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OPTICAL AND BIOPHYSICAL PARAMETERS OF BIOTISSUES IN THE NORMAL STATE AND IN THE CASE OF PATHOLOGY AND MULTIPLE SCATTERING-BASED METHODS FOR THEIR DETERMINATION IN THE VISIBLE AND NEAR IR SPECTRAL REGIONS

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Multiple scattering-based methods for determination of the elementary volume of biotissues, light pressure index, and imaginary and real parts of the refraction index of the disperse phase of biotissues are considered. Results of determination of optical and biophysical parameters of blood in the normal state and in the case of pathology are presented. Possibilities for optical tomography are discussed. It is shown that the multiple scattering spectroscopy makes it possible to increase the amount of biophysical information on erythrocytes.

The interest in investigations of optical properties of biotissues is connected with development of methods of noninvasive technology, laser surgery and therapy, and optical tomography.

It is well known that biological tissues are strongly scattering media with low, but selective, absorption [1-3] in the visible and near IR regions of the spectrum. When the optical-range radiation propagates in these media with the thickness $l \sim 0.5 - 1$ mm, conditions favorable for multiple scattering are realized. Therefore, in order to obtain optical and hence biophysical information on biotissues it is worthwhile to investigate spectral dependences of coefficients of diffuse reflection and transmission with application of the radiation transfer theory to processing of experimental results. Methods of investigation of biotissues were developed in the 1980s in our laboratory for one of the most important biotissues of the organism, blood, which on the one hand is one of components of various biotissues, and on the other hand is most simple for optical investigations. In addition, its investigations made it possible to determine a number of diagnostic parameters for medicine [4, 5].

The method is based on the experimental proof of the applicability of the transfer theory to investigation of integral characteristics of the light field for weakly absorbing "soft" (the refraction index of the disperse medium relative to the connecting medium $n \to 1$) closely packed particles (the relative fraction of the volume taken by particles $C_v \geq 0.2$) using an erythrocyte suspension as an example, introduction and measurements of effective parameters of the elementary volume for media with various packings of particles [1, 6-9], followed by generalization of this ideology for biotissues of any nature that correspond with respect to their optical parameters to the proposed approach to investigations.

Methods of Determination of Parameters of the Elementary Volume. Parameters of the elementary volume (indices of attenuation ε_{ef}, absorption k_{ef}, scattering σ_{ef}, and light pressure β_{ef}, and the mean cosine of the scattering indicatrix μ_{ef}) can be determined in two limiting cases: multiple scattering and the so-called thickness regime, when an increase in the layer thickness does not lead to variations in the diffuse reflection coefficient R and the diffuse transmission coefficient $T \sim \exp(-\gamma\varepsilon l)$ (γ being the absorption coefficient in the thickness regime) [10].

We shall dwell in more detail on methods of multiple scattering since no other methods provide information on absorption and light scattering indices, the imaginary part of the complex-valued refraction index of biological tissues within the spectral range 0.6–1.2 μm (the region of weak absorption) [1-4], and dimensions of large particles and their assemblies [5, 11-13]; they provide higher accuracy of determination of the real part of the complex-valued refraction index [13], the oxygenation degree of blood hemoglobin [4, 14] and mitochondria of

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TABLE 1. Results of Measurements and Calculations of Parameters of the Elementary Volume of the Suspension of Erythrocytes in Physiological Solution

λ, nm	R_0	$T_{12}(l_1; l_2)$	C_{v0}	ε_0, cm^{-1}	k_0, cm^{-1}	Λ_0^*	β_0, cm^{-1}	μ_0
700	0.25	0.56	0.07	250	0.40	0.9984	0.51	0.9863
$^*\Lambda_0 = (\varepsilon_0 - k_0)/\varepsilon_0 = \sigma_0/\varepsilon_0$ when $C_{v0} \leq 1-0.2$.								

biocells [15], the concentration of hemoglobin derivatives [4, 16], its decay products [17, 18], the concentration of water in biotissues etc. [19], and the mean cosine of the scattering indicatrix [9, 11, 20, 21].

The absorption coefficient k_{ef} was determined by the formula proposed by Rozenberg back in 1967 (he has formulated principles of the spectroscopy of weakly absorbing disperse media) [10], which we have modified [1] in order to measure not three, but two parameters that reduced the number of quantities being measured and improved the accuracy of measurements:

$$k_{ef} = (q\gamma)_{ef}\,(\gamma\varepsilon)_{ef}\,. \tag{1}$$

It should be noted that the parameter $x = \gamma\varepsilon$ was determined from the absolute or relative coefficient of diffuse transmission T, and $y = q\gamma$ was determined from the coefficient of diffuse reflection R; two methods of calculation [1, 21-22] were used to determine x and y with boundary conditions determined by different methods [1, 17-18]. Inadequacy of methods of consideration of boundary conditions has stimulated investigations that are being presently carried out in our laboratory, and results of the investigations can be applied to arbitrary biotissues, not just to blood, as in [1, 17, 18].

It should be noted that, in addition to the high information content within the framework of a single experiment, absence of sample preparation, approaching *in vivo* conditions, and the confidence of the results which stems from the facts enumerated above, the spectroscopy of multiply scattered radiation provides information on absorption of the substance with the accuracy that is improved with the intensity of light scattering, providing thus the possibility that cannot be provided by other methods to determine weak absorption and to evaluate from this quantity low concentrations of minority chromophores in the sample under investigation.

The parameter $p_{ef} = x_{ef}/y_{ef} = 1/3\varepsilon_{ef}(1 - \mu_{ef})$ also being determined from the coefficients R and T along with the absorption coefficient k_{ef} is sufficient for calculation of diffuse reflection R_{mult} and T_{mult} of multilayer structures that model human organs [23, 24].

Within the framework of this approach we have developed a method for determination of the cross-section of light pressure β_{ef} on a layer [9]

$$\beta_{ef} = \left(\frac{\varepsilon_{ef}}{3q_{ef}}\Lambda_{ef} + k_{ef}\right) \approx \frac{\varepsilon_{ef}}{3q_{ef}} + k_{ef} \quad \text{when} \quad \Lambda_{ef} = \frac{\sigma_{ef}}{\varepsilon_{ef}} \to 1\,. \tag{2}$$

The force of the pressure of light $F = \beta_{ef}E/c$ (E being the illumination intensity at the given layer depth l, c being the speed of light); using relationship (2) one can calculate the force of the pressure of light of laser radiation in a layer under the condition of constancy of optical properties of the medium.

As for determination of the attenuation index ε_{ef}, only in the case of very small particles ($\rho = 2\pi r n_m/\lambda << 1$, r being the particle radius, n_m being the refraction index of the connecting medium, plasma in the case of blood) and large erythrocyte-like particles ($\rho >> 1$) can this quantity be found under conditions of multiple scattering in accordance with the relationships [13]:

$$\underset{\rho < 0.1}{\varepsilon_{ef}} = \frac{1}{3}p_{ef}, \quad C_v \geq 0.1\,; \tag{3}$$

$$\underset{\rho \geq 200}{\varepsilon_{ef}} = p_{ef}\,q_{as}\,(1.1 - C_v), \quad C_v \geq 0.1\,.$$

TABLE 2. Values of the Imaginary Part κ of the Complex-Valued Refraction Index and Limiting Dimensions of Particles r_{max} at Which the Values of κ do not Depend on r_{max}

κ	r_{max}, μm
10^{-3}	5
10^{-4}	60
10^{-5}	600

For erythrocytes in plasma $q_{as} = 32$ at their relative refraction index $n = 1.036$. In other cases the attenuation index of biotissues ε_{ef} can be determined just under conditions of single scattering which are realized at layer thickness $l \leq 0.04$ mm [6, 25].

Table 1 presents parameters of the elementary volume for the suspension of erythrocytes in the physiological solution obtained by the aforementioned methods from the diffuse reflection coefficient and relative transmission of two layers T_{12} with thicknesses l_1 and l_2.

Methods for Determination of the Complex-Valued Refraction Index, Particle Dimensions, and a Series of Biophysical Parameters. It has been shown in [1, 4, 20, 21] for a suspension of erythrocytes and whole blood that the imaginary part of the complex-valued refraction index

$$\kappa = \frac{k_{ef}\lambda}{1.1254\pi C_v f(C_v) n_m}, \tag{4}$$

where

$$f(C_v) = \frac{y_{ef}}{y_0} \frac{C_v}{1.1 - C_v};$$

$y_0 = q_0\gamma_0$ is the parameter determined from the diffuse reflection coefficient of the layer R_0 at $C_v \leq 0.1-0.2$. For blood and suspension of erythrocytes $f(C_v) = 1.0-1.5$ within the spectral region 650–1000 nm, reaching its maximum at limiting values of $C_v \to 1$.

Realization of the condition $R \geq 0.10$ is the criterion of applicability of the relationships (1)-(4) (i.e., the lower boundary of values of the diffuse reflection coefficient is predetermined in the course of the experiment). As is shown in [1, 4] in this case the imaginary part of the complex-valued refraction index depends on the volume concentration of particles, but not by their dimensions and shape; in this case certain relationships between values of κ and maximum particle dimensions r_{max} are fulfilled, as follows from Table 2.

From the coefficients of diffuse reflection R and transmission T of an optically thick layer one can determine both the imaginary part of the complex-valued refraction index, and the generalized parameter $Q_0 = q_0 C_{v0}/\varepsilon_0\lambda$ that is related unambigously with the real part of the relative refraction index of particles or subunits of the disperse phase $n = n_{part}/n_m$ (n_{part} being the absolute refraction index of subunits within the spherical approximation [13]):

$$Q_0 = a(\Delta n)\rho^b, \tag{5}$$

$b \approx 0.7$; $\Delta n = n - 1$; $a = 32$ and 22 for $n = 1.036$ and 1.045, respectively.

The expression is applicable when $10 \leq \rho \leq 100-200$ and $C_v \leq 0.2$. When $C_v \geq 0.2$, which occurs in the case of biotissues, one should take into account the dependences of q_{ef} and ε_{ef} on C_v, as has been done for erythrocytes [6-9]. Values of Δn determined for erythrocytes using the algorithm (5) coincide with results obtained by different methods and data from the literature. However, the sensitivity of this method is higher since other methods are based upon the dependence of one of the parameters of the elementary volume on n, whereas in the

TABLE 3. Optical and Biomedical Parameters of Blood of Patients with Cardiovascular Diseases (1-4), Anemia (5), and Donors (6-8)

Sample	$\lambda_1 = 633$ nm	$\lambda_2 = 650$ nm	$\lambda_3 = 805$ nm		C_{O_2}	C_v	C	C_{chol}
	R,%	R,%	R, %	Q_0			g/liter	
1	1.8	1.9	6.0	305	0.40	0.37	137	2.44
2	2.0	2.5	7.7	200	0.42	0.36	145	2.36
3	2.2	2.0	6.2	205	0.42	0.44	132	2.43
4	2.2	2.6	9.3	410	0.31	0.44	153	2.24
5	2.0	2.6	9.3	72	0.87	0.26	87	1.44
6	7.0	9.0	13.0	111	0.67	0.43	–	–
7	7.3	7.0	13.0	104	0.66	0.40	126	–
8	6.3	7.3	12.0	92	0.72	0.40	147	–

Note. C and C_{chol} are hemoglobin and cholesterol concentrations, respectively.

present method dependences of two parameters are taken into account, namely, ε_0 and q_0, whose sensitivity to Δn is especially high for the cases when $n = 1.02-1.07$. This range covers variations in the refraction index n of all biotissues [1, 4]. In the method under consideration the effect of n on the shape of particles has not been investigated, and it should be noted that the imaginary part up to the values $\kappa \leq 10^{-4}$ does not affect the accuracy of the method [13].

As follows from the expression (5), in order to determine Δn and n, one should known the mean particle dimensions r; on the contrary, at known n and the generalized parameter Q_0 (for which one should know the volume concentration of the disperse medium C_{v_0}) one can determine particle dimensions r. The method was certified for erythrocytes and their assemblies at higher C_v values when cooperative effects take place [4, 5, 13]. Until recently, the method has been the only acceptable method for evaluation of dimensions of subunits of biotissues whose relative fraction $C_v \to 1$.

Optical and Biophysical Parameters of Biotissues in the Normal State and in Pathology. A number of investigations of absorption spectra of blood of healthy humans in the visible and near IR regions bear witness that the heme absorption spectrum of the hemoglobin molecule [1, 4] in the combination of its two main derivatives: oxy-HbO_2 and deoxy-Hb forms [4, 5], is the most optically active component. In the case of various diseases the HbO_2-to-Hb concentration ratio changes towards an increase in the Hb amount, i.e., deoxygenation that is especially pronounced in patients with cardiovascular diseases (CVD).

However, spectral variations in blood of patients with cardiovascular diseases are caused by not only such hemoglobin derivatives as oxy-, deoxy-, and methemoglobin, but also the increased concentration of hemoglobin decay products: hematin, verdoglobin, and bilirubin [26]. Inasmuch as the blood pH decreases in the case of hypoxy (enhanced deoxygenation of erythrocyte hemoglobin), cleavage of bonds that connect heme with the globin part is facilitated compared to oxyhemoglobin [27]. In view of the fact that the diffuse reflection coefficient of blood of CVD patients $R \leq 0.10$, the method of weak absorption has been modified in [28] in order to calculate the absorption coefficient C_{O_2} of whole blood. With the use of earlier developed methods we calculated relative oxyhemoglobin concentrations C_{O_2} in dark blood and the parameter Q_0 that correlates with the mean dimensions of erythrocytes and their assemblies. We have found that these values and the relative refraction index of erythrocytes differ substantially from those in healthy humans (Table 3). Spectroscopic investigations of patients with oncological diseases bear witness to the increased methemoglobin and doxyhemoglobin concentration compared to the normal state [29, 30]. Presently, we carry out investigations on whole blood of patients with diabetes and lupus with the aim of developing optical diagnostic methods.

TABLE 4. Values of the Absorption Coefficient k_{ef} (cm^{-1}) for Tissue Samples in the Normal State and in the Case of Pathology

Sample	Tissue type	k_{ef}, nm				C_{O_2}
		600	700	825	900	
1	Tumor	1.20	0.19	0.06	0.27	0.22
	Normal tissue	1.45	0.18	0.17	0.29	0.65
2	Tumor	0.50	0.09	0.04	0.150	0.20
	Normal tissue	–	0.31	0.33	0.50	0.75
3	Tumor	1.61	0.24	0.18	0.31	0.69
	Normal tissue	4.10	0.28	0.41	0.63	0.86

TABLE 5. Optical Properties of Biotissues*)

Wavelength, nm	Tissue type				
	Rabbit muscle	Rabbit liver	Rabbit lung	Human adipose tissue	Donor blood
	k_{ef}, cm^{-1}				
633	0.33	–	0.72	0.75	–
650	0.31	–	0.67	–	19.8
700	0.29	1.55	0.47	–	8.6
805	0.19	0.88	0.36	0.2	5.1
845	0.23	0.73	0.33	–	6.1
900	–	–	0.44	–	–
	$q_{ef} = 1/3(1 - \mu_{ef})$				
633	24.5	–	7.9	14	–
650	–	–	–	–	–
700	26.0	11.0	6.8	–	102
805	21.3	11.0	6.7	–	98
845	–	–	–	–	–
900	17.9	–	7.4	–	–
	ε_{ef}, cm^{-1}				
633	365	330	413	180	–
650	–	–	–	–	4410
700	333	300	400	–	5108
805	308	260	377	100	4280
845					4019
900	347	317	420	–	–

*)Results are obtained by A. Ya. Khairullina and T. V. Oleinik.

Spectra of $R(\lambda)$, $T(\lambda)$, and $k_{ef}(\lambda)$ of tumors of the mammary gland bear witness to the strong difference of the oxygenation degree of tumors compared to the normal tissue, changes in dimensions of tumor cells compared to the normal state, and their absorptivity [29, 30]. High values of the diffuse reflection coefficients of tumor tissues

TABLE 6. Values of Optical and Statistical Parameters of Time-Dependent Intensity Fluctuations at Various Asphericity Parameters p of Erythrocytes

Asphericity parameter p	Optical and time-dependent statistical parameters				
	B	$\lambda = 633$ nm			$\lambda_1 \leq 1300$ nm; $\lambda_2 \geq 633$ nm
		$(\Delta\omega_{disk}/\Delta\omega_{sph})_0$	$(\sqrt{\varepsilon/kq})_{disk}/(\sqrt{\varepsilon/kq})_{sph}$	$(\Delta\omega_{disk}/\Delta\omega_{sph})_T$	$\frac{\Delta\omega(\lambda_1)_T}{\Delta\omega(\lambda_2)_T}\frac{\sqrt{(kq)_{\lambda_2}}}{\sqrt{(kq_{\lambda_1})}}$
1	1	1	1	1	1.26
3	1.306	0.90	1.16	1	1.41
5	1.398	0.82	1.41	1.16	1.58

compared to the normal state in the region 450–480 nm can be explained by a decrease in the hemoglobin concentration in the tissues and a decrease in the number of mitochondrii. Distinctive features observed in the longwave spectral region are related to hemoglobin deoxygenation (in the presence of blood) and cell mitochondria (Table 4) [29, 30].

Investigations of mammary and thyroid glands carried out recently have revealed the presence of hemoglobin derivatives of different decay degree and variations in the concentration of water in tumors, which should be taken into account in the course of surgical operations with the use of lasers, and in diagnostics.

Optical properties of other biotissues can be judged from Table 5. We obtained these data using the algorithms presented above with the exception of the attenuation index ε_{ef}, which was determined in an optically thin layer [7, 23]. Comparison of the results with data from the literature and reasons for certain differences are discussed in [23] and are related to pitfalls in the methods of investigations used by these authors.

In order to solve problems of diagnostics of the status of blood and tumors, and identification of biotissues of various nature (lungs, bone tissue, etc.) *in vivo* (i.e., under layers of skin, muscles, etc.) we have developed the method of calculation of diffuse reflection coefficients of layers of biotissues simulating organs of humans and animals [23, 24]. Model calculations carried out for blood in cases of CVD and tumors under layers of skin and muscles bear witness to the efficiency of the approaches proposed [20].

Possibilities of Multiwavelength Dynamic Spectroscopy Applications for Investigation of Biophysical Parameters of Erythrocytes. An analysis of possibilities of the dynamic spectroscopy is based on experimental results obtained in [31-34] which used autocorrelation functions of time-dependent fluctuations of the radiation backscattered by an erythrocyte suspension in which the Brownian character of their motion manifests itself.

It is shown in [35] that experimental values of halfwidths of spectra of time-dependent intensity fluctuations in the thickness regime at weak absorption ($R \geq 0.10$, $\lambda = 633$ nm, $C_{v0} \leq 0.07$) are related in a simple manner with the spectrum halfwidth at simple scattering $\Delta\omega_0$:

$$\Delta\omega_T = 4\left(\frac{\varepsilon_0}{k_0 q_0}\right)\Delta\omega_0 , \tag{6}$$

where $\Delta\omega_0 = 2DS^2$; $S = \frac{2\pi \sin \gamma/2}{\lambda}$; $D = k_B T/(6\pi\eta a_r)B$; $B = p^2/\sqrt{p^2-1}\arctan(\sqrt{p^2-1})$; k_B is the Boltzmann constant; T is the temperature of the medium; η is the viscosity coefficient of the medium; p is the asphericity parameter of erythrocytes; a_r is the semimajor axis of the rotation ellipsoid if erythrocytes are approximated by rotation ellipsoids; and γ is the scattering angle.

In Eq. (6) the quantity $\varepsilon_0/k_0 q_0$ can be determined from the diffuse reflection coefficient R_0 or from the brightness coefficient of the backscattered radiation ($\gamma \sim 180^0$).

As follows from Eq. (6) and data from [36], the attenuation index ε_0, and consequently the halfwidth $\Delta\omega_T$ of the spectrum, depend on the asphericity parameter p. Therefore, if the halfwidth parameters of intensity fluctuations spectra $\Delta\omega_T$ for two wavelengths $\lambda \leq 1330$ nm (the values of ε_0 for spherical and aspherical particles coincide at $\lambda \geq 1330$ nm), and the values of absorption coefficients k_0 and the parameter $q_0 = 1/3(1-\mu_0)$ are

known, one can determine both the values of the erythrocyte diameter $d = 2a_r$ and the values of the asphericity parameter (Table 6). It should be noted that in the case of strong absorption (λ = 440 nm) $\Delta\omega_T = \Delta\omega_0$, i.e., even in the case of the optically thick layer determination of geometrical parameters of erythrocytes is possible [4, 37]. Inasmuch as the attenuation index depends not only on the shape of particles but on the microrelief of the surface (in the case of the rigid membrane), the values of $\Delta\omega_T$ contain, in accordance with Eq. (6), information on the microrelief [31, 34]. It also seems advisable to carry out investigations on erythrocyte flicker (mechanical vibrations of the membrane) under conditions of the thickness regime [37].

As has been shown in our previous works [31, 34], the halfwidth of the spectrum of time-dependent intensity fluctuations contains, in accordance with Eq. (6), information on not only dynamic and geometric parameters of erythrocytes, but also their absorptivity. Therefore, the blood oxygenation degree can be determined not only from the intensity of scattered radiation, but from time-dependent spectral characteristics, i.e., from the different physical quantity. Effects of this type should also manifest themselves for other types of motion of erythrocytes, e.g., in vessels, and should be taken into account in investigations.

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