Modeling the electrical properties of dysmorphic erythrocytes in pathology

© S.N. Mamaeva[1], A.N. Pavlov[1], G.V. Maksimov[2]

[1] North-Eastern Federal University, Yakutsk, Russia
[2] Moscow State University, Moscow, Russia
E-mail: sargylana_mamaeva@mail.ru

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A mathematical model of the electrical properties of erythrocytes in normal and pathological conditions is presented. Using the proposed model, the role of the surface charge of erythrocytes in changing the speed of cell movement under the influence of an external electric field has been investigated. It is assumed that the presented model will allow for the description of the movement of erythrocytes with adsorbed viral particles as a mechanism for metastasis and recurrence in the development of oncological diseases.

Keywords: erythrocytes, viral particles, surface charge, mathematical modeling, dynamics of erythrocyte movement, scanning electron microscopy.

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The increasing number of oncological diseases, their relapses, and metastatic spreading poses a research challenge of identifying the mechanisms of disease onset and development at molecular and cellular levels.

It is known that the functional state of erythrocytes (*Er*) depends on the surface charge of their membrane [1]. Under normal conditions at a physiological pH value, erythrocytes carry an excess negative charge on their surface, which causes electrostatic repulsion of cells. The *Er* surface charge may be reduced when the membrane properties change (when sialic acids split off) [2] under the influence of intravascular microcirculation factors (blood pH and viscosity), when certain plasma factors are adsorbed on the membrane, etc. Certain correlations between changes in the *Er* electrical characteristics and clinical manifestations of various diseases (arterial hypertension, type 2 diabetes mellitus, non-alcoholic steatohepatitis) have been identified [3]. The amount of reversibly and irreversibly altered *Er* forms, which are induced by changes in electrical potentials, increases in this case [4]. There is reason to believe that the number of negative charges, which are accountable for the disaggregated state of cells, on the *Er* surface decreases. This has a direct effect on the rheological parameters of blood.

Examining the erythrocytes of patients diagnosed with cervical cancer (CC) via scanning electron microscopy (SEM), we have discovered dysmorphic cells with nanoscale particles on their surface. It was found that the sizes of nanoparticles correspond to the sizes of viral particles (VPs) of human papillomaviruses (HPV) [5]. Combined with the fact that cervical cancer is caused by HPV types 16 and 18, the results reported in [5] suggest that VPs may attach to the *Er* membrane, altering the electrical properties of *Er*.

It is evident that a physicomathematical model needs to be formulated and implemented in order to gain an insight into the physical properties of erythrocytes and VPs in pathology. Such models may be incorporated into a comprehensive method for studying the characteristics of diseases at the cellular level with both experimental and theoretical approaches to solving the problem at hand, and the results obtained may be used to develop a systematic differential method for disease diagnostics.

Thus, the task of determining the surface charge of erythrocytes in human blood is relevant at present, since they have a tendency to alter their parameters depending on the disease. The aim of the present study is to construct a mathematical model (MM) for monitoring the changes in *Er* surface charge with account for changes in the shape and binding of VPs and the influence of *Er* electric charge variations on electrophoretic mobility.

The presented model serves for determining the surface charge of dysmorphic erythrocytes with VPs attached to them in pathology. Erythrocytes in the normal condition are approximated by an rotational ellipsoid. This model relies on the assumption that changes in the *Er* shape and size during VP binding are needed to stabilize the initial strength of the electric field that prevents the formation of *Er* conglomerates. Thus, we propose to consider the mechanism of VP adsorption on the *Er* surface based on Coulomb interactions between VPs and charges on the *Er* surface, which eventually lead to a change in the *Er* shape. Figure 1, *a* shows an example SEM image of erythrocytes in IgA nephropathy in a child with hematuria.

In the MM, such *Er* shapes as normocytes and ovalocytes are approximated by second-order surfaces: a spheroid and an rotational ellipsoid. The following equations were used to determine the surface charge and the surface electric field strength of *Er*:

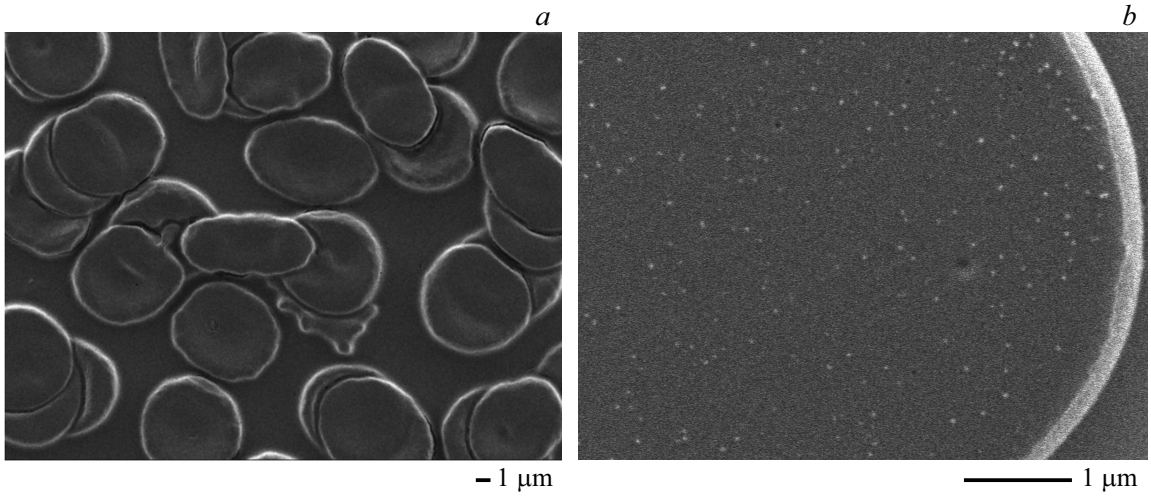

Figure 1. SEM images of erythrocytes in pathology. *a* — Dysmorphic erythrocytes; *b* — nanoparticles on the erythrocyte surface.

– *Er* surface charge density equation

$$\sigma = \varepsilon\varepsilon_0 E_{er},$$

where ε_0 is the permittivity of vacuum, ε is the permittivity of a liquid, and E_{er} is the electric field strength in the vicinity of the *Er* surface;

– equation of the surface charge of an *Er* approximated by an rotational ellipsoid

$$q = 4\pi abc\varepsilon\varepsilon_0 E_{er}\left(\frac{1}{a^2}+\frac{1}{b^2}+\frac{1}{c^2}\right)^{1/2},$$

where a, b, and c are the principal semi-axes.

In addition, the numerical experiment provides an opportunity to determine the VP surface charge on the *Er* surface on the basis of the following equation:

$$q_{pat} = q_{norm} + Nq_{nano},$$

where N is the number of VPs on the *Er* surface. Standard values of the *Er* surface charge ($q_{norm} = 5.93 \cdot 10^{-14}$ C), spheroid constants $a_{norm} = 0.20 \cdot 10^{-6}$ m and $b_{norm} = c_{norm} = 3.75 \cdot 10^{-6}$ m for approximation of normal erythrocytes, and principal semi-axes $a_{pat} = 9.37 \cdot 10^{-6}$ m, $b_{pat} = 5.21 \cdot 10^{-6}$ m, and $c_{pat} = 0.20 \cdot 10^{-6}$ m of the rotational ellipsoid for approximation of erythrocytes in pathology were used in numerical calculations.

For example, the number of VPs on the *Er* surface for a patient with cervical cancer was estimated at $N \approx 1545$ based on the SEM image in Fig. 1, *b*. The average surface charge of a dysmorphic *Er* was found to be $q_{pat} = 5.26 \cdot 10^{-14}$ C in numerical calculations, and the VP charge was estimated at $q_{nano} = 0.78 \cdot 10^{-17}$ C.

Calculations revealed that the *Er* near-surface charge decreases when VPs attach to the *Er* surface (with the change in erythrocyte shape and size taken into account).

The obtained calculated data on the *Er* surface charge in pathology were used in the model of *Er* dynamics under the influence of external electric field $\mathbf{E}_{ext}$. As a first approximation, the motion of erythrocytes is considered to remain steady over time in a thin buffer liquid layer on a smooth flat surface between two planar electrodes (an infinite flat structure).

In the study of *Er* dynamics, *Er* are regarded as point charges (with the numerical values determined by the method presented above) exposed to external and internal electric fields. With these assumptions taken into account, the calculation of electrical characteristics and determination of the *Er* dynamics may be performed with the use of two models specified by the following equations:

– equation of motion of erythrocytes with viscosity and their spatial charge taken into account

$$m_{er}\dot{\mathbf{v}} = q_{er}\frac{\mathbf{E}}{\varepsilon} - SC\frac{\rho v^2}{2}\frac{\mathbf{v}}{v}, \qquad (1a)$$

where m_{er} is the *Er* mass, ρ is the buffer liquid density, C is the solution resistance coefficient, S is the maximum cross section of the body, q_{er} is the *Er* surface charge, $\mathbf{E} = \mathbf{E}_{ext} + \mathbf{E}_{int}$, $\mathbf{E}_{ext}$ is the external electric field, $\mathbf{E}_{int}$ is the internal electric field of *Er* spatial charges in liquid, and $\mathbf{v}$ is the *Er* velocity;

– Navier–Stokes equation of motion for erythrocytes

$$(\mathbf{v}\cdot\nabla)\mathbf{v} = -\frac{\rho_{ch}}{\rho_{er}}\mathbf{E} + \frac{\eta}{\rho_{er}}\Delta\mathbf{v} + \frac{\eta}{3\rho_{er}}\nabla(\nabla\cdot\mathbf{v}), \qquad (1b)$$

where ρ_{ch} is the density of *Er* spatial charges in liquid $\left(\frac{\rho_{ch}}{\rho_{er}} = \frac{q_{er}}{m}\right)$, ρ_{er} is the *Er* mass density, and η is the buffer coefficient;

– equation of electric displacement of the electric field of the *Er* spatial charge

$$\mathrm{div}\mathbf{D}_{int} = \rho_{ch}, \qquad \mathrm{rot}\mathbf{E}_{int} = 0, \qquad (2)$$

where ρ_{ch} is the density of *Er* spatial charges in liquid that is easy to calculate as $\rho_{ch} = \frac{q_{er}n}{V}$, n is the number of erythrocytes in liquid volume V, and $\mathbf{D}_{int} = \varepsilon\varepsilon_0\mathbf{E}_{int}$;

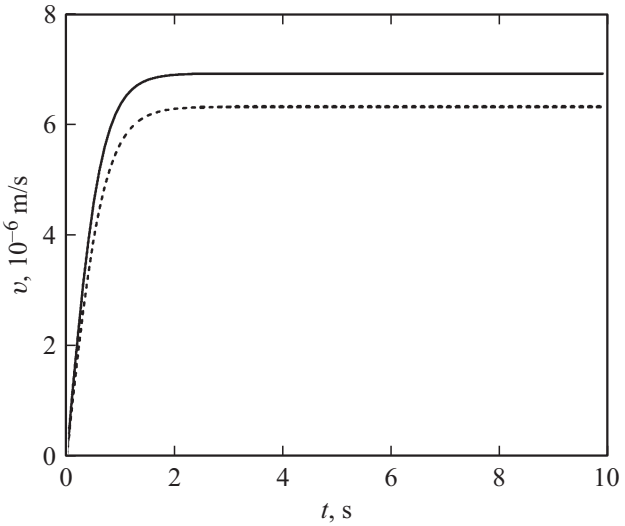

Figure 2. Dependences of erythrocyte velocities on time for different surface charge values under otherwise equal conditions of the numerical experiment. Solid curve — $q_{norm} \approx 6 \cdot 10^{-14}$ C; dotted curve — $q_{pat} \approx 5 \cdot 10^{-14}$ C.

5) continuity equation:

$$\mathrm{div}(\rho_{ch}\mathbf{v}) = 0. \tag{3}$$

The first model is comprised of Eqs. (1a), (2), and (3), while the second model incorporates Eqs. (1b), (2), and (3).

Since an infinite flat system is considered, all the sought-for quantities depend only on coordinate y. Therefore, the solution in the first model is sought in the form $v_x = v_x(y)$, $v_y = v_y(y)$, $\rho_{ch} = \rho_{ch}(y)$, $\mathbf{E} = E_{int}(y)\mathbf{e}_x + E_{int}(y)\mathbf{e}_y$, and the second model has a solution of the form $v_y = v_y(y)$, $\rho_{er} = \rho_{er}(y)$, $\mathbf{E} = E_y(y)\mathbf{e}_y$.

Thus, a system of four ordinary first-order differential equations is obtained in the first model:

$$\dot{v}_x = \frac{q_{er}}{m_{er}}\frac{E_{int\,x}}{\varepsilon} - C\frac{\rho v_x^2}{2}S,$$

$$\dot{v}_y = \frac{q_{er}}{m_{er}}\frac{E_{ext} + E_{int\,y}}{\varepsilon} - C\frac{\rho v_y^2}{2}S,$$

$$\dot{\rho}_{ch} = \frac{\rho_{ch}}{v_y}\dot{v}_y, \dot{E}_{int\,y} = \frac{\rho_{ch}}{\varepsilon_0\varepsilon}\dot{y},$$

while a system of three ordinary first-order differential equations corresponds to the second model:

$$\dot{y} = v_y(y), \dot{v}_y = G(y)\dot{y},$$

$$\dot{G}(y) = \frac{3\rho_{er}}{4\eta}\left(v_y^2 G(y) + \frac{e}{m}E_y(y)\right).$$

Figure 2 shows one result obtained using the MM with the *Er* dynamics equation applied with account for the resistance of the medium in which erythrocytes are moving, the viscosity, and the spatial charge of erythrocytes under the influence of an external electric field: a comparison of *Er* velocities in normal and pathological conditions (i.e., at different erythrocyte surface charges).

The obtained data on *Er* velocities under the same numerical experiment conditions reveal that the velocities of dysmorphic erythrocytes are significantly lower than the velocities of normal ones. This was confirmed in experiments [6].

Thus, the proposed model was used to assess changes in *Er* surface charges in pathology with validation of the *Er* size and electrical charges of VPs on the *Er* surface. The spread of VPs within blood channels by attachment to the *Er* surface in pathology is the probable cause of tumor metastasis and relapses of oncological diseases.

In addition, the MM for determination of the *Er* surface charge in pathology was used to model the motion of erythrocytes in a buffer liquid under the influence of an external electric field and estimate the velocity of this motion. The implementation of this MM revealed a significant dependence of the *Er* dynamics on the surface charge. The results of MM-based numerical experiments, which offer good prospects for improvement and a high level of parameter variability, may be used to interpret the results of experiments on electrophoretic mobility of erythrocytes in various pathological conditions.

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Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed voluntary consent was obtained from each study participant.

Conflict of interest

The authors declare that they have no conflict of interest.

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