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AGGREGATES OF MULTILAYERED PARTICLES: THE SPECTRAL CHARACTERISTICS OF LIGHT SCATTERING AND SIZE DISTRIBUTION FUNCTIONS

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Abstract: In the paper, a new mathematical model for calculating the spectral characteristics of biological particles imitating blood corpuscles, as well as their aggregates has been put forward. The model takes into account the aggregate structure and multiple light scattering effect on them. The methods and algorithms based on the T-matrix technique for calculating the laser radiation scattering on a biological cluster were considered. A particle size distribution function was determined on a basis of *in vitro* simulation experiment on light scattering by particle aggregates. A discussion of the obtained results was presented.

Keywords: T-matrix method, erythrocytes, Tikhonov regularization method

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ОПРЕДЕЛЕНИЕ СПЕКТРАЛЬНЫХ ХАРАКТЕРИСТИК СВЕТОРАССЕЯНИЯ И ФУНКЦИИ РАСПРЕДЕЛЕНИЯ ПО РАЗМЕРАМ ДЛЯ АГРЕГАТОВ ИЗ МНОГОСЛОЙНЫХ ЧАСТИЦ

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Аннотация. В статье представлена новая математическая модель для расчета спектральных характеристик биологических частиц, имитирующих форменные элементы крови, а также их агрегатов с учетом структуры и эффектов многократного светорассеяния. Рассмотрены методы и алгоритмы, базирующиеся на методе Т-матриц расчета рассеяния лазерного излучения на группе биологических частиц. Определена функция распределения частиц по размерам на основе данных модельного эксперимента по рассеянию света агрегатами биологических частиц в случае *in vitro*. Представлено обсуждение полученных результатов.

Ключевые слова: Т-матрица, эритроцит, метод регуляризации Тихонова, многократное светорассеяние, форменный элемент крови

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Introduction

The blood test is an essential tool in modern medical diagnostics, serving as a sensitive method for monitoring the variation in health parameters. Furthermore, such characteristics of blood cells as size, deformability and shape immediately affect the processes of gas exchange in the tissues.

Measuring the optical characteristics of blood cells is crucial for developing new methods to diagnose biological structures used in diverse biomedical applications [1, 2], for example, for diagnosing blood conditions. Constructing suitable mathematical models describing the propagation of light in biological tissues can contribute substantially to tackling this challenge.

Early diagnostics of platelet dysfunction (deviations in platelet size and shape, changes in their aggregation properties) and related clotting disorders is important for identifying the risks of diseases closely linked to such conditions. This primarily applies to coronary heart disease.

The absorption and scattering efficiency of laser radiation largely depends on activated platelets prone to aggregation and thrombogenicity.

The process of erythrocyte aggregation, caused by natural damage in this case, can trigger hypercoagulability by releasing erythrocytic coagulation factors into the blood.

Each specific disease accompanied by pathological aggregation of blood cells requires comprehensive study to carefully select the most effective laboratory technique for monitoring and analyzing this process. The main factors influencing such pathological processes and the mechanisms behind them are impairments in the structure and function of erythrocytes, especially their ability to aggregate.

The optical characteristics of blood are very sensitive to the aggregation parameters of such cell types as erythrocytes and platelets; in particular, such processes affect the absorption and scattering efficiency of laser radiation by blood.

Exploring the quantitative relationships between biological properties and optical characteristics of biological particle aggregates is of immediate interest for advancing new approaches in optical biopsy, optical tomography, analysis of photodynamic and photothermal destruction of tissues and cells forming them. In particular, potential aggregation between the simulated particles should be taken into account. This study reports on numerical simulation of multiple light scattering by particle aggregates imitating the given biological structures, carried out for the first time to quantitatively study the assembly of biological particles into aggregates.

Our goal was to describe in detail the newly developed mathematical model for interaction of laser radiation with aggregates of biological structures with varying degree of complexity and organization in different cell types, testing the model proposed in specific scenarios.

Solution of the light scattering problem for the case of particle aggregate

The phenomena of light scattering by particle aggregates (clusters, ensembles, etc.) even having simple shapes can be rather difficult to interpret since these phenomena are governed by the interactions of fields from all particles comprising the aggregate. It should be borne in mind that each particle modifies the field not only in the vicinity of the others (multiple scattering), but also due to far-field interference.

In general, multiple scattering should be accounted for by rigorous numerical methods. Some of these methods explicitly take into account the interactions between particles [3] (like the superposition T-matrix approach [4–6] and the discrete dipole approximation (DDA) [7]), while others regard the aggregate as a cluster, i.e., a single particle of complex shape (like the finite-difference time-domain method [8]).

Multiple scattering can be computed iteratively [9, 10], for example, by the successive order-of-scattering technique, which is considered a special case of the superposition method.

Let us focus on the problem of multiple light scattering by an ensemble of particles imitating blood cells that contain nuclei, plasma membranes and cytoplasm inherent to the given biological structure, characterized by various geometric and optical parameters close to the simulated object.

The decomposition coefficients corresponding to the fields of incident light and light scattered by the aggregate can be related by calculating the T-matrix for laser scattering by an aggregate composed of multilayered particles within the strict theory of multiple light scattering. Since multiple interactions within the aggregate components are taken into account, it can be concluded that the scattered fields are connected.

T-matrices are calculated in a local coordinate system associated with the center of the corresponding particle for each of the aggregate particles, since they are independent of incident radiation. We follow the standard representation of the electromagnetic field incident on the *j*th particle as the sum of the initial incident field of the light wave and the field scattered by an ensemble of other particles located in a medium with a refractive index *n*, writing the expression [11]:

$$E_{inc}(j) = E_0(j) + \sum_{l \neq j} E_{scat}(l, j), \tag{1}$$

where $E_{scat}(l,j)$ is the sum of the fields scattered by the *j*th particle (we use *l*, *j* to denote the indices to emphasize the transition from the *l*th to the *j*th coordinate system.

We apply the T-matrix to calculate the field scattered by the *j*th particle; it is included in this equation as $E_{scat}(l,j)$. A local coordinate system associated with the *j*th particle was selected to calculate the T-matrix.

Relying on the translational properties of vector spherical wave functions, we can further transform the decompositions with respect to these functions from coordinate systems associated with the *j*th particles to the coordinate system of the *l*th particle. As a result, we obtain a system of linear algebraic equations (SLAE) for finding the coefficients of the light field scattered by an ensemble of multilayered particles a^j_{mn}, b^j_{mn}:

$$\begin{gathered}\begin{pmatrix} a^j \\ b^j \end{pmatrix} = T^j_{12}\left[\begin{pmatrix} p^{i,j} \\ q^{i,j} \end{pmatrix} + \sum_{l \neq j}\begin{pmatrix} A(l,j) & B(l,j) \\ B(l,j) & A(l,j) \end{pmatrix}\begin{pmatrix} a^j \\ b^j \end{pmatrix}\right], \\ T^j_{12} = T^j_1 + T^j_2,\ T^j_1 = \begin{pmatrix} a^j_{n_{1p}} & 0 \\ 0 & b^j_{n1q} \end{pmatrix},\ T^j_2 = \begin{pmatrix} 0 & a^j_{n_{1q}} \\ b^j_{n1p} & 0 \end{pmatrix};\end{gathered} \tag{2}$$

the expressions for the coefficients $a^j_{n_p}$, $b^j_{n_q}$, $a^j_{n_q}$, $b^j_{n_q}$ given here are provided in [11, 12], while the quantities $A(l,j)$ and $B(l,j)$ are defined in [13, 14].

Problems on light scattering by dielectric objects imitating biological structures, in particular blood cells, often entail solving the so-called ill-conditioned SLAE.

SLAE of the form (2) was solved via a stable algorithm of biconjugate gradients [15]. This method is based on the conjugate gradient squared method and does not allow for unstable behavior of the residual and accumulation of round-off errors.

Convergence to the required solution was substantially improved by using the algorithm for solving preconditioned SLAE as an LU-decomposition [16].

Analyzing the graph in Fig. 1, showing the dependences of relative residual norm on the iteration number for the method of preconditioned biconjugate gradients, we can conclude that the method used clearly has satisfactory convergence.

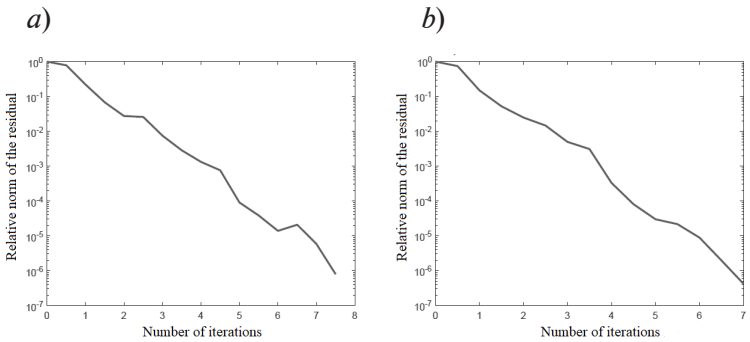

Fig. 1. Values of relative residual norm as a function of iteration number, obtained by the method of preconditioned biconjugate gradients.
Case of 4 particles in a layer, spaced 2 μm (*a*) and 1 μm (*b*) apart. Their parameters are given in Table

Table

Computational parameter sets for the problem of particle aggregates

Particle parameter	Parameter value for particle				
	I	II	III	IV	V
Distance between particles is 2 μm (Figs. 1,a and 2) and 1 μm (Fig. 1,b)					
Diameter, μm	6.5	6.5	7.0	7.6	–
Diameter, μm particle nucleus particle cytoplasm	 4.0 5.0	 4.0 6.0	 4.0 6.5	 4.0 6.5	
Refractive index of nucleus	1.37				
Refractive index of cytoplasm	1.00				
Refractive index of plasma membrane	1.33				
Distance between particles is 2 μm (Fig. 3) and 1 μm (Fig. 4)					
Diameter, μm	6.5	6.5	7.0	7.6	8.0
Diameter, μm particle nucleus particle cytoplasm	 4.0 5.0	 4.0 6.0	 4.0 6.5	 4.0 6.5	 3.0 4.0
Refractive index of nucleus	1.37				
Refractive index of cytoplasm	1.00				
Refractive index of plasma membrane	1.33				
Distance between particles is 2 μm (Fig. 5)					
Diameter, μm	6.6	6.6	7.1	7.7	8.1
Diameter, μm particle nucleus particle cytoplasm	 4.0 5.0	 4.0 6.0	 4.0 6.5	 4.0 6.5	 3.0 4.0
Refractive index of nucleus	1.37				
Refractive index of cytoplasm	1.34				
Refractive index of plasma membrane	1.33				
Distance between particles is 2 μm (Fig. 7)					
Diameter, μm	6.5	6.5	7.0	6.6	6.0
Refractive index of nucleus	1.37	1.33	1.33	1.37	1.37
Distance between particles is 1 μm (Fig. 9)					
Diameter, μm	6.5	6.5	7.0	8.6	12.0
Refractive index of nucleus	1.37	1.33	1.33	1.37	1.37

We developed a software package for computing T-matrices, taking into account multiple scattering for multilayered spherical structures. The T-matrix for spherical scatterers assumes a diagonal shape [17].

The software we have developed was used for fairly detailed analysis of the spectral characteristics of laser radiation (wavelength range from 400 to 650 nm) scattered by multilayered spherical particles.

Finding the numerical values of the coefficients a^j_{mn}, b^j_{mn} from expression (2), we can calculate such physical quantities as the absorption cross section (C_{abs}), scattering cross section (C_{sca}) and extinction cross section (C_{ext}), determined by the following procedure [18]:

$$C_{scat} = \frac{W_{scat}}{I_i},\ C_{ext} = \frac{W_{ext}}{I_i},\ C_{abs} = C_{ext} - C_{scat}, \tag{3}$$

where I_i is the intensity of incident light,

$$W_{scat} = \int_A S_{scat} \cdot e_r dA,\ W_{ext} = -\int_A S_{ext} \cdot e_r dA; \tag{4}$$

here

$$S_{scat} = \frac{1}{2}\Re[E^j_{scat} \times H^{j*}_{scat}],\ S_{ext} = \frac{1}{2}\Re[E^j_{inc} \times H^{j*}_{scat} + E^j_{scat} \times H^{j*}_{inc}]; \tag{5}$$

$$W_{scat} = \frac{1}{2}\Re\int_0^{2\pi}\int_0^{\pi}[E_{scat(\theta)}H^*_{scat(\phi)} - E_{scat(\phi)}H^*_{scat(\theta)}]r^2 \sin\theta d\theta d\phi, \tag{6}$$

$$W_{ext} = \frac{1}{2}\Re\int_0^{2\pi}\int_0^{\pi}[E_{inc(\phi)}H^*_{scat(\theta)} - E_{inc(\theta)}H^*_{scat(\phi)} - E_{scat(\theta)}H^*_{inc(\phi)} + E_{scat(\phi)}H^*_{inc(\theta)}]r^2 \sin\theta d\theta d\phi, \tag{7}$$

where

$$E_{inc(\theta)} = \sum_{n=1}^{\infty}\sum_{m=-n}^{n} E_{mn}\left[-ip^0_{mn}\psi'_n\tau_{mn} + q^0_{mn}\psi_n\pi_{mn}\right]\frac{e^{im\phi}}{kr}, \tag{8}$$

$$E_{inc(\phi)} = \sum_{n=1}^{\infty}\sum_{m=-n}^{n} E_{mn}\left[iq^0_{mn}\psi_n\tau_{mn} + p^0_{mn}\psi'_n\pi_{mn}\right]\frac{e^{im\phi}}{kr}, \tag{9}$$

$$H_{inc(\theta)} = \frac{k}{\omega\mu^0}\sum_{n=1}^{\infty}\sum_{m=-n}^{n} E_{mn}\left[ip^0_{mn}\psi_n\tau_{mn} - q^0_{mn}\psi'_n\pi_{mn}\right]\frac{e^{im\phi}}{kr}, \tag{10}$$

$$H_{inc(\phi)} = \frac{k}{\omega\mu^0}\sum_{n=1}^{\infty}\sum_{m=-n}^{n} E_{mn}\left[iq^0_{mn}\psi'_n\pi_{mn} + p^0_{mn}\psi_n\tau_{mn}\right]\frac{e^{im\phi}}{kr}, \tag{11}$$

$$E_{scat(\theta)} = \sum_{n=1}^{\infty}\sum_{m=-n}^{n} E_{mn}\left[-ia^j_{mn}\xi'_n\tau_{mn} - b^j_{mn}\xi_n\pi_{mn}\right]\frac{e^{im\phi}}{kr}, \tag{12}$$

$$E_{scat(\phi)} = \sum_{n=1}^{\infty}\sum_{m=-n}^{n} E_{mn}\left[-ib^j_{mn}\xi'_n\tau_{mn} - a^j_{mn}\xi'_n\pi_{mn}\right]\frac{e^{im\phi}}{kr}, \tag{13}$$

$$H_{scat(\theta)} = \frac{k}{\omega\mu^0}\sum_{n=1}^{\infty}\sum_{m=-n}^{n} E_{mn}\left[ia^j_{mn}\xi_n\pi_{mn} + b^j_{mn}\xi'_n\tau_{mn}\right]\frac{e^{im\phi}}{kr}, \tag{14}$$

$$H_{scat(\phi)} = \frac{k}{\omega\mu^0}\sum_{n=1}^{\infty}\sum_{m=-n}^{n} E_{mn}\left[ib^j_{mn}\xi'_n\pi_{mn} - a^j_{mn}\xi_n\tau_{mn}\right]\frac{e^{im\phi}}{kr}; \tag{15}$$

the following notations are used here: $\psi_n(\rho) = \rho j_n(\rho)$, $\xi_n(\rho) = \rho h^{(1)}_n(\rho)$ are the Riccati–Bessel functions; $E_{mn} = |E_0| i^n (2n+1)\frac{(n-m)!}{(n+m)!}$; the quantities q^0_{mn}, p^0_{mn} are defined in [11].

Substituting the expressions for the quantities $E_{inc(\theta)}$, $E_{inc(\phi)}$, $H_{inc(\theta)}$, $H_{inc(\phi)}$, $E_{scat(\theta)}$, $E_{scat(\phi)}$, $H_{scat(\theta)}$, $H_{scat(\phi)}$ to Eqs. (6) and (7), we obtain:

$$C_{scat} = \frac{4\pi}{k^2}\sum_{n=1}^{\infty}\sum_{m=-n}^{n}(n+1)(2n+1)\frac{(n-m)!}{(n+m)!}\left(\left|a^j_{mn}\right|^2 + \left|b^j_{mn}\right|^2\right), \tag{16}$$

$$C_{ext} = \frac{4\pi}{k^2}\sum_{n=1}^{\infty}\sum_{m=-n}^{n}(n+1)(2n+1)\frac{(n-m)!}{(n+m)!}\Re(p^{*0}_{mn}a^j_{mn} + q^{*0}_{mn}b^j_{mn}). \tag{17}$$

Based on expressions (12) for the θ-component of the scattered radiation intensity, we obtain

$$I_{scat(\theta)} = I_i \cdot \left| E_{scat(\theta)} \right|^2 .$$

We have thus obtained the formulas for determining the dependences of the above spectral characteristics on the wavelength of incident laser radiation (see Figs. 2–5).

We should note that the computations by the superposition T-matrix method in this paper were based on the Finite Difference Time Domain (FDTD) approach. A mathematical approach described in [12] was used for the problem on scattering by a multilayered sphere.

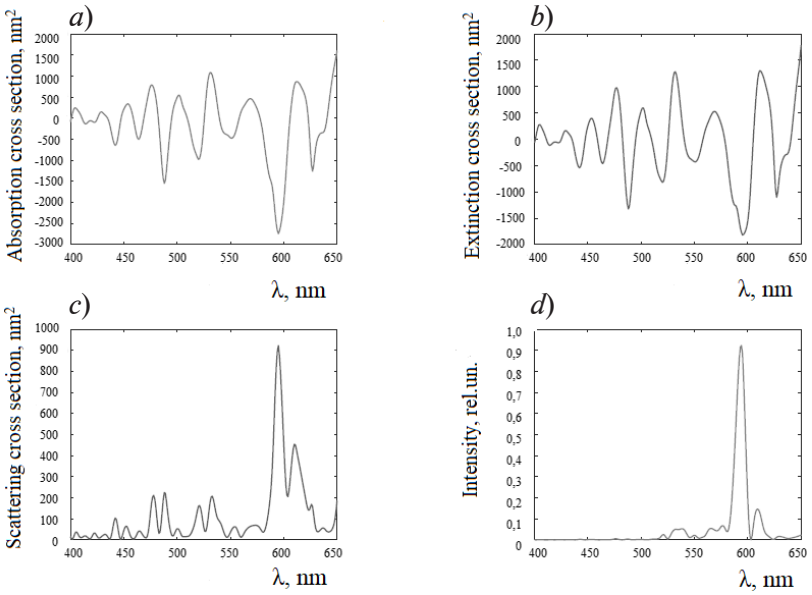

Fig. 2. Graphical representation of absorption cross sections (*a*), extinction cross section (*b*), scattering cross section (*c*) and scattered light intensity as functions of laser radiation wavelength incident at zero angle (*d*), for the given parameters of the problem
(4 particles in the layer, spaced 2 μm apart, see Table)

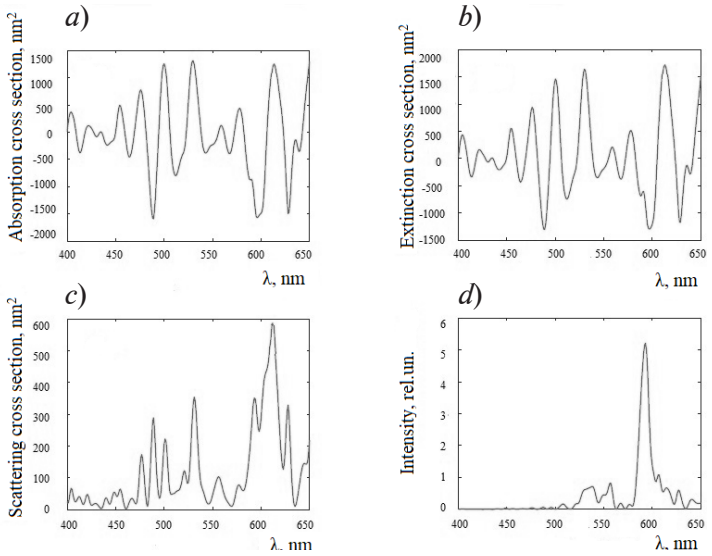

Fig. 3. Graphical representation of absorption cross sections (*a*), extinction cross section (*b*), scattering cross section (*c*) and scattered light intensity as functions of laser radiation wavelength incident at zero angle (*d*), for the given parameters of the problem
(5 particles in the layer, spaced 2 μm apart, see Table)

Determining the function for the size distribution of blood cells

The known variable (measured approximately) here is the intensity of light scattered by the aggregate of multilayered particles $I_{blood}(\lambda)$ imitating blood cells. Solving the problem should yield the size distribution of blood cells.

In this case, the quantity $I_{blood}(\lambda)$ is found through a model experiment to demonstrate the capabilities of the method (see graphs in Fig. 2,*d*–5,*d*).

Adopting the standard approach for such cases, the problem posed can be described by a linear Fredholm integral equation of the first kind, taking the following form:

$$Au \equiv \int_{\rho\min}^{\rho\max} I(\rho,\lambda)u(\rho)d\rho = f(\lambda), \tag{18}$$

where A is the integral operator; $I(\rho,\lambda)$ is the kernel of the integral equation; ρ is the equivalent radius, $\rho = ka$ (k is the magnitude of the wave vector, a is the particle radius); $u(\rho)$ is the required distribution of the cells over the sizes (equivalent radii); $f(\lambda)$ is the scattered light intensity by an ensemble of multilayered spherical particles, found by the model experiment, $f(\lambda) \equiv I_{blood}(\lambda)$.

This problem belongs to the class of so-called inverse ill-posed problems. The core of the integral equation $I(\rho,\lambda)$ is defined as the intensity of light scattered in the direction of the angle θ selected in the experiment by a multilayered spherical particle. We assume that $I(\rho,\lambda)$ is a continuous function in a rectangle

$$\Omega = ([c,d]\times[a,b]) \text{ and } f(\lambda) \in L_{2[c,d]},$$

where $a \equiv \rho_{\min}$, $b \equiv \rho_{\max}$, $c \equiv \lambda_{\min}$, $d \equiv \lambda_{\min}$.

Let $u(\rho)$ be a smooth function, when instead of f, its approximate value f_δ is known, such that $\|f - f_\delta\|_{L_{2[c,d]}} \le \delta$. Then we select the solution space as $U = W^1_{p[a,b]}$.

Let function $I_h(\rho,\lambda)$ be given instead of function $I(\rho,\lambda)$, while

$$\left\|I(\rho,\lambda) - I_h(\rho,\lambda)\right\|_{L_2(\Omega)} \le h;$$

then $\|A - A_h\|_{W^1_2 \to L_2} \le h$, where A_h is the approximation for the integral operator A with an accuracy h in the operator norm, which corresponds to the kernel $I_h(\rho,\lambda)$.

Notably, inversion of the operator A for the inverse problem (see expression (18)) is unstable for space $W^1_{p[a,b]}$. Then the Tikhonov regularization method can be used to numerically find the distribution $u(\rho)$.

Let us write the Tikhonov equation [19, 20]:

$$(A_h^* A_h + \alpha C)u^\alpha = A_h^* f,$$

where A_h is an operator from the space $W^1_{2[a,b]}$ to the subspace $L_{2[c,d]}$; A_h^* is an operator from $L_{2[c,d]}$ to $W^1_{2[a,b]}$ (conjugated to A_h); C is some operator whose matrix is defined in monograph [20].

Notably, we assume in this statement that there is no information about the smoothness of the exact solution; then we regard the operator A_h from the initial integral equation as acting from $L_{2[a,b]}$ to $L_{2[c,d]}$. In this case, the smoothing functional takes the form

$$M^\alpha[u] = \left\|A_h u^\alpha - f_\delta\right\|^2_{L_{2[c,d]}} + \alpha\left\|u\right\|^2_{L_{2[c,d]}} \to \min, \tag{19}$$

and the Tikhonov equation takes the form

$$(A_h^* A_h + \alpha E)u^\alpha = A_h^* f,$$

where E is the unit operator.

The function u^α minimizing the functional (19) depends on the value of the regularization parameter α.

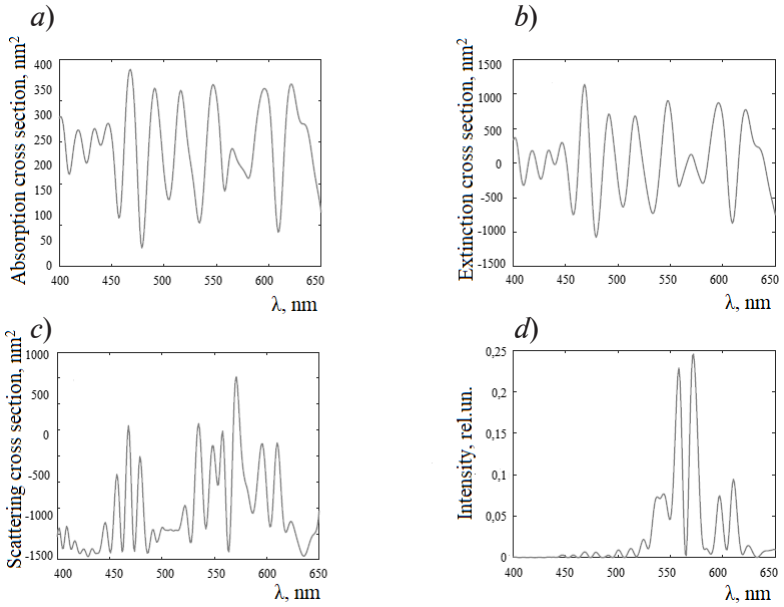

Fig. 4. Graphical representation of absorption cross sections (*a*), extinction cross section (*b*), scattering cross section (*c*) and scattered light intensity as functions of laser radiation wavelength incident at zero angle (*d*), for the given parameters of the problem
(5 particles in the layer, spaced 1 μm apart, see Table)

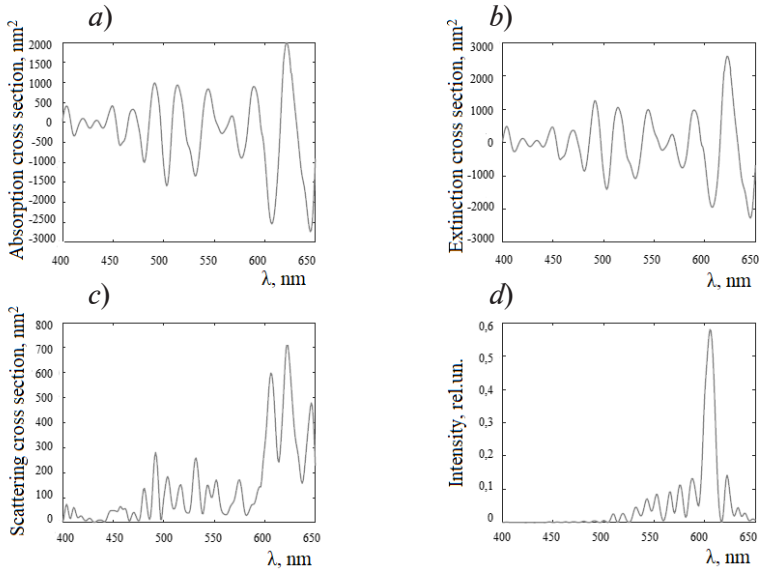

Fig. 5. Graphical representation of absorption cross sections (*a*), extinction cross section (*b*), scattering cross section (*c*) and scattered light intensity as functions of laser radiation wavelength incident at zero angle (*d*), for the given parameters of the problem
(5 particles in the layer, spaced 2 μm apart, see Table)

The regularization parameter providing optimal agreement between the experimental data and a priori information is selected for this case by the following approaches: relative residual method, quasi-optimality criterion, smoothing functional principle, *L*-curve method [19, 20]. The software package we have developed in this study was used to select the regularization parameter automatically by the predefined errors of both the integral equation kernel and the experimental data (see Figs. 6 and 8 below).

Results and discussion

The results obtained (see Fig. 2–5) confirm that the mathematical approach outlined in the study and the software package we have developed here based on it allow detecting the aggregation of simulated particles and their parameters, since varying the distance between the particles is accompanied by not only variation in the numerical values of spectral characteristics but also in the shape of the curves, as can be seen from the figures. We considered multiple light scattering by an ensemble of spherical particles with inclusions of concentric spheres with different radii.

Figs. 2,*d*–5,*d* graphically represent the scattering intensities and scattering cross sections of laser radiation as functions of radiation wavelength for different problem parameters (the parameters are summarized in Table).

It should be noted that the scattering cross section characterizes the efficiency of angle-resolved light scattering by a particle. In particular, the differences in both the scattering cross sections and its intensities for different biological substances follow from the difference in the sizes of the blood cells themselves, as well as the variability in their internal structures.

To find the erythrocyte distribution function over the equivalent radii, we solved the problem on mathematically describing the interaction of laser radiation with an aggregate consisting of a finite number of particles, taking into account their structure and the effects of multiple light scattering, as well as with the exactly given geometric and optical characteristics. Erythrocytes act as model particles. It bears mentioning that simulating the erythrocyte as a homogeneous scatterer is fairly reasonable, as it lacks cellular organelles and has a thin cell membrane (with little effect on light scattering). Some studies even generally assume the erythrocyte to be a structurally homogeneous sphere [21, 22].

To illustrate the methods described above, let us first consider the size distributions of erythrocytes used in medical practice [23]:

$$u(\rho) = A_1 \cdot e^{B_1(\rho - b_1)^2}, \tag{20}$$

$$u(\rho) = A_2 \cdot e^{B_2(\rho - b_2)^2} + A_3 \cdot e^{B_3(\rho - b_3)^2}. \tag{21}$$

The normal distribution is described by a formula of the type (20) ($A_1 = 1$, $B_1 = -3$, $b_1 = 3$); the bimodal distribution corresponds to a formula of the type (21), while the fraction of abnormally large cells amounts to 30% ($A_2 = 0.80$, $B_2 = -1.00$, $b_2 = 3.00$, $A_3 = 0.25$, $B_3 = -2.30$, $b_3 = 5.0$) [23].

We used different methods to select the regularization parameter α for the normal size distribution of erythrocytes:

by the residual, where $\|Au^\alpha - f\|/\|f\| = \delta$, the value of $\alpha = 0.00216$ (Fig. 6,*a*);

by the quasi-optimality criterion, where $\|\alpha u^\alpha / d\alpha\|$, the value of $\alpha = 1.1059 \cdot 10^{-9}$ (Fig. 6,*b*);

by the *L*-curve criterion, where $L^* = \lg\|Au^\alpha - f\|, \lg\|u^\alpha\|$, the value of $\alpha = 2.7648 \cdot 10^{-8}$ (Fig. 6,*c*);

by the smoothing functional principle, where $(\alpha\|u^\alpha\|^2 + \|Au^\alpha - f\|^2)/\|f\|^2) = C\delta^2$, the value of $\alpha = 0.00216$ (Fig. 6,*d*).

The optimal value of the regularization parameter amounted to

$$\alpha_{opt} = 0.002160 \text{ for } h = 0.11, \delta = 0.10.$$

Let us examine the graphs of the two functions in Fig. 7. The size distribution function (20) is represented by a continuous curve, and the result of the numerical solution to the inverse problem is represented by dotted curves with the noise level on the right side of Eq. (18) taken to equal 5%. Evidently, the curves practically coincide. It is thus clear that the shape of particle size distribution defined by expression (20) was restored with high accuracy from numerical solution to the problem of the form (18). Moreover, we can reasonably assume that the resulting distribution curve is close to the standard Price–Jones curve characterizing the distribution of erythrocytes in the blood of a healthy person [24].

The same as for the case of normal distribution, Fig. 8 illustrates the selection of the regularization parameter α for the case of bimodal size distribution of erythrocytes. The following results were obtained for the selection: by residual, $\alpha = 0.012805$ (Fig. 8,*a*); by quasi-optimality criterion, $\alpha = 1.311200 \cdot 10^{-9}$ (Fig. 8,*b*); by *L*-curve criterion, $\alpha = {}^{8-}10 \cdot 3.27810$ (Fig. 8,*c*); by smoothing functional principle, $\alpha = 0.00216$ (Fig. 8,*d*).

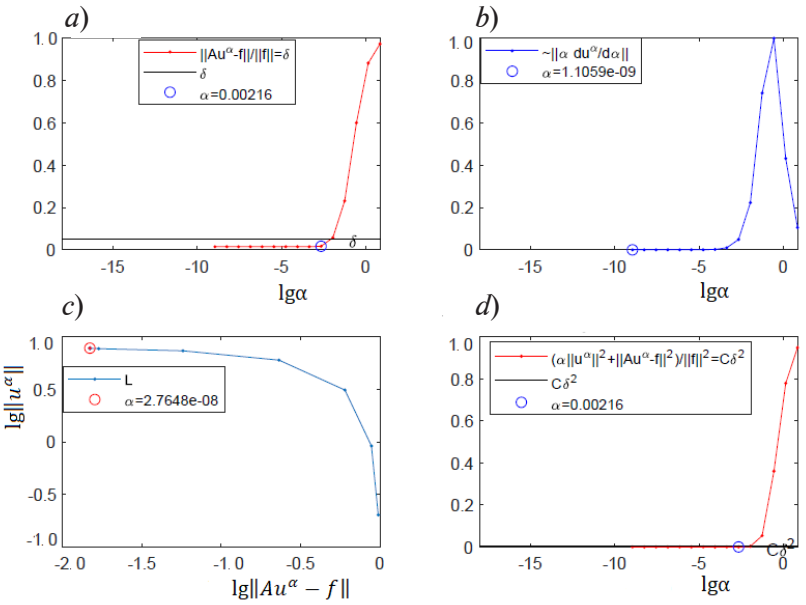

Fig. 6. Regularization parameter found by relative residual method (*a*), by quasi-optimality criterion (*b*) and *L*-curve criterion (*c*), by smoothing functional principle (*d*).
Case of normal size distribution of the particles.
The final optimal value of the required parameter is given in the text

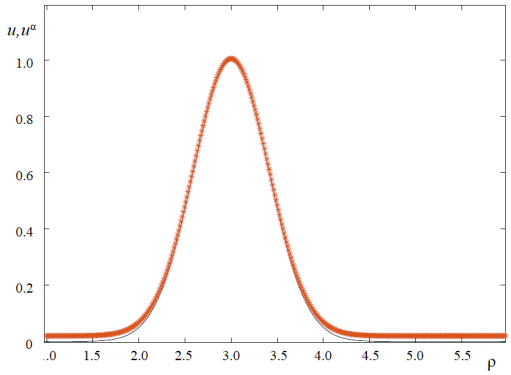

Fig. 7. Computed functions $u(\rho)$ (see Eq. (20), black solid curve) and $u^{\alpha}(\rho)$ (numerical solution of the inverse problem, colored curve) for distributions of 5 particles over the equivalent radii ρ;
particles are spaced 2 μm apart (see Table)

The optimal value of the regularization parameter amounted to

$$\alpha_{opt} = 0.012805 \text{ for } h = 0.11, \delta = 0.10.$$

Let us now consider the computational data presented in Fig. 9. A predetermined asymmetric bimodal size distribution (21) is shown by a continuous line. Such a distribution simulates the presence of fractions of normal and abnormally large erythrocytes.

The numerical solution of the problem allowed to reconstruct the intensities of both peaks on the particle size distribution with a high degree of accuracy (the peaks correspond to the fractions of typical and abnormally large cells).

The solution obtained by minimization corresponds to the model dependences predetermined for different types of distributions with an acceptable degree of accuracy. The error estimate that we obtained gives a satisfactory representation of the noise level in the right-hand side.

Thus, we have conclusively proved that a priori information about the smoothness and finiteness of the solution can be used to accurately reconstruct the distribution of erythrocytes over the equivalent radii and determine the variations in their width, which has major practical implications for modern medicine [25].

The mathematical model developed can serve for determining the size distribution function for particles imitating blood cells *in vitro*.

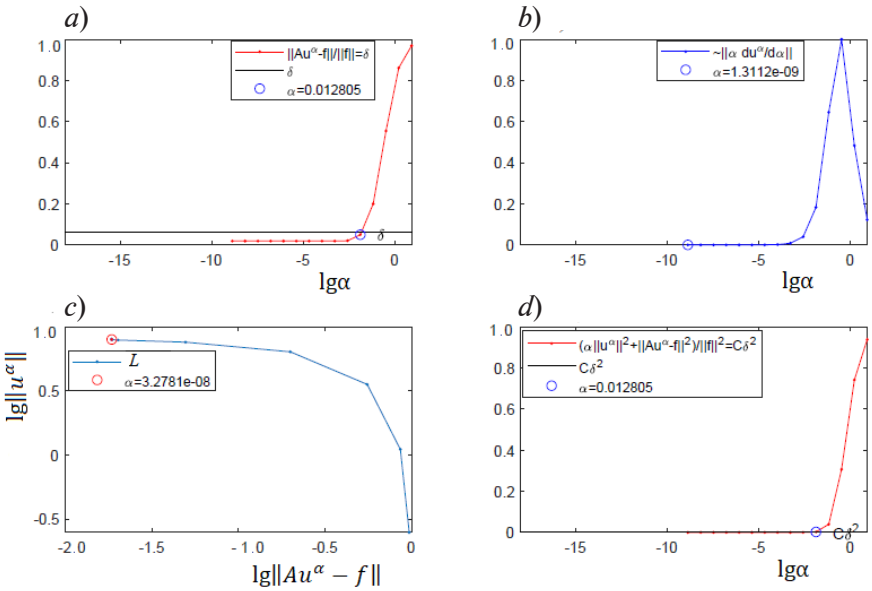

Fig. 8. Regularization parameter found by relative residual method (*a*), by quasi-optimality criterion (*b*) and *L*-curve criterion (*c*), by smoothing functional principle (*d*).
Case of bimodal size distribution of the particles.
The final optimal value of the required parameter is given in the text

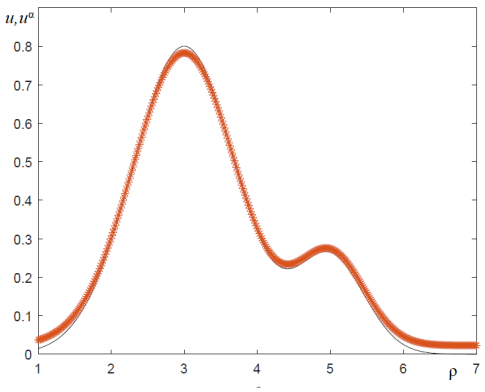

Fig. 9. Computed functions $u(\rho)$ (see Eq. (21), gray solid curve) and $u^{\alpha}(\rho)$ (numerical solution of the inverse problem, colored curve) for distributions of 5 particles along the equivalent radii ρ;
particles are spaced 1 μm apart (see Table)

Conclusion

Let us now summarize our key findings.

1. We have constructed a conceptually new model suitable for predicting the spectral characteristics in aggregates of spherical particles with a complex structure. The model can be used *in vitro* and takes a self-consistent approach to describing multiple light scattering by biological structures.

2. The model proposed can successfully yield the spectral distributions of optical parameters in a biological medium, which vary depending on different factors and induce fluctuations in the function and morphology of biological tissues (for example, aggregation of blood cells).

3. Effective software has been developed based on the given mathematical model, allowing to extract the size distributions of blood cells from the experimental data.

4. The results provided by the model show good sensitivity to fluctuations in the geometric characteristics of blood cell nucleus and plasma membrane. Such sensitivity allows to examine the physiological processes occurring in the body: for example, as the refractive index of the medium is increased by 0.34 (and, accordingly, the diameter of the simulated particles by 0.1 μm), the spectral characteristics of these particles change significantly (see the curves in Figs. 3 and 5). We should note that the changes in the size of the cell nucleus are often associated with the changes in metabolism in the human body induced by cell damage or physiological dysfunction.

The type of simulation outlined in this paper can be used to diagnose various conditions. For example, it is argued in [26] that the variations in the refractive index of the medium in the cell nucleus point to an initiating division process (mitosis), while [27] has established that the nucleus of a cancer cell exhibits internal structural changes compared to normal cells, associated with the geometric characteristics of the object considered.

The mathematical model constructed and the software based on it allow finding and analyzing the spectral characteristics for the optical parameters of the biological medium, in particular accounting for dynamics.

5. The new mathematical model provides a means for finding the particle distribution function over the equivalent radii for spherical particles with different structures, changing their geometric and optical characteristics, taking into account multiple scattering, which has major implications for medical practice.

An important result achieved in this study is that we developed a software package for computing light scattering by an aggregate whose structure includes layered spherical particles, additionally offering the options for accurately reconstructing the distribution of erythrocytes over the equivalent radii and measuring the variation in the width of such distributions. The software is valuable as an effective flexible tool for practitioners in biomedical optics; the optical characteristics and sizes of the biostructure considered can be tailored to record the dependences between them via a single automated setup.

The functions offered by the software package make it possible to collect a database for particles with different optical and geometric characteristics. This means that in the future, we will be able to comprehensively investigate the correlations between the optical characteristics and parameters of the biological substances simulated and their biological properties.

Data on the tendency towards aggregation in blood cells should open new avenues for qualitative assessment of changes in aggregation/disaggregation interactions accounting for the dynamics of the corresponding indicators.

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