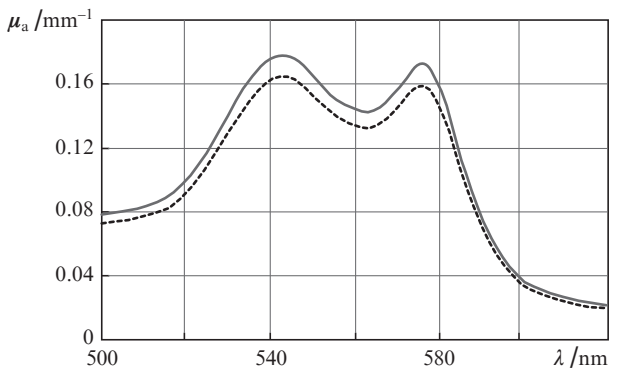

Figure 3. Original (solid curve) and reconstructed (dashed curve) spectra of the absorption spectrum in the biotissue model in the presence of an external radiation source whose maximal intensity is by two times smaller than the minimal values of the measured intensity of probe radiation, passed through the tissue.

to the wrong calculation of the absolute values of the absorption and transport scattering coefficients, but it does not affect the result of the composition reconstruction, since if condition (6) is satisfied, then the difference of shapes of the reconstructed spectra from the original ones will be insignificant. In the numerical experiment it was revealed that even for the calibration error, close to one, the relative error of the calculation of relative concentrations of the biological chromophores does not exceed 1%, which is comparable with the given accuracy of the reconstruction algorithm. This statement was also confirmed in the experimental studies of the biological phantom.

3.2. Biological phantom results

Figure 4a presents the characteristic spectra of light diffusely scattered in the biological phantom, and measured at the distances 1.5 and 3 mm from the radiation source at different partial pressures of oxygen. The figure clearly demonstrates the recorded changes of the spectral intensity, from which the oxyhaemoglobin dissociation curve was reconstructed. The signal-to-noise ratio in the chosen spectral region did not exceed 1 dB. The results of blood oxygenation reconstruction in the biological phantom at different partial pressures of the gas are presented in Fig. 4b. It is seen that the reconstructed curve of oxyhaemoglobin dissociation agrees well enough with the literature data [26]. The observed error was due to the instability of the zero signal level in the absence of probing radiation (additive non-noise interference).

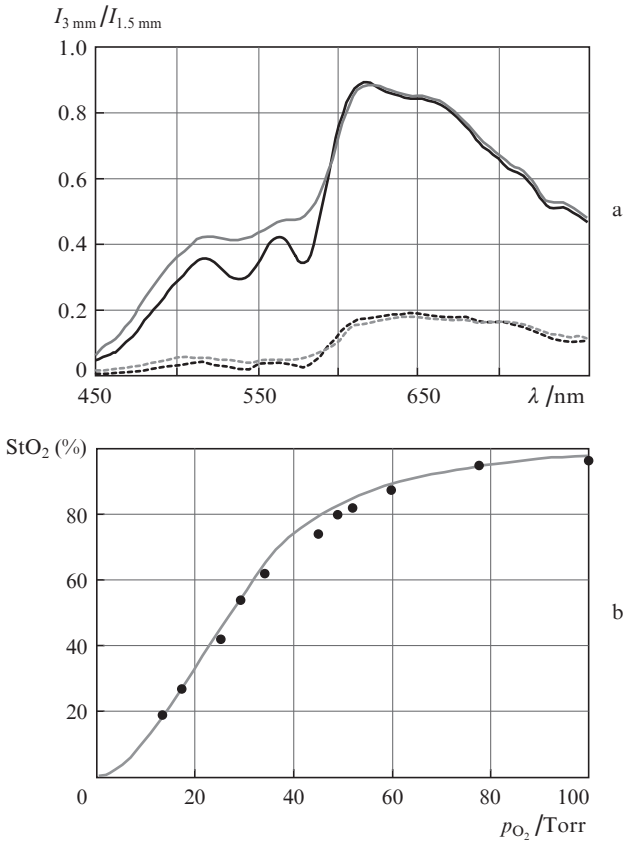

Figure 4. (a) Spectra of diffusely scattered light in the biological phantom, measured at the distance 1.5 mm (solid curves) and 3 mm (dashed curves from the source of probing radiation at the partial oxygen pressure of 78 Torr (black curves) and 25 Torr (grey curves) as well as (b) oxyhaemoglobin dissociation curve [26] (grey curve) and the reconstructed dependence of the blood oxygenation in the biological phantom upon the partial pressure of oxygen at the temperature 37°C and pH = 7.4 (black points).

3.3. Results obtained in laboratory animals

The problem of calculating the haemoglobin oxygenation was also successfully solved in the course of approbation of the proposed method of the DOS measurement in laboratory animals. Figure 5a shows examples of reconstructed spectra of the light absorption coefficient in the tumour tissue during the long-term observation of the animal. The spectral band for the reconstruction was chosen in the long-wavelength region because of high noise in the short-wavelength region of the recorded spectra of diffusely scattered light. It is important to note that the shape of the reconstructed spectra corresponds to the real one, but the absolute values of the reconstructed and the real light absorption coefficients in the studied object can essentially differ due to the incomplete calibration of the experimental setup. This fact made it impossible to determine the absolute values of the concentrations of biological chromophores in the tumour, but it had no effect on the accuracy of calculating the tissue oxygenation. The results of the haemoglobin oxygenation calculation from the reconstructed spectra of light absorption are presented in Fig. 5b. It is seen that oxygenation of blood in the tumour

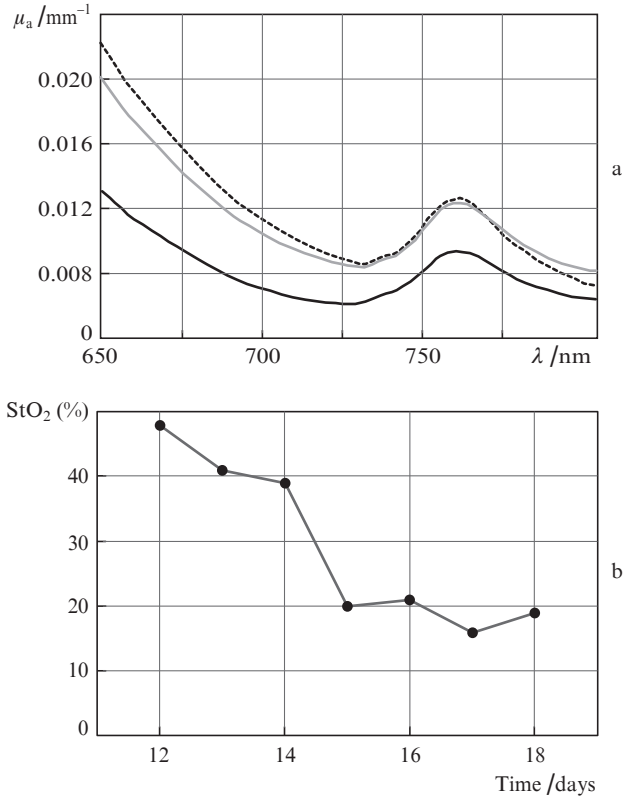

Figure 5. (a) Reconstructed spectra of the light absorption coefficient in the tumour tissue in 12 (black curve), 14 (grey curve), and 16 days (dashed curve) after the tumour subinoculation as well as (b) values of the blood oxygenation in the tumour, measured in the course of monitoring.

decreases as the tumour grows, and finally approaches the constant level. Similar values of blood oxygenation and its variation with the tumour growth have been observed previously by other authors [27]. We should also note that in the study of biotissues the additional error appears in the calculation of blood oxygenation, caused by the presence of the chromophores not taken into account (melanin, collagen, etc.), the tissue structuration, and the level of haematocrit in blood [28]. The value of this error cannot be determined, because it depends only on the tissue sample. However, if the measurements are performed in the visible wavelength range, the effect of the above factors is not essential.

4. Conclusions

In the present paper, we propose an original approach to the measurement of blood oxygenation in a biotissue based on the spectroscopy of diffusely scattered light. The measurement procedure includes four stages. First, the spectral intensity of diffusely scattered light is measured at the tissue surface (in reflection geometry), the distance between the tips of the source and receiver fibres being 1.5 and 3 mm. Then from the recorded data the absorption and transport scattering coefficient are approximately reconstructed using the iteration scheme, derived from the solution of the diffusion RTE for the infinite uniform medium. At the next stage, the reconstructed spectrum of absorption coefficient is approximated by the linear combination of individual absorption spectra of oxyhaemoglobin, deoxyhaemoglobin, water and lipids, and the spectrum of the transport scattering coefficient is presented in the form of a power function of the wavelength. The resulting approximation parameters serve as the initial point for the numerical solution of the diffuse reflection equation with the boundary effects taken into account. At the final stage, the corrected coefficients are used to calculate the blood oxygenation in the studied object.

The approbation of the proposed method of DOS measurements using the simulated measurements of the spectral intensity of diffusely scattered light has shown that the error of reconstructing the relative concentrations of biological chromophores is determined by the given accuracy of the calculation algorithm if the signal-to-noise ratio exceeds 1 dB. In this case, no correct calibration of the DOS system is required. However, the presence of external light sources can introduce an additional error to the composition calculation, which does not exceed the ratio of the maximal interference magnitude to the minimal signal value.

These results were confirmed by the approbation of the developed method in the biological phantom, which has shown good agreement of the reconstructed curve of haemoglobin dissociation with literature data. The results of monitoring the blood oxygenation in the tumour on the murine body also agreed with the data published by other research teams.

Thus, it is possible to acknowledge the relevance of the proposed approach based on the spectroscopy of diffusely scattered light in application to the measurement of blood oxygenation and the necessity of its further development for clinical use.

Acknowledgements. The authors express their gratitude to M.B. Prudnikov and V.I. Plekhanov for the fabrication of the contact fibre-optical probe for the DOS system prototype.

The work was supported by the Russian Foundation for Basic Research (Grant No. 16-32-60093 mol_a_dk).

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