

## Mathematical model of the motion of asymmetric erythrocytes along narrow capillaries

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**Abstract** — A mathematical model of the motion of 3-dimensional erythrocytes along fragments of capillary networks consisting of a small number of narrow capillaries is constructed. The model takes into account the lengths and inner diameters of capillaries, the form and position of an erythrocyte in a capillary, the viscosity of the plasm and the contents of an erythrocyte, the volume and surface area of an erythrocyte, the elastic characteristics of an erythrocyte, the membrane rolling of an erythrocyte, and the intervals between the entries of erythrocytes into the capillary network. The formulas for the dependence of pressure differential causing the blood flow in fragments of capillary networks on the parameters of the model are obtained. The dependences of the blood flow rate through a capillary tee on the lengths of capillaries forming the tee, on the pressure differential at the ends of the tee, and on the intervals between the entries of erythrocytes into the tee are obtained.

Experimental and theoretical studies of hemodynamics in a microcirculation system allows us to describe quantitatively the interrelated motion of the viscous plasm and elastic cells (erythrocytes) along capillaries. In order to describe the motion of the plasm, we may use the basic hydrodynamic equations (equations of motion and continuity), and the form of erythrocytes is characterized by equations of the mechanics of a deformed solid body. The simultaneous solution of those equations subject to the corresponding boundary conditions determines the spatial distribution of the pressure in the plasm, the velocity of the plasm and erythrocytes, and the energy consumption for the blood motion in capillaries. The existing models using these relations simulate the complicated character of interaction of blood cells in microvessels only in the first approximation [2, 4, 5, 7–12, 15, 16, 19, 21, 25, 26]. Thus, the rheological properties of blood were considered in [26], the erythrocyte membrane rolling in wide capillaries (with the diameter exceeding the diameter of the erythrocyte) was considered in [16]. An asymmetric form of an erythrocyte in a wide vessel was considered in [8], the motion of an erythrocyte having a symmetric parachute shape was considered in [15], in papers [4, 12] erythrocytes had the shape of elastic balls and in [5] were shaped as cylinders. A 2-dimensional model with a rolling membrane was constructed in [19]. However, such important characteristics as the volume and surface area of erythrocytes were not taken into account in those models. The amount of oxygen transported by an erythrocyte depends on its volume and the rate of oxygen release from an erythrocyte is determined by its surface area. A three-dimensional model of the motion of an erythrocyte along a capillary was

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constructed in [9, 10], this model takes into account the volume and surface area of the erythrocyte whose membrane rolls. Based on this model, the motion of a set of erythrocytes along separate capillaries and fragments of capillary networks was considered. The formulas describing the dependence of the pressure gradient causing the blood flow through fragments of capillary networks on the parameters of the model were obtained. The dependences of the rate of blood flow through a capillary tee on the lengths of the capillaries forming the tee, on the pressure differential at the ends of the tee, and on the intervals between the moments of entrance of erythrocytes into the tee are obtained. Since practically any capillary network can be constructed from various tees, the models and the results obtained here can be easily generalized to capillary networks of any structure.

## 1. DESCRIPTION OF THE MODEL

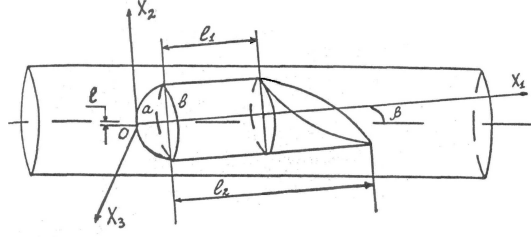
### 1.1. Motion of an erythrocyte along a capillary

Constructing the model, we assume that a capillary is a cylindrical pipe with the inner diameter  $D$ , along which an erythrocyte is moving uniformly. The plasma is a viscous incompressible Newtonian fluid filling the space between erythrocytes and forming a thin layer between the surface of an erythrocyte and the wall of the capillary. There is no flow through the walls of the capillary and the membrane of the erythrocyte. An erythrocyte is an elastic body with the Young modulus 6000–8000 N/m<sup>2</sup> and the Poisson coefficient 0.5 [3]. The surface area and volume of an erythrocyte are assumed to be constant under deformation. In the motion of an erythrocyte along a capillary, its membrane rolls (the motion resembles that of a tractor or tank tracks) with some constant frequency  $f$  [18].

In very narrow cylindrical capillaries, an erythrocyte fills the space of the capillary almost completely and its shape is close to cylindrical. Therefore, the middle part of the erythrocyte was approximated by a cylinder. The front part of the erythrocyte (relative to the motion direction) was approximated by a half-ellipsoid of rotation due to the following arguments. First, doing so we achieve the smoothness of junction between the cylinder and the half-ellipsoid (the tangents at the points of the junction coincide), which is important for the plasma flow around the erythrocyte. Second, the form of the half-ellipsoid is determined by its semi-axes. Varying these semi-axes, we can get various forms of the front (relative to the motion direction) part of the erythrocyte. Therefore, the surface of the erythrocyte was approximated by a truncated cylinder (with the minimal and maximal generatrices  $l_1$  and  $l_2$ , respectively) bounded from one side by the half of the ellipsoid of rotation with the semi-axes  $a, b, b$  (Fig. 1).

Then, according to [1], the volume of the erythrocyte is

$$V = \pi b^2 \left( \frac{2a}{3} + \frac{l_1 + l_2}{2} \right) \quad (1.1)$$



**Figure 1.** Model of an erythrocyte in a capillary in the Cartesian coordinates  $OX_1X_2X_3$ . The surface of the erythrocyte is approximated by the truncated cylinder (with the minimal and maximal generatrices  $l_1, l_2$ , respectively) bounded from one side by the half of the ellipsoid of rotation with the semiaxes  $a, b$ ;  $\beta$  is the angle between the axes of the capillary and the cylinder (erythrocyte),  $l$  is the distance from the point  $O$  to the axis of the capillary.

the surface area of the erythrocyte is

$$\begin{aligned}
 S &= A + 2\pi b l_1 + \pi b (l_2 - l_1) + \pi b (4b^2 + (l_2 - l_1)^2)^{1/2} \\
 A &= \pi b \left( b + \frac{a \arcsin \varepsilon}{\varepsilon} \right), \quad \varepsilon = \frac{(a^2 - b^2)^{1/2}}{a}, \quad a > b \\
 A &= \pi b^2, \quad a = b \\
 A &= \pi b \left( b + \frac{a^2}{2b\varepsilon} \ln \left( \frac{1+\varepsilon}{1-\varepsilon} \right) \right), \quad \varepsilon = \frac{(b^2 - a^2)^{1/2}}{b}, \quad a < b.
 \end{aligned} \tag{1.2}$$

Solving these equations with respect to  $l_1$  and  $l_2$ , one can express  $l_1$  and  $l_2$  through  $a, b, V, S$ . Therefore, the form of the erythrocyte is determined either through  $a, b, l_1, l_2$ , or through  $a, b, V, S$ .

The position of the erythrocyte in the capillary is determined by the distance  $l$  from the point  $O$  positioned on the axis of the cylinder (erythrocyte) to the axis of the capillary and by the angle  $\beta$  between the axes of the cylinder (erythrocyte) and the capillary (Fig. 1).

In order to describe the motion of the erythrocyte in a capillary, we use the system of equations describing the hydrodynamics of plasm subject to the form and position of the erythrocyte in the capillary. The pressure in the thin gap between the erythrocyte and the wall of the capillary varies in the axial and azimuthal directions, whereas in the radial direction it remains practically constant. The plasm flow in the capillary is assumed to be laminar. The forces of inertia are negligibly small. Taking into account these assumptions, we can assume that the motion of the plasm is described by the Poiseuille law in the intervals between erythrocytes and by the system of Reynolds equations for the lubricating layer in the gap between the erythrocyte and the wall of the capillary; in the cylindrical system of coordinates  $(X_1, r, \varphi)$  the latter system has the form [9, 12, 14]:

$$\frac{\partial P}{\partial X_1} = \frac{\mu}{r} \frac{\partial}{\partial r} \left( r \frac{\partial u}{\partial r} \right) \tag{1.3}$$

$$\frac{\partial P}{\partial \varphi} = \frac{\mu}{r} \frac{\partial}{\partial r} \left( r \frac{\partial w}{\partial r} \right) \quad (1.4)$$

$$\frac{\partial P}{\partial r} = 0 \quad (1.5)$$

$$\frac{\partial w}{\partial \varphi} + \frac{\partial(ru)}{\partial X_1} + \frac{\partial(rv)}{\partial r} = 0 \quad (1.6)$$

where  $\mu$  is the viscosity of the plasm,  $u, w, v$  are the axial, azimuthal, and radial components of the plasm velocity, respectively,  $P(X_1, \varphi)$  is the pressure of the plasm,  $P, u, v$ , and  $w$  are functions  $2\pi$ -periodic with respect to  $\varphi$ .

The cylindrical system of coordinates  $(X_1, r, \varphi)$  is related to the Cartesian system of coordinates  $(X_1, X_2, X_3)$  in the following way (Fig. 1):

$$X_1 = X_1, \quad X_2 = r \cos \varphi, \quad X_3 = r \sin \varphi, \quad r^2 = X_2^2 + X_3^2.$$

The system of Reynolds equations was solved in the system of coordinates  $(X_1, r, \varphi)$  (Fig. 1). The boundary conditions for hydrodynamic equations include kinematic conditions posed on the velocity and dynamic conditions posed on forces. The latter conditions involve the tangent stresses and the pressure.

The boundary conditions posed on the velocity (nonslipping conditions) have the form:  $u = W_1, w = 0$  for  $r = R$  on the surface of the erythrocyte;  $u = U_1, w = 0$  for  $r = R + h$  on the wall of the capillary, where  $U_1$  and  $W_1$  are the projections of  $U$  (velocity of the wall) and  $W$  (velocity of the membrane) onto the axis  $X_1$ ,  $r = r(X_1, \varphi)$  is the distance from the axis  $X_1$  to the membrane of the erythrocyte,  $h = h(X_1, \varphi)$  is the width of the gap between the erythrocyte and the wall of the capillary.

In addition, the following conditions are posed on the surface of the erythrocyte and the wall of the capillary. These conditions ensure the nonpermeability of the erythrocyte's membrane and the wall of the capillary for a liquid, subject to the continuity equation and the nonslipping condition [9, 14, 22]:

$$\begin{aligned} v &= \frac{w}{r} \frac{\partial r}{\partial \varphi} + u \frac{\partial r}{\partial X_1} = W_1 \frac{\partial r}{\partial X_1}, \quad r = R \\ v &= \frac{w}{r} \frac{\partial r}{\partial \varphi} + u \frac{\partial r}{\partial X_1} = U_1 \frac{\partial r}{\partial X_1}, \quad r = R + h. \end{aligned}$$

These conditions can be rewritten in the form

$$\begin{aligned} v &= W_1 \frac{\partial r}{\partial X_1}, \quad r = R \\ v &= U_1 \frac{\partial r}{\partial X_1}, \quad r = R + h \end{aligned}$$

or

$$\begin{aligned}\frac{v}{W_1} &= \frac{\partial r}{\partial X_1}, & r &= R \\ \frac{v}{U_1} &= \frac{\partial r}{\partial X_1}, & r &= R + h.\end{aligned}$$

This means that at a point lying on the membrane of the erythrocyte (or on the wall of the capillary) the ratio of the velocities (in the radial direction and in the direction along the axis  $X_1$ ) is equal to the ratio of the increments (in the radial direction and in the direction along the axis  $X_1$ ). This is natural considering the fact that the first one is determined by the form and position of the erythrocyte in the capillary, and the second one is determined by the motion of the wall of the erythrocyte and the surface of the capillary with respect to the system of coordinates  $OX_1X_2X_3$ , and also due to the assumption on non-slipping and nonpermeability of the erythrocyte's membrane and the wall of the capillary for a liquid.

Due to the fact that plasm is a viscous fluid, tangent stresses (axial  $\sigma_m$  and azimuthal  $\sigma_\beta$ ) act on the surface of the erythrocyte in addition to normal stresses (plasm pressure) [9, 10, 14, 22]:

$$\begin{aligned}\sigma_m &= \mu \frac{\partial u}{\partial r} \\ \sigma_\beta &= \mu \left( \frac{\partial w}{\partial r} - \frac{w}{r} \right).\end{aligned}$$

Integrating equations (1.3), (1.4) with respect to the width of the gap  $h$  and taking into account the boundary conditions, we get

$$\begin{aligned}u &= \frac{1}{4\mu} \frac{\partial P}{\partial X_1} \left( r^2 - R^2 - \frac{\ln(r/R)(h^2 + 2Rh)}{\ln(1 + h/R)} \right) + W_1 + (U_1 - W_1) \frac{\ln(r/R)}{\ln(1 + h/R)} \\ w &= \frac{1}{\mu} \frac{\partial P}{\partial \varphi} \left( r - R - h \frac{\ln(r/R)}{\ln(1 + h/R)} \right).\end{aligned}$$

Integrating equation (1.6) with respect to the width of the gap  $h$  and substituting the expressions for  $u$  and  $w$  into it, we get the elliptic differential equation

$$A_1 \frac{\partial^2 P}{\partial X_1^2} + A_2 \frac{\partial P}{\partial X_1} + A_3 \frac{\partial^2 P}{\partial \varphi^2} + A_4 \frac{\partial P}{\partial \varphi} + A_5 = 0 \quad (1.7)$$

whose coefficients are functions of  $R, h, \mu, X_1, \varphi, U_1, W_1$  and have the form

$$A_1 = \left( -2R^2 - 2Rh - h^2 + \frac{2Rh + h^2}{\ln(1 + h/R)} \right) \frac{2Rh + h^2}{16\mu}$$

$$\begin{aligned}
A_2 &= \frac{\partial A_1}{\partial X_1} \\
A_3 &= \left( -h^2 - 2Rh + \frac{2h^2}{\ln(1+h/R)} \right) \frac{1}{2\mu} \\
A_4 &= \frac{\partial A_3}{\partial \phi} \\
A_5 &= \frac{\partial}{\partial X_1} \left( (U_1 - W_1) \left( \frac{(R+h)^2}{2} - \frac{2Rh+h^2}{\ln(1+h/R)} \right) + W_1 \left( \frac{2Rh+h^2}{2} \right) \right) \\
&\quad + (R+h) U_1 \frac{\partial h}{\partial X_1}.
\end{aligned}$$

Thus, if we know  $D, \mu, U, f, a, b, V, S, l, \beta$ , we can determine  $W, R, h, U_1, W_1$  and hence the coefficients  $A_1, A_2, A_3, A_4, A_5$  of the equation.

In the construction of the model we assume that  $U, \mu, D, V, S$  are known. The parameters  $f, a, b, l, \beta$  are determined from additional conditions. Consider those conditions. According to experimental data, in a uniform motion of an erythrocyte along a capillary its membrane rolls with some constant frequency  $f$  [18]. The relation between the membrane rolling frequency  $f$  and the velocity  $W$  of a point of the erythrocyte is determined in the following way [18, 20]:

$$W = n \times \nabla(f F(X_1)) \quad (1.8)$$

where  $n$  is the unit normal to the surface of the erythrocyte,  $F$  is the function satisfying the relation

$$F'(X_3) = T(X_3)$$

where  $T(X_3)$  are the lengths of closed guidelines along which the points of the membrane move (the prime symbol denotes the derivative with respect to  $X_3$ ) (Fig. 1).

In the rolling of the membrane of the erythrocyte (this resembles the tank-treading motion), the points positioned on the surface of the erythrocyte move along closed lines [18, 20]. In the uniform motion of an erythrocyte in a capillary of a constant diameter with fixed other parameters of the model, these closed lines retain their length, and these lengths can be calculated. The motion of the points lying on the membrane of the erythrocyte is realized in planes parallel to the plane  $(X_1, X_2)$  [20]. Thus, the line along which some fixed point of the membrane of the erythrocyte moves is the intersection of the surface of the erythrocyte and a plane parallel to the plane  $(X_1, X_2)$ . If we know the form of the erythrocyte, we can calculate the length of the closed line easily. The number of these lines is infinite. However, the calculations were performed at the nodes of the grid  $(X_1, \phi)$  with certain mesh sizes in  $X_1$  and  $\phi$ . Therefore, we calculated a finite number of lines. We determined the number of these closed lines in the following way. Any point on the surface of the erythrocyte is determined by its coordinates  $(X_1, \phi)$ . The mesh size in  $\phi$  was taken

from 0.01 to 0.1 radians. Therefore, the lower bound for the number of different lines was estimated (due to the arguments of symmetry) by the expression  $\pi / 2 / 0.1 \approx 3.14 / 2 / 0.1 \approx 15$ , and the upper one by  $\pi / 2 / 0.01 \approx 3.14 / 2 / 0.01 \approx 157$ . Therefore, the number of lines in calculations was taken from 14 to 160. The choice of the number of lines was determined by the fact that the mesh sizes in  $\varphi$  and  $X_1$  should be close in magnitude.

Averaging the external forces acting on the erythrocyte, we get  $G_1$ , which is the external force (per unit area) acting upon the end surface of the erythrocyte (along the axis  $X_1$ ), and  $G_2$ , which is the external force (per unit area) acting on the lateral surface of the erythrocyte. Therefore, we assume that the elastic properties of the erythrocyte are approximately described by the generalized Hooke law

$$P_1 - P_2 = E \Delta c / c \quad (1.9)$$

where  $\Delta c$  is the absolute elongation (contraction) of the length of the erythrocyte

$$l = a + (l_1 + l_2) / 2 \quad (1.10)$$

measured along the axis  $X_1$ ,  $E$  is the Young modulus of the erythrocyte,  $\Delta G_1$  and  $\Delta G_2$  are the increments of  $G_1$  and  $G_2$ ,  $P_1 = -\Delta G_1$  and  $P_2 = -\Delta G_2$  are the stresses [22].

The condition of the uniform motion (rolling) of the membrane of the erythrocyte means that the sum of the forces acting on the membrane of the erythrocyte from the outside ( $F_1, F_2$ ) and from the inside ( $F_3$ ) is equal to zero, i.e.,

$$F_2 = F_1 + F_3 \quad (1.11)$$

where  $F_1$  and  $F_2$  are the external forces acting on the membrane:  $F_1$  represents the forces acting for  $X_2 \geq 0$  and  $F_2$  represents the forces acting for  $X_2 < 0$  (Fig. 1).

$$F_3 = C \mu_+ f S$$

where  $\mu_+$  is the viscosity of the content of the erythrocyte, which is approximately 5 times lower than the viscosity of the plasm [27],  $f$  is the rolling frequency of the membrane of the erythrocyte,  $S$  is the surface area of the erythrocyte,  $C$  is the coefficient characterizing the interaction (cohesion) of the membrane and the contents of the erythrocyte.

The condition of the rectilinear uniform motion of the erythrocyte along the capillary means that the sum of the forces ( $F_i$ ) acting on the erythrocyte (as a solid body) and the sum of their momenta ( $M_i$ ) are equal to zero (summation with respect to  $i$ ), i.e.,

$$\sum F_i = 0 \quad (1.12)$$

$$\sum M_i = 0. \quad (1.13)$$

As the result, we obtain system of equations (1.7)–(1.9), (1.11)–(1.13) with the unknowns  $P(X_1, \varphi)$ ,  $a$ ,  $b$ ,  $l$ ,  $\beta$ ,  $f$ . For each of the unknowns we define the range of

possible values in the following way:  $0 \leq P < 1000 \text{ N/m}^2$ ,  $0 < a < 2D$ ,  $0 < b < D/2$ ,  $0 \leq l < D/2$ ,  $0 \leq \beta \leq \pi/2$ ,  $0 \leq f < 100 \text{ r/s}$ . The system of equations was solved by the finite difference method [17]. For the boundary condition we used the assumption that pressure equals zero in the neighbourhood of the front (relative to the motion direction) part of the erythrocyte:  $P$ ,  $u$ ,  $v$ , and  $w$  are  $2\pi$ -periodic functions of  $\varphi$ . The estimation of the accuracy of the solution was carried out according to the Runge principle [17]. The mesh size was taken depending on the sizes of the capillary and the erythrocyte, in  $X_1$  it varied from 0.01 to 0.1  $\mu$  and in  $\varphi$  from 0.01 to 0.1 radians, which allows us to determine the pressure distribution in the neighbourhood of the erythrocyte with the accuracy up to 0.01–0.1  $\text{N/m}^2$ .

The calculations were performed for different values of capillary diameters ( $D = 3\text{--}7 \mu$ ), of the velocities of erythrocytes in the capillary ( $U = 0.1\text{--}10.0 \text{ mm/s}$ ), of plasm viscosity ( $\mu = 1\text{--}2 \text{ cP}$ ), of the volume of the erythrocyte ( $V = 80\text{--}110 \mu^3$ ), of the surface area of the erythrocyte ( $S = 120\text{--}150 \mu^2$ ), of the Young modulus of the erythrocyte ( $E = 6000\text{--}8000 \text{ N/m}^2$ ), of the Poisson coefficient of the erythrocyte ( $\nu = 0.5$ ), of the coefficient of cohesion of the membrane and the contents of the erythrocyte ( $C = 0\text{--}1000$ ) typical for a microcirculatory channel [6, 23, 24].

The calculations performed for the medium-size model ( $D = 4 \mu$ ,  $\mu = 1.2 \text{ cP}$ ,  $U = 1 \text{ mm/s}$ ,  $V = 94 \mu^3$ ,  $S = 135 \mu^2$ ,  $C = 100$ ,  $E = 7000 \text{ N/m}^2$ ,  $\nu = 0.5$ ) showed that the erythrocyte has a form characterized by the parameters  $a = 0.20 \mu$ ,  $b = 1.97 \mu$ , the position is  $l = 0.004 \mu$ ,  $\beta = 0.0000009$  radians (the axes of the cylinder (erythrocyte) and the capillary practically coincide and hence, taking into account the accuracy of the calculations, we can assume that  $l = 0$  and  $\beta = 0$ ), its membrane performs 16 rotations per second, the pressure differential at its ends is  $24.22 \text{ N/m}^2$ , which is approximately 1.3 times greater than the pressure required for the translation at the same velocity of a plasm column equal in size to the erythrocyte [9].

The dependence of the pressure differential  $\Delta P$  at the ends of the erythrocyte on the parameters of the model was approximated by the expression [9, 10]:

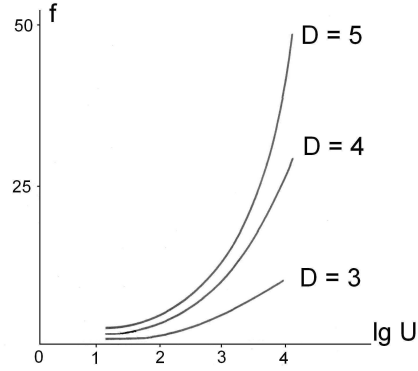
$$\Delta P = \frac{32 \mu U}{D} \left( \frac{1}{D\alpha} + \frac{V^2}{S^3} \frac{\delta E}{\mu f + \gamma} \right) \quad (1.14)$$

where  $D$  is the diameter of the capillary,  $\mu$  is the viscosity of the plasm,  $U$  is the velocity of the erythrocyte,  $V$  is the volume of the erythrocyte,  $S$  is the surface area of the erythrocyte,  $E$  is the Young modulus of the erythrocyte,  $l$  is the length of the erythrocyte measured along the axis  $X_1$ ,  $f$  is the erythrocyte membrane rolling frequency,  $\alpha$  is the ratio of the velocities of the erythrocyte and plasm,  $\delta = 0.00029$  and  $\gamma = 0.0042$  are constants.

The first term at the right-hand side of the expression gives the hydrodynamic resistance according to the Poiseuille formula, the second term gives the additional hydrodynamic resistance caused by the erythrocyte.

In order to calculate the pressure differential  $\Delta P$  at the ends of the erythrocyte, we have to know  $\mu$ ,  $U$ ,  $D$ ,  $\alpha$ ,  $E$ ,  $l$ ,  $V$ ,  $S$ ,  $f$ . If the values of  $a$ ,  $b$ ,  $l_1$ ,  $l_2$  are known, then  $l$ ,  $V$ , and  $S$  can be determined by formulas (1.1), (1.2), (1.10) presented above. According to experimental data [13, 24] for conditions typical for a microcirculatory





**Figure 2.** Dependence of rolling frequency  $f$  (rotations per second) of the membrane of the erythrocyte on its velocity  $U$  ( $\mu/s$ ) for different values of diameter  $D$  of the capillary ( $\mu$ ). The volume of erythrocyte is  $V = 94 \mu^3$ , its surface area is  $S = 135 \mu^2$ , the Young modulus is  $E = 7000 \text{ N/m}^2$ , the Poisson coefficient is  $\nu = 0.5$ , the plasma viscosity is  $\mu = 1.2 \text{ cP}$ .

channel we have  $\alpha \in (1.0 - 1.3)$ . Therefore, we can assume  $a \approx 1.15$  in narrow capillaries. If the diameter  $D$  of the vessel and the velocity  $U$  of the erythrocytes are known, then for the estimation of the frequency  $f$  of the erythrocyte membrane rolling we can use the results of the calculations presented, e.g., in Fig. 2.

Therefore, if the numeric values of  $\mu$ ,  $U$ ,  $D$ ,  $\alpha$ ,  $E$ ,  $l$ ,  $V$ ,  $S$ ,  $f$  are known, we can estimate the pressure differential  $\Delta P$  at the ends of the erythrocyte causing its motion along the capillary.

The dependence of the pressure differential causing the motion of the erythrocyte along the capillary on the microhemodynamic parameters has been used in analysis of the mechanism of erythrocyte motion in fragments of capillary networks. Two general elements can be pointed out in the construction of networks, namely, the capillaries themselves that are pipes of circular cross-sections and the points of their junction, branching (bifurcations). Therefore, analysis of microhemodynamics in capillary networks requires a successive consideration of the motion of a set of erythrocytes in separate vessels, through bifurcations, and over capillary networks.

## 1.2. MOTION OF ERYTHROCYTES IN A CAPILLARY

Let a capillary contain  $n$  erythrocytes moving at the velocity  $U_e$  typical for a micro-circulatory channel. Then, according to the previous section, the pressure differential at the ends of the erythrocyte is

$$\Delta P_e = a_1 U_e + b_1$$

where  $a_1$  and  $b_1$  are constants.

It is assumed that the distances between the erythrocytes of the length  $\Delta l_e$  in the capillary are such that the flow between them satisfies the Poiseuille law

$$\Delta P_p = \frac{8 \mu U_p \Delta l_p}{(D/2)^2}$$

where  $U_p$  is the velocity and  $\Delta l_p$  is the length of the plasm column in the capillary,  $\Delta P_p$  is the pressure differential at the ends of the plasm column,  $\mu$  is the viscosity of the plasm,  $D$  is the diameter of the capillary.

Then at the ends of the capillary of the length  $\Delta L$  containing erythrocytes of the length  $\Delta l_e$  the pressure differential is

$$\begin{aligned}\Delta P_p &= \frac{8\mu U_p \Delta l_p}{(D/2)^2} (\Delta L - n \Delta l_e) + n(aU_e + b) \\ &= U_e(an + c(\Delta L - n \Delta l_e)) + nb\end{aligned}$$

where

$$c = \frac{8\mu U_p}{(D/2)^2 U_e}.$$

If the capillary contains  $n$  erythrocytes, then  $\Delta P$  can be approximated by the expression

$$\Delta P = \frac{32\mu U}{D} \left( \frac{\Delta L}{D\alpha} + \frac{V^2}{S^3} \frac{\delta E n}{\mu f + \gamma} \right). \quad (1.15)$$

Since hematocrit  $H$  is related to the number  $n$  of erythrocytes in the capillary by the formula

$$H = \frac{4nV}{\pi D^2 \Delta L}$$

then, substituting the expression for  $n$  into formula (1.15), we get

$$\Delta P = \frac{32\mu U \Delta L}{D} \left( \frac{1}{D\alpha} + \frac{V^2}{S^3} \frac{\delta E}{\mu f + \gamma} \frac{\pi D^2 H}{4} \right). \quad (1.16)$$

If the intervals between the entrance of erythrocytes into the capillary are the same and equal to  $\zeta$ , the time when the erythrocyte is inside the capillary is  $T = \Delta L/U$ , the number of erythrocytes in the vessel is  $n = T/\zeta = \Delta L/(U\zeta)$ , then, substituting  $n$ , we get

$$\Delta P = \frac{32\mu U \Delta L}{D} \left( \frac{1}{D\alpha} + \frac{V^2}{S^3} \frac{\delta E}{\mu f + \gamma} \frac{1}{U\zeta} \right). \quad (1.17)$$

### 1.3. MOTION OF ERYTHROCYTES THROUGH CAPILLARY TEES

Knowing the mechanism of translation of erythrocytes along a capillary, we can proceed to the consideration of the model of a tee, which is a junction of three pipes AO, OB, OC at a point O. Either the blood enters the tee through two vessels (OB, OC) and flows out through one (AO), or, vise versa, enters through one vessel (AO) and flows out via two others (OB, OC). In the first case the erythrocytes come into a single vessel from both daughter vessels, whereas in the second case the erythrocytes meet an alternative at the bifurcation (point O): to go further through

one vessel or through the other. The model states that the erythrocyte enters the vessel which has the greater voluminal blood flow. In the case of equal blood flows in the vessels OB and OC, the erythrocyte goes into any of them with the probability 0.5. In order to determine the direction of the erythrocyte (into the vessel OB or into OC), we used the generator of pseudorandom numbers uniformly distributed in the interval (0, 1). If the drawn number was less than 0.5, the erythrocyte was directed to one vessel (OB), and if it was greater than 0.5, then to the other one (OC). If the number 0.5 was drawn, the next pseudorandom number was generated, etc.

If the number of erythrocytes in the tee capillaries and the pressure at the tee ends are known, then, taking into account the mass conservation law (the quantities of blood incoming to the bifurcation in unit time ( $Q^3$  for a divergent tee,  $Q^1, Q^2$  for a convergent one) and outgoing from it ( $Q^1, Q^2$  for a divergent tee,  $Q^3$  for a convergent one) are equal), we can compose a set of relations of the form

$$a_i \Delta P_i + b_i V_i + c_i = 0, \quad i = 1, 2, 3 \quad (1.18)$$

$$Q^1 + Q^2 = Q^3 \quad (1.19)$$

where  $V_i$  is the blood flow velocity in the  $i$ th vessel ( $V_1, V_2, V_3$  are the blood flow velocities in the vessels AO, OB, OC),  $\Delta P_i$  is the pressure differential at the ends of the  $i$ th capillary,  $a_i, b_i, c_i$  are coefficients.

It is assumed that the walls of capillaries are impermeable for a liquid. The required values are the velocities ( $V_1, V_2, V_3$ ) in the capillaries and the pressure ( $P$ ) in the bifurcation. Therefore, we have the system of four equations with four unknowns. Solving this system, we determine the velocities in the vessels and the pressure in the branching (bifurcation) for a given distribution of erythrocytes over the tee capillaries. This distribution changes in the course of time and hence the velocities in the vessels and the pressure in the branching (bifurcation) change as well.

#### 1.4. MOTION OF ERYTHROCYTES OVER CAPILLARY NETWORKS

Knowing the mechanism of the blood motion in a tee, we can proceed to the consideration of an arbitrary capillary network, which is a set of capillaries joined in a particular manner. It is assumed that not more than 3 vessels are joined at a particular point (branching, bifurcation). In the construction of the model we assume that the geometry of the capillary network, the pressure values at the ends of the network, and the erythrocyte incoming frequency are known. It is required to determine the mechanism of erythrocyte motion in the network. If the network has  $n$  capillaries joined at  $m$  points (bifurcations), then we can get  $n$  relations relating the pressure gradients  $\Delta P_i$  at the ends of the  $i$ th capillary to the velocity  $V_i$  of the blood flow

$$a_i \Delta P_i + b_i V_i + c_i = 0, \quad i = 1, 2, \dots, n \quad (1.20)$$

where  $a_i, b_i, c_i$  are coefficients, and  $m$  relations obtained from the mass conservation law.

Two variants are possible. Either the quantities of blood incoming per unit time to the  $j$ th bifurcation,  $Q_j^1$ ,  $Q_j^2$ , and outgoing,  $Q_j^3$ , are equal (for a convergent tee), or the quantities of blood incoming per unit time to the  $j$ th bifurcation,  $Q_j^3$ , and outgoing from it,  $Q_j^1$ ,  $Q_j^2$ , are equal (for a divergent tee). Thus, we have

$$Q_j^1 + Q_j^2 = Q_j^3, \quad j = 1, 2, \dots, m. \quad (1.21)$$

The motion of erythrocytes at subsequent moments of time is characterized by their coordinates and velocities. Therefore, the unknowns are the  $n$  blood flow velocities in the capillaries and the  $m$  pressure values at the bifurcations. Thus, we have a system of  $n + m$  equations with  $n + m$  unknowns. Solving this system by the Gauss method, we determine the blood flow velocities and pressures in the capillary network under the condition that the distribution of erythrocytes over the capillaries of the network is known. However, since the cells move along the capillaries, their distribution changes in the course of time. Thus, if we know the structure of the capillary network and the incoming frequency of erythrocytes at the entrances of the network, we can determine the motion of erythrocytes and the variation of the blood flow velocities in the capillaries and the pressure at the branchings (bifurcations) of the network in time.

## 2. RESULTS AND THEIR DISCUSSION

The analysis of the sensitivity of the model of a single erythrocyte motion to small variations of the parameters showed the following. If we take the medium-size model as the base ( $D = 4\mu$ ,  $\mu = 1.2$  cP,  $U = 1$  mm/s,  $V = 94 \mu^3$ ,  $S = 135 \mu^2$ ,  $C = 100$ ,  $E = 7000$  N/m<sup>2</sup>,  $\nu = 0.5$ ), the calculations show that under a change in the parameters  $U$ ,  $\mu$ ,  $h$ ,  $f$ ,  $\beta$ ,  $l$ , and  $a$  by 10% the pressure differential  $\Delta P$  is also changed by some value. The most sensitive parameter is the gap width  $h$ . As  $h$  changes by 10%, the pressure differential  $\Delta P$  at the ends of the erythrocyte decreases by 20.5%. The viscosity of the plasm  $\mu$  is less sensitive (its increase by 10% results in the increase of  $\Delta P$  by 10%). The parameters next sensitive in the descending order are the velocity  $U$  of the erythrocyte (increase by 5.6%) and the parameters characterizing the position of the erythrocyte in the capillary  $l$  and  $\beta$  (increase by 4.1% and 6.6%, respectively). The least sensitive parameters are the membrane rolling frequency  $f$  (decrease by 1.4%) and the length of the front (relative to the motion direction) part of the erythrocyte  $a$  (increase by 2.3%).

Thus, for small variations of the parameters of the model (up to 10%) the pressure differential at the ends of the erythrocyte causing its motion along the capillary varies insignificantly, i.e., the model is not very sensitive to small (up to 10%) variations of the parameters.

In the model from [9], under an increasing velocity  $U$ , the difference of the normalized (with respect to the plasm pressure in the capillary  $Pp$ ) pressures  $Pe/Pp$  at the ends of erythrocytes decreases, here  $Pe$  is the pressure at the ends of the erythrocyte,  $Pp$  is the pressure at the ends of the plasm column equal in length to the

erythrocyte. Thus, in the capillary with the diameter  $5\mu$  for the velocity  $U = 500\mu/s$  the difference of normalized pressures at the ends of the erythrocyte is  $\Delta = 1.5$ , for  $U = 1000\mu/s$  it is  $\Delta = 1.3$ , and for  $U = 10000\mu/s$  it is  $\Delta = 1.2$ . That is, under the increase in the velocity  $U$  of the erythrocyte, the relative resistance to the motion of the erythrocyte along the capillary decreases. In this case, when  $U$  decreases from 1000 to 500  $\mu/s$  or when  $U$  increases to 10000  $\mu/s$ , the value  $\Delta$  changes by approximately the same quantity. This means that under a decrease in  $U$  the value  $\Delta$  quickly grows, i.e., under a decrease in the velocity of the erythrocyte the relative resistance offered to the erythrocyte sharply increases. This phenomenon is explained by the fact that under the decrease in the velocity of the erythrocyte the cell membrane rotation frequency decreases, the gap width between the erythrocyte and the wall of the capillary sharply decreases due to the elastic properties of the erythrocyte and hence the viscous forces acting on the erythrocyte from the plasma increase, which increases the relative hydrodynamic resistance offered to the erythrocyte.

Consider the blood flow through the tees. The rate of the blood flow through a capillary tee depends on the parameters of the model. Thus, under the variation of  $\Delta P$  at the ends of the tee from 200 N/n<sup>2</sup> to 400 N/m<sup>2</sup> (with fixed other parameters of the model) the blood flow rate increases (Fig. 3). This can be explained in the following way. Due to the increase of  $\Delta P$  at the ends of the tee, on the one hand, we get the increase in the velocity of erythrocytes positioned in the capillaries of the tee and, on the other hand, the number of erythrocytes positioned in the tee decreases. The increase in the velocity of erythrocytes increases the resistance offered to each erythrocyte. The total influence of these two factors (the decrease of the number of erythrocytes in the tee and the increase of the resistance offered to each erythrocyte) leads to the fact that for blood flow velocities typical for a microcirculatory channel ( $\approx 10^2 - 10^3 \mu/s$ ) the dependence of the voluminal blood flow  $Q$  of the pressure differential  $\Delta P$  at the ends of the tee can be approximated by the expression of the form

$$Q = a_1 \Delta P + b_1$$

where  $a_1$  and  $b_1$  are constant values (Fig. 3).

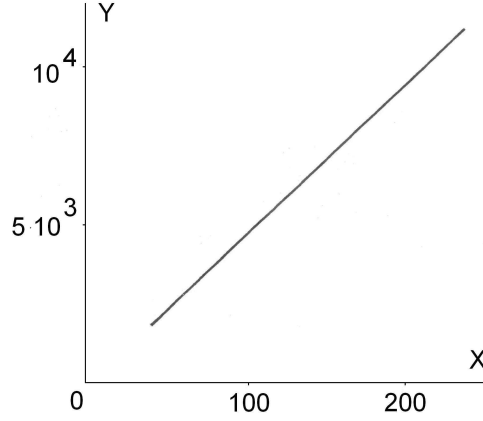
Thus, in a tee composed of vessels with the length  $100\mu$  and the diameter  $4\mu$  for the interval  $\zeta = 0.05$  s between the entrance of erythrocytes into the network, we have

$$Q = 31.7 \Delta P - 35.9$$

and increasing the diameter up to  $4.5\mu$  and decreasing the interval up to 0.03 s we have

$$Q = 50.6 \Delta P + 2.5.$$

Consider the dependence of the blood flow rate  $Q$  on the intervals  $\zeta$  between the entry of erythrocytes in the divergent tee AOBC. The intervals  $\zeta$  between the entry of erythrocytes in the tee are bounded from below, because in the process of the entrance of erythrocytes into the tee each next erythrocyte can enter the tee only after the previous erythrocyte has entered the tee. The lower bound of the intervals



**Figure 3.** Dependence of blood flow rate  $Q$  ( $\mu^3/\text{s}$ ) (axis  $Y$ ) through the divergent tee on pressure differential  $\Delta P$  ( $\text{N}/\text{m}^2$ ) (axis  $X$ ) at its ends. The diameters of capillaries forming the tee are  $4\mu$ , the lengths of capillaries are  $100\mu$ . The pressure values at the points B and C are 0 and 0  $\text{N}/\text{m}^2$ , respectively. The interval between the entrance of erythrocytes in the tee is 0.05 s.

$\zeta_{\min}$  between the entrance of erythrocytes into the tee can be estimated as follows:

$$\zeta_{\min} = \frac{\Delta l_e}{U}$$

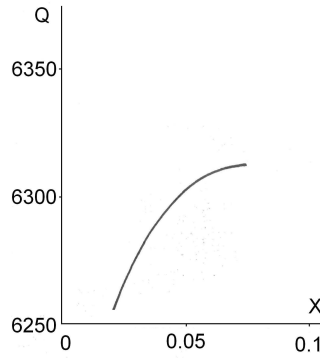
where  $\Delta l_e$  is the length of the erythrocyte at the entrance to the tee,  $U$  is the velocity of its motion at the entrance.

The intervals  $\zeta$  between the entry of erythrocytes into the tee are bounded from above because if we assume that the tee at any time moment must contain at least one erythrocyte, the upper bound of the intervals  $\zeta_{\max}$  can be estimated in the following way:

$$\zeta_{\max} = \frac{\Delta l_1 + \Delta l_2}{U_{\min}}$$

where  $U_{\min}$  is the minimal velocity of the erythrocyte in its motion in the tee,  $\Delta l_1$  is the length of the vessel AO,  $\Delta l_2$  is the length of the vessel OB (if the erythrocyte follows the route A-O-B) or the vessel OC (if the erythrocyte follows the route A-O-C).

The dependence of the blood flow velocity on the time intervals  $\zeta$  between the entries of erythrocytes into a divergent capillary tee is nonlinear. Thus, in the vessel AO of the tee AOBC for  $\zeta = 0.05$  s we have  $Q = 6304 \mu^3/\text{s}$ , and for  $\zeta = 0.03$  s and  $\zeta = 0.07$  s the mean value of  $Q$  equals  $6276 \mu^3/\text{s}$  and  $6313 \mu^3/\text{s}$ , respectively. Thus, under the increase of the interval  $\zeta$  between the entrance of erythrocytes into the tee the blood flow rate  $Q$  increases. If we continue to increase the intervals  $\zeta$  between the entries of erythrocytes into the tee, we can get the state when in some time intervals the tee does not contain erythrocytes at all (the tee contains the plasm only), and in some time intervals the tee contains a single erythrocyte. Under an essential increase of  $\zeta$  instead of a single value of  $Q$  we get four values alternating

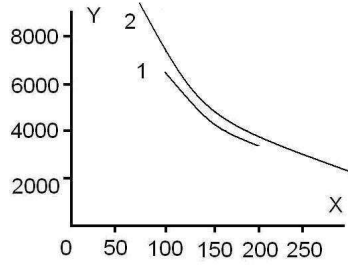


**Figure 4.** Dependence of the blood flow rate  $Q$  ( $\mu^3/\text{s}$ ) through the divergent tee on the size of the intervals  $\zeta$  (s) (axis X) between the entries of erythrocytes into the tee. The diameters of the capillaries forming the tee are  $4\mu$ , the lengths of the capillaries are  $100\mu$ . The pressure at the points A, B, and C is 200, 0, and 0  $\text{N}/\text{m}^2$ , respectively.

in some way. Namely, the first value corresponds to the case when the tee contains no erythrocytes, the second one means that the erythrocyte is in the vessel AO, the third and fourth ones mean that the erythrocyte is in the vessels OB or OC (the latter two may coincide). In the case considered for the divergent tee AOBC, the sequence of the values of  $Q$  for large values of  $\zeta$  is the following: first (the tee has no erythrocytes), second (the erythrocyte is in the vessel AO), third (coinciding with the fourth when the erythrocyte is either in the vessel OB, or in OC), first, second, etc. If we average these values of  $Q$ , we get a straight line positioned slightly below the line corresponding to the case when the tee contains no erythrocytes ( $Q = 6978 \mu^3/\text{s}$  in the case of absence of erythrocytes in the tee).

Consider the dependence of the blood flow rate in the tee on the length of the capillaries forming this tee (Fig. 5). The lengths of the capillaries forming the tee are bounded from below. As we consider the blood flow in capillaries, each capillary must contain at least one erythrocyte, i.e., the length of each capillary must be greater than the length of the erythrocyte in the capillary. The lengths of the capillaries forming the tee are bounded from above, because under an increase of their lengths for a given pressure differential at the ends of the tee the moment may come when the blood stops its motion. If the lengths of the capillaries forming the tee grow (under unchanged other parameters of the model), the number of erythrocytes in the tee grows, which, according to formula (1.16), leads to the increase of the resistance to the blood motion in the vessels of the tee and in the tee as a whole. In its turn, the latter results in a decrease in the blood velocity and the voluminal blood flow (under a constant pressure differential at the ends of the tee) (Fig. 5, curve 1). The comparison with the hyperbola  $Q = 697778/l$  describing the case when the tee contains no erythrocytes (curve 2) shows that curve 1 lies slightly lower than curve 2. For example, for  $l = 100\mu$  the difference between curves 1 and 2 is  $545 \mu^3$  and for  $l = 200 \mu^3$  it is  $322 \mu^3$  (Fig. 5).

The rate of the blood flow through the capillary network essentially influences



**Figure 5.** The dependence of the blood flow rate  $Q$  ( $\mu^3/\text{s}$ ) (axis  $Y$ ) in the divergent tee AOBC, the length of the vessels forming the tee is  $l$  ( $\mu$ ) (all lengths and diameters of the vessels in the tee are the same). The diameters of the capillaries forming the tee are equal to  $4 \mu$ . The pressure at the points A, B, and C is equal to 200, 0, and 0  $\text{N/m}^2$ , respectively. The intervals  $\zeta$  between the entries of erythrocytes into the tee are equal to 0.05 s (curve 1). Erythrocytes are absent in the tee (curve 2 being the hyperbola  $Q = 697778/l$ ).

the processes of oxygen transport to tissues and removal of metabolism products. An important issue is the determination of the dependence of the rate of blood flow through the capillary network on the pressure differential at the ends of the network. Therefore, we performed a comparison with data from other studies focused on blood flows in narrow capillaries. The comparison was performed in the following way. The data obtained for a single erythrocyte taken from [9, 12, 19] were substituted into the model of the motion of erythrocytes through a divergent tee (1.18), (1.19). As the result, we got the dependences of the blood flow rate  $Q$  on the pressure differential  $\Delta P$  at the ends of the tee for different models and for blood flow velocities typical of a microcirculatory channel (Fig. 6).

In this case, the higher is the pressure differential at the ends of the tee, the less essential is the difference between the models. Thus, for the pressure differential at the ends of the tee  $\Delta P = 200 \text{ N/m}^2$  the blood flow rate is 10118, 9731, and 9195  $\mu^3/\text{s}$  in the models from [9, 12, 19], i.e., the difference is approximately 11%, whereas for  $\Delta P = 400 \text{ N/m}^2$  we have 20260, 19525, and 19181  $\mu^3/\text{s}$  and the difference is about 6% (Fig. 6). These dependences of  $Q$  on  $\Delta P$  are close to linear for a divergent tee and can be approximated by the expression

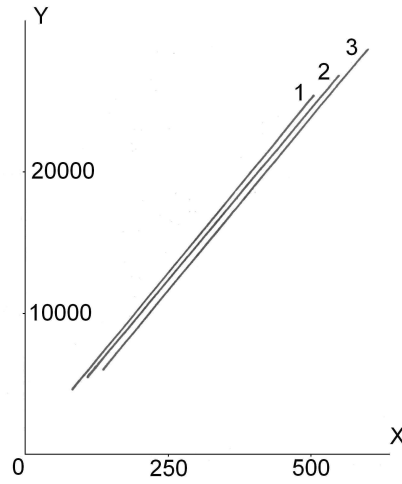
$$Q = a_1 \Delta P + b_1$$

where  $a_1$  and  $b_1$  are coefficients.

Thus, the comparison of the dependence of blood flow rates on the pressure differential at the ends of the tee in narrow capillaries has shown that in [9] this dependence is slightly stronger, i.e., for the same pressure differential at the end of the tee, other conditions being equal, the blood flow rate  $Q$  is greater by 6–11% (Fig. 6).

The comparison with experimental data shows the following. It is known that the mean blood flow velocities in capillaries are about 0.3–1 mm/s and pressure differentials are 5–8 mmHg per 1 mm of capillary length (0.7–1.0  $\text{N/m}^2/\mu$ ) [23, 24]). For example, in our model (Fig. 6) for the pressure differential of 200  $\text{N/m}^2$  at the ends of the tee composed of vessels of the length 100  $\mu$ , diameter 4  $\mu$ , and the





**Figure 6.** The dependence of the blood flow rate  $Q$  ( $\mu^3/\text{s}$ ) (axis Y) in a divergent tee (equations (1.18), (1.19)) on pressure differential  $\Delta P$  ( $\text{N}/\text{m}^2$ ) (axis X) at the ends of the tee (at the point A the pressure is  $\Delta P$ ). The diameters of the capillaries forming the network are  $4.5 \mu$ , the lengths of the capillaries are  $100 \mu$ , the intervals between the entrance of erythrocytes into the tee are  $0.05 \text{ s}$ . The pressure at the points B and C is equal to zero. Models: 1 – [9], 2 – [12], 3 – [19].

interval between the entrance of erythrocytes into the network  $\zeta = 0.05 \text{ s}$ , we have the following rate of the voluminal blood flow:

$$Q = 31.7 \Delta P - 35.9 = 31.7 \times 200 - 35.9 = 6304.1 \mu^3/\text{s}$$

and the velocity in the vessel AO of the divergent tee is

$$U_{AO} = Q/(\pi r^2) = 6304.1/(3.14 \times 4) = 502 \mu/\text{s}.$$

Since  $0.502 \text{ mm/s}$  belongs to the interval  $0.3\text{--}1.0 \text{ mm/s}$  typical for a capillary channel [23, 24], this means that the results of the calculations are in a good accordance with the experimental data. Thus, the dependence of  $Q$  on  $\Delta P$  in different models are close to each other (Fig. 6) and agree with the experimental data.

However, there are qualitative differences between the models. In contrast to other models, our model takes into account the Young modulus of the erythrocyte, the volume of the erythrocyte and its surface area. It is known that the amounts of oxygen and products of metabolism transported by an erythrocyte are determined by its volume, and the rate of release (or absorption) of oxygen and products of metabolism is determined by its surface area. On the other hand, for some diseases (e.g., for sickle-cell anemia) the stiffness of erythrocytes grows (the Young modulus of the erythrocyte is changed), so that the motion of erythrocytes is essentially changed and erythrocytes become destroyed in very narrow capillaries. Moreover, in contrast to other models, we have developed formulas (1.15)–(1.17) allowing us to estimate the dependence of the pressure differential at the ends of the capillary on such parameters as the diameter of the capillary, the velocity, volume, and

surface area of the erythrocyte, the Young modulus of the erythrocyte, hematocrit, and other parameters. The model constructed for capillary trees (1.18), (1.19) can be easily generalized to a capillary network of any structure (1.20), (1.21) under the condition that not more than 3 vessels are joined at one point. All this suggests that the model can be used for construction of other models capable to calculate the transport of oxygen and products of metabolism both for normal conditions (in a healthy organism) and for various diseases (for example, for sickle-cell anemia).

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