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Letter

The critical pressure for driving a red blood cell through a contracting microfluidic channel

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ABSTRACT

When a red blood cell (RBC) is driven by a pressure gradient through a microfluidic channel, its passage or blockage provides a measure of the rigidity of the cell. This has been developed as a means to separate RBCs according to their mechanical properties, which are known to change with pathological conditions such as malaria infection. In this study, we use numerical simulations to establish a quantitative connection between the minimum pressure needed to drive an RBC through a contracting microfluidic channel and the rigidity of the cell membrane. This provides the basis for designing such devices and interpreting the experimental data.

Red blood cells (RBCs) are extremely flexible. This allows the RBCs to pass through microcapillaries of size much smaller than theirs. When infected by the malaria parasite *Plasmodium falciparum*, the RBC gradually loses its deformability, which leads to blockage of the blood circulation in microcapillaries. As models for this process, microfluidic assays have been designed in which the critical pressure required to push red cells through a contraction is used as a measure of the cell's deformability [1,2]. Similar devices have been used to separate cells according to their size and rigidity [3]. Since RBCs are known to rigidify under pathological conditions such as malaria infection [4], microfluidic channels also hold promise as a diagnostic and fractionation tool [5]. Compared with alternative methods to measure mechanical properties of RBCs, such as cell stretching by optical tweezers [6] and micropipette aspiration [7], the microfluidic channel has the advantage of closely mimicking the flow geometry in vivo.

Ma and coworkers [2,3] have designed a "microfluidic funnel ratchet," which consists of a series of contractions followed by sudden expansions (Fig. 1). In such a device, the critical pressure drop for pushing the cell through the channel depends on the deformability of the cell. The more flexible the cell, the less pressure needed. However, no quantitative correlation exists that relates the measured critical pressure drop to the shear and bending moduli of the cell. Ma et al. [2,3] employed the Young–Laplace equation to estimate the cell's cortical tension from the measured critical pressure drop. In this model, the cell was treated as a liquid drop with a constant cortical tension T_c, which was related to the critical pressure drop ΔP_c through

$$\Delta P_c = T_c\left(\frac{1}{R_a}-\frac{1}{R_b}\right), \tag{1}$$

where R_a and R_b are the radii of curvature at the cell's front and back. However, the cell membrane is elastic and differs considerably from a fluid interface. For example, the in-plane tension will likely vary along the membrane according to the local strain. Besides, the bending rigidity of the membrane may also play a role.

To address these issues, we carry out numerical simulations using a more realistic representation of the mechanical properties of the cell, with an elastic membrane enclosing a viscous cytosol. The physical model and numerical method are based on the recent study of Wu and Feng [8]. The cell membrane is represented by a discrete particle–spring network (Fig. 2(a)), with elasticity against in-plane strain and bending (Fig. 2(b)). The fluids inside and outside of the membrane are discretized by particles as well (Fig. 2(c)), using the framework of smoothed particle hydrodynamics [9]. We

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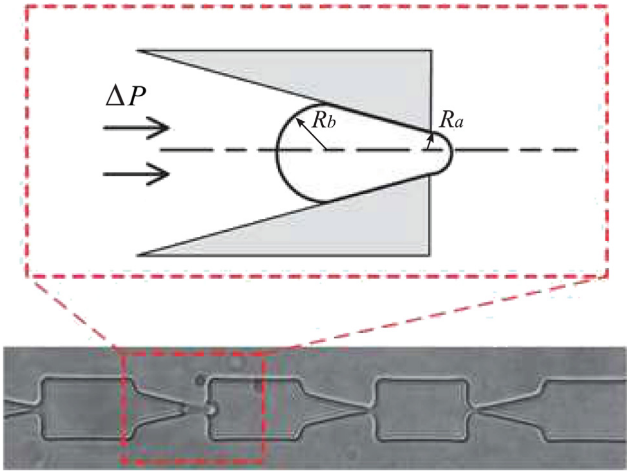

Fig. 1. The geometry of the microfluidic device studied by Ma et al. [2,3]. *Source:* Adapted from Ref. [2] with permission © Royal Society of Chemistry.

use linear springs of an elastic coefficient k_s such that the elastic energy for in-plane deformation is

$$E_s = \sum_{i,j} \frac{k_s}{2} (L_{ij} - L_{ij,0})^2, \tag{2}$$

where the summation is over all pairs of adjacent vertices i and j, L_{ij} is the length of the spring connecting them, and $L_{ij,0}$ is its resting length. In addition, we adopt the following bending energy [10]:

$$E_b = \sum_{i,j} 2k_b \tan^2\left(\frac{\theta_{ij}}{2}\right), \tag{3}$$

where k_b is the bending modulus and the summation is over all pairs of neighboring triangles i and j and θ_{ij} is the angle between their normals. Note that this bending energy assumes zero spontaneous curvature for the membrane.

The red cells are known to conserve their surface area. In our particle model, this is implemented through an energy penalty against local area dilatation:

$$E_A = \frac{k_d}{2} \sum_{j=1}^{N} \left(\frac{A_0^j - A^j}{A_0^j}\right)^2 A_0^j, \tag{4}$$

where k_d is a constant, A_0^j is the undeformed area of the jth triangle, and the summation is over all N triangles of the RBC membrane. Finally, we include an energy penalty against the change of the total cell volume:

$$E_V = \frac{k_v}{2} V_0 \left(\frac{V_0 - V}{V_0}\right)^2, \tag{5}$$

where k_v is a constant coefficient, and V_0 is the initial volume of the cell. Under large forcing and severe cell deformation, this volume constraint helps to prevent fluid particles from penetrating the membrane. Using Eqs. (2)–(5), we write the total elastic energy of the cell membrane as $E_m = E_s + E_b + E_A + E_V$. The elastic force acting on each membrane particle can then be calculated as

$$\boldsymbol{f}_m = -\partial E_m / \partial \boldsymbol{r}, \tag{6}$$

$\boldsymbol{r}$ being the position of the membrane particle.

The fluid motion is solved by using the smoothed particle hydrodynamics (SPH) method [9]. For the membrane particles, the elastic force $\boldsymbol{f}_m$ is added to the hydrodynamic force on the right-hand side of the momentum equation. We have tested convergence of the results with respect to spatial resolution. For an initial particle spacing $d \leq 0.15R_0$, R_0 being the radius of the undeformed RBC, the numerical results no longer depend on d. Thus, the simulations have been carried out using $d = 0.15R_0$.

The surface of the undeformed red cell is obtained from the formula of Evans and Fung [11]:

$$D(r) = \sqrt{1 - (r/R_0)^2} \left[C_0 + C_1 (r/R_0)^2 + C_2 (r/R_0)^4\right], \tag{7}$$

where $D(r)$ is the thickness of the RBC as a function of distance from the center, and R_0 is the RBC's radius. In our simulation, we set $(R_0, C_0, C_1, C_2) = (3.9, 0.81, 7.83, -4.39)$ μm [12]. With these parameters, the red cell's volume and surface area are about 92 μm^3 and 132 μm^2, respectively, in agreement with experimental values [13,14]. The triangular mesh on the cell surface was automatically created by the commercial software GAMBIT. Once this

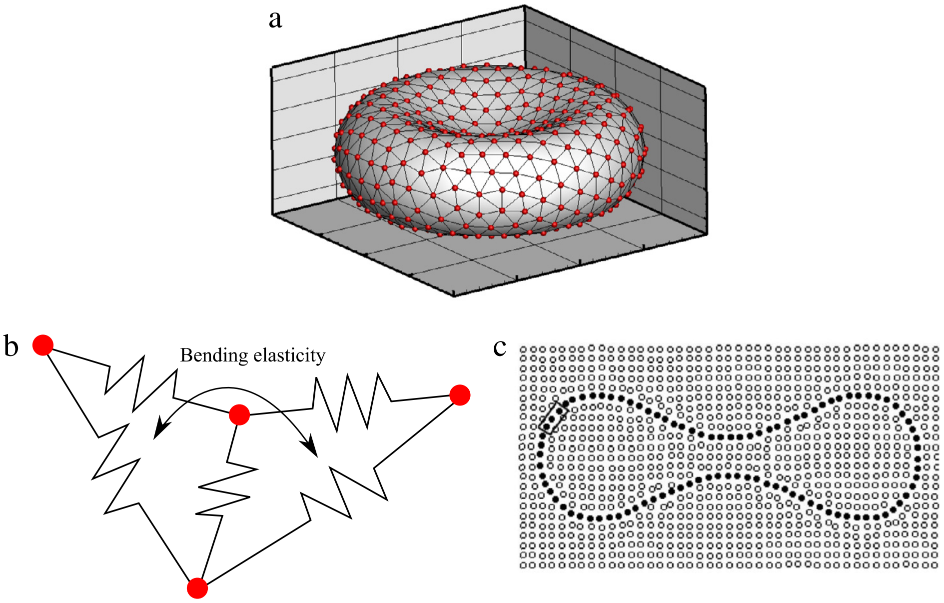

Fig. 2. (a) The RBC membrane is modeled by a triangular particle–spring meshwork. (b) Each segment is an elastic spring (Eq. (2)), and there is bending elasticity between neighboring triangles (Eq. (3)). (c) The interior and exterior fluids are discretized by particles, whose movement approximates the Navier–Stokes equation in the smoothed-particle-hydrodynamics framework [9].