3D simulation of aggregation of red blood cells for the study of the optoacoustic response

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Abstract. The paper presents mathematical modeling of the distribution of different shapes of red blood cells in plasma. The obtained two-dimensional and three-dimensional tissue models are designed to simulate acoustic response as a result of optoacoustic effect and to calculate the number of red blood cells and determine their shape. The results of mathematical modeling allow preparing the model solutions of blood using polystyrene microspheres. Red blood cells produce quasi-spherical assemblies in different pathologies that occupy a large part of volume (from 30 % to 50 %). The purpose of the research was to simulate spherical aggregates without intersections with the same parameters and unique spatial distribution determined by the structural factor. The main benefit of presented method was investigation of different aggregate compactness with the same size of aggregates containing erythrocytes of different shapes. In the result of 3D computer simulation the total maximum volume fraction of cells was 16 %. The procedure of cells distribution account in aggregates allowed obtaining maximum aggregate compactness ϕ₁ = 40 %.

1. Introduction

The quantitative analysis of the properties of biological media provides the necessary physiological information for effective diagnosis by optical method. Currently, the most commonly used methods for determining optical properties require invasive procedures and subsequent in vitro analysis. These methods are based on attenuation using spectrophotometry, reflection coefficient, fluorescence spectroscopy, Raman spectroscopy. The potential benefits of non-invasive method in vivo will be significant and will help to speed up the time for therapeutic decision. The optoacoustic method is based on the analysis of the acoustic signal generated by the absorption of laser radiation in a liquid medium. Thus, optoacoustic methods are promising in the field of study of blood composition, namely the establishment of hematocrit level, determining the percentage of aggregation of red blood cells, etc. The authors had conducted a number of theoretical and experimental studies in the field of optoacoustic interaction to create an optoacoustic cytometer [1, 2].

2. Materials and methods

In this study the authors used equal cells with random distribution within aggregate. The shape of the cell can be simulated as a sphere with radius a equivalent volume of which is given as \(V_\text{c}=4/3\pi a^3\). The cells have density \(\rho_\text{c}\) and compressibility \(k_\text{c}\), and their environment is characterized by density \(\rho_0\) and compressibility \(k_0\). It was assumed that the changes in acoustic parameters of cells were minor [3], so
that multiple scattering considering the Born’s approximation was ignored. The cell’s unit, designated \( V_{ag} \), is considered spherical, that correspond to human tissues (e.g., aggregates of red blood cells in pathological cases or breast tumors). Then the authors assume that the distance from \( V_{ag} \) to the observation point is much greater than the dimensions of \( V_{ag} \) (i.e., far field approximation).

Let \( n_c \) is the quantity of the equal cells inside the aggregate with centers located in the positions \( r_j \), \( j = 1, \ldots, n_c \) and taking into account the change of the variable \( r_0 = r_0 - r_j \), \( r_0 \) – position in three-dimensional space, \( n_0 \) – direction of incident wave, \( V_a \) – sphere volume of radius \( \alpha \).

The choice of sphere was induced by the spherical distribution of cells in aggregates. To correspond to the low-frequency approximations of the amplitude of scattering field from the spheres aggregates and from the equivalent hollow sphere, their radii of rotation \( R_g \) must be equal. The radius of rotation of the particle corresponds to the average square distance of the particle points from its mass center. In the case of a system of \( n_c \) spheres of radius \( \alpha \), the radius of rotation is determined as

\[
R_g = \sqrt{\frac{3}{5} a^2 + \frac{1}{n_c} \sum_{j=1}^{n_c} |r_j|^2},
\]

where \( r_j \) – position vector of the \( j \)-th cell relative to the center of the aggregate [4,8]. Thus, the radius \( r_0 \) of the equivalent hollow sphere must be expressed as

\[
r' = \sqrt{\frac{5}{3} R_g}.
\]

The spatial distribution of cells within one unit was modelled, for this the authors set the radius of the cell as \( \alpha = 2.75 \mu m \), which corresponds to the size of the red blood cell usually used in computer blood modeling.

3. Results and discussion

The authors assumed the radius of the unit \( r_{ag} \) as the radius of the outer shell (Figure 1) and assembly with the compactness \( \phi_i \), which sets the number of cells \( n_i \) in the unit. Cells were evenly distributed so that cells within the radius \( r_{ag} \) could overlap. The total amount of intersecting pairs was calculated. Then, by randomly selecting a cell, the system was modified. If the amount of intersecting pairs of the renewed system was not greater than in the former one, the change was assumed. The process was repeated until the overlap occurred. It made possible to achieve an aggregate compactness of \( \phi_i \) up to 40 \% in three dimentional case, whereas the other method using occasional serial absorption [4, 5] allowed obtaining a compactness of about 30 \%.

Figure 1. Cell aggregates of radius \( r_{ag}/\alpha = 7 \), left with compact factor \( \phi_i = 10 \% \), and right with compact factor \( \phi_i = 40 \% \)

Figure 1 shows the spatial locations of cells within the same assembly for two aggregates of 10 \% and 40 \% with the same aggregation radius \( r_{ag}/\alpha = 7 \). The radius of rotation was calculated using equation
(1). For the unit shown in Figure 1, the change in compact factor from 10 % to 40 % causes the slight increase in the rotation radius from $R_g = 13.47 \, \mu m$ to $R_g = 14.26 \, \mu m$.

![Figure 2. Cell assembly of biconcave red blood cells](image)

Figure 2 shows the spatial locations of assemblies of biconcave erythrocytes within the same unit with different spatial distributions.

Polystyrene microspheres (PST) with a diameter of 5 mµ (LLC "Diafarm") were selected for modeling of red blood cells. The size of polystyrene spheres is corresponded to the size of red blood cells. The microspheres were studied using a microscope Olympus X-71 NTEGRA Vita (Figure 3).

![Figure 3. Models of red blood cells](image)

Figure 3. Models of red blood cells a) model solution of polystyrene microspheres (Olympus X-71) b) mathematical models of red blood cells in hematocrit H=0.4 and the amount of N=673.

4. Conclusion
In three-dimensional computer simulation the total maximum volume fraction of cells was 16 %. The procedure of cells distribution account in aggregates allowed obtaining maximum aggregate compactness $\phi_i = 40 \%$ (Figure 1). For comparison, a standard method using occasional serial absorption [4, 6] gives compact factor about 30 %. Thus, the maximum total volume fraction [6] $\phi_{fr, max}$ was also 40 %. As a result, the maximum of the total volume part $\phi_{max}$ was restricted to $\phi_{max} = \phi_{i, max} \phi_{fr, max} = 16 \%$. 
To obtain the spatial distribution of cells the authors used method that was not based on a general physical model of interaction between cells [1, 2]. The method was used to create simulated environments. The purpose was to create an environment containing non-intersecting spherical assemblies, with all units having the equal radius and compact factor with a unique spatial distribution of the cell determined by the structural factor. The main benefit of this method was to have different aggregate compactness with the same size of aggregates containing erythrocytes of spherical shape and biconcave erythrocytes. With the help of the obtained mathematical models of tissues, it is possible to simulate the acoustic signal formed as a result of the optoacoustic effect when exposed by laser [1, 2, 9, 10]. Further, using polystyrene microspheres, it is possible to simulate the distribution of erythrocytes in the liquid and carry out experimental measurements using the LIMO laser system to determine the number of spheres in the liquid by analyzing the optoacoustic signal.

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