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Prediction of non-inertial focusing of red blood cells in Poiseuille flow

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Abstract

The motions of a red blood cell in Poiseuille flows in a range of channel widths are simulated using a two-dimensional model. For a range of initial off-centerline distances in a 12- μm channel, cell trajectories converge to a specific off-centerline position and exhibit tank-treading motions. This behavior coexists with initial positions that lead to migration towards the centerline. The predicted off-centerline focusing effect is shown to depend on the curvature of the flow profile and on interactions with both solid boundaries.

I. INTRODUCTION

When deformable particles such as red blood cells flow along narrow channels, the particles may migrate across the fluid streamlines, as a result of interactions with the walls [1] or with the curvature of the velocity profile in the channel [2, 3]. When blood flows in microvessels, this migration causes the formation of a cell-depleted cell-free layer near the walls, which underlies the Fåhræus-Lindqvist effect, i.e. the reduction in the apparent viscosity of blood relative to its bulk value [4, 5]. Such migration also has potential significance for the design of microfluidic devices to manipulate or sort deformable particles [6].

In many cases of interest, including blood flow in microvessels, inertial effects are negligible and the fluid motion is governed by the equations of Stokes flow. A number of theoretical studies have examined the lateral migration of deformable particles in bounded or unbounded Poiseuille flows without inertial effects. In general, these studies show a tendency for particles to migrate to the centerline of the flow [2, 7–9]. Danker et al. [10] studied the motion of vesicles in an unbounded Poiseuille flow and found that the behavior depended on the ratio of the internal to external fluid viscosities. Below a critical viscosity ratio, the vesicles migrate toward the flow centerline in a tank-treading motion. However, above this critical viscosity ratio, vesicles tumble and migration is suppressed. In two-dimensional simulations of red blood cell motion in an unbounded Poiseuille flow, Kaoui et al. [3] found that the behavior depends on the relationship of perimeter to cell area. Cells with large excess perimeters approach asymmetric slipper shapes, with centers slightly displaced from the centerline of the flow. The results of Shi et al. [11] show similar behavior in the limit of small Reynolds number.

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In Poiseuille flow with significant inertial effects, the Segré-Silberberg effect is observed [12, 13], in which lateral migration of rigid, spherical particles results in their focusing at a distance of $0.6R$ from the center of a tube with radius R . For rigid particles, this effect cannot occur in the absence of inertial effects, as the reversibility of Stokes flow then implies no net migration [14]. Shi et al. [11] considered the motion of red blood cells in a bounded Poiseuille flow with inertial effects, using two-dimensional simulations. For cells with small excess perimeters, a range of Reynolds numbers was found for which the equilibrium cell positions were strongly displaced from the channel center-line. These results demonstrate the possibility of eccentric focusing of deformable particles in the presence of inertial effects.

Mortazavi and Tryggvason [15] used two-dimensional simulations to study the motion of fluid drops in a bounded Poiseuille flow for a range of Reynolds numbers. In the limit of small Reynolds number, the motion was found to depend on the viscosity ratio of the interior of the fluid droplet to that of the suspending medium. For a viscosity ratio of 0.125, the drops migrate towards the centerline. However, for a viscosity ratio of 1.0 the drops migrate away from the centerline until interactions with the wall impede the migration. This result shows non-inertial eccentric focusing of fluid drops. However, non-inertial eccentric focusing of other types of deformable particles, such as vesicles or red blood cells, has not previously been demonstrated.

In this paper, we present two-dimensional simulations of the motion of deformable red blood cells in a bounded Poiseuille flow without inertial effects. We predict a focusing effect in the absence of inertial effects, such that cells with a range of initial positions relative to the centerline in $12\text{-}\mu\text{m}$ channel focus to a single position and orientation in a tank-treading motion. We show that proximity to solid boundaries and curvature of the flow profile both contribute to this effect.

II. METHODS

A. Simulation of viscoelastic red blood cells

A previously described two-dimensional (2D) model is used to represent the motion and deformation of the RBC [8, 16]. 2D models have been used in a number of previous theoretical studies of deformation and lateral migration of vesicles and RBCs in channel flow [2, 3, 17–20]. A potential limitation of 2D models for RBCs is that they may fail to represent viscous dissipation in the membrane resulting from shear deformations during tank-treading motions. The 2D model used here is designed to include this effect. The cross-sectional shape of the RBC is represented by a set of N viscoelastic elements connected at nodes. A further set of N internal viscous elements connects these nodes to a central node. The viscous internal elements represent both the viscosity of the cell's interior and the viscous dissipation in the cell membrane during tank-treading. The external nodes act as elastic hinges to represent the cell membrane's resistance to bending.

The external elements of the model cell have forces acting on them as a result of the fluid flow. Consequently, the longitudinal (tension) force, $t_j(s)$, transverse (shear) force, $q_j(s)$, and bending moment, $m_j(s)$, acting in the external element $j = 1, \dots, N$ are functions of the

distance s along the element from the node j to $j + 1$, where $0 \leq s \leq l_j$ and l_j is length of element j . The equations of mechanical equilibrium are:

$$\frac{dt_j}{ds} = -g_j \quad \frac{dq_j}{ds} = -f_j \quad \frac{dm_j}{ds} = q_j \quad (1)$$

where $f_j(s)$ and $g_j(s)$ are the normal and tangential components of the fluid loading. With ϕ_j and θ_j defined as the angle from reference of internal element j and external element j respectively, the equilibrium equations for the x -component and y -component of forces at node j are:

$$t_j(0)\cos\theta_j - t_k(l_k)\cos\theta_k - q_j(0)\sin\theta_j + q_k(l_k)\sin\theta_k + T_j\cos\phi_j = 0 \quad (2)$$

$$t_j(0)\sin\theta_j - t_k(l_k)\sin\theta_k + q_j(0)\cos\theta_j - q_k(l_k)\cos\theta_k + T_j\sin\phi_j = 0 \quad (3)$$

where $k = j - 1$ ($k = N$ if $j = 1$) and T_j represents the j th internal element's tension. Equilibrium of forces at the central node results in:

$$\sum_{j=1}^N T_j \cos\phi_j = \sum_{j=1}^N T_j \sin\phi_j = 0 \quad (4)$$

The interior of a three-dimensional red blood cell is effectively incompressible, so that it deforms at constant volume, and thus the membrane deforms at nearly constant surface area. In two dimensions, the analogous properties are the perimeter and area in the model-cell plane. These properties are not kept constant, but are constrained to values that would represent the possible shapes of a three-dimensional cell with fixed surface area and volume. In the model, variations of perimeter are resisted by elastic control over element lengths, and variations of cell area A are resisted by assigning an interior pressure to the cell:

$$p_{int} = k_p(1 - A/A_{ref}) \quad (5)$$

where A_{ref} and k_p are constants.

B. Equations of Fluid Flow

The suspending medium is assumed to be an incompressible fluid with zero Reynolds number, so that the inertial effects of flow can be neglected and the governing equations are those of Stokes flow. The pressure and velocity components fields are expressed as $p(x, y)$ and $\mathbf{u}(x, y)$ where $\mathbf{u} = (u, v)$. The components of stress are:

$$\begin{aligned} \sigma_{xx} &= 2\mu \frac{\partial u}{\partial x} - p & \sigma_{xy} &= \mu \left(\frac{\partial u}{\partial y} + \frac{\partial v}{\partial x} \right) \\ \sigma_{yy} &= 2\mu \frac{\partial v}{\partial y} - p \end{aligned} \quad (6)$$

where μ is the fluid viscosity. The equations for equilibrium of stresses yield:

$$\frac{\partial \sigma_{xx}}{\partial x} + \frac{\partial \sigma_{xy}}{\partial y} = 0 \quad \frac{\partial \sigma_{xy}}{\partial x} + \frac{\partial \sigma_{yy}}{\partial y} = 0 \quad (7)$$

The divergence of the velocity field is given by:

$$e = \frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} \quad (8)$$

with $e = 0$ for an incompressible fluid.

The fluid loadings on segment j are:

$$f_i = -p_{int} - \sigma_{xx} \sin^2 \theta_j + 2\sigma_{xy} \sin \theta_j \cos \theta_j - \sigma_{yy} \cos^2 \theta_j \quad (9)$$

$$g_j = (\sigma_{xx} - \sigma_{yy}) \sin \theta_j \cos \theta_j - \sigma_{xy} (\cos^2 \theta_j - \sin^2 \theta_j) \quad (10)$$

No-slip conditions for the cell's velocity are imposed along the membrane, so that the local fluid and cell velocities match. By combining equations 1–10, the equilibrium equations for a given configuration of the cell can be expressed as a linear system with the velocity and pressure fields in the fluid and the velocities of the nodes as unknowns.

C. Computational Method

The system of coupled equations for the cell's motion along with the surrounding fluid is solved using a finite-element package (FlexPDE version 5.1.4, PDE Solutions Inc., Antioch, CA). Generally, $N = 20$ nodes are used to represent the red blood cell. At each time step, the coupled equations governing the external fluid and the cell deformation are solved simultaneously using the FlexPDE package. The cell shapes are then updated using the computed nodal velocities and specified time step with an explicit Euler scheme. The time step is 0.25 or 0.5 ms, depending on the centerline velocity.

D. Boundary Conditions

In Poiseuille flow (Figure 1 (a)), a constant pressure gradient p is superimposed, and boundary conditions are taken to be $u(x, -w) = u(x, w) = 0$ resulting in parabolic or

Poiseuille flow $u = \frac{\Delta p}{2\mu}(w^2 - y^2)$ in the absence of a cell where $2w$ is the width of the channel. In order to explore the effects of interactions with the opposite wall, an “expanded” Poiseuille flow is considered, in which the domain is extended to a channel width of $2w_c$ without altering the profile in the original domain (Figure 1 (b)). An analogous approach was previously used by Kaoui et al. [21]. In order to directly compare initial positions of cells in the standard, the y -coordinates are shifted so that the maximum of the parabolic profile occurs at $y = 0$. Given the effective width of an underlying Poiseuille profile $2w$, the

parabolic profile remains $u = \frac{\Delta p}{2\mu}(w^2 - y^2)$ with $u(x, -w) = 0$ and $u(x, w) = 0$. This gives

boundary conditions of $u(x, -w) = 0$ and $u(x, 2w_c - w) = \frac{\Delta p}{2\mu}(w^2 - (2w_c - w)^2)$

E. Parameter Values

Channel widths are taken to be 10-, 12- or 14- μm . For the 12- μm channel, an “expanded” Poiseuille flow in a 20- μm channel is also considered. Parameters and variables are non-dimensionalized with respect to a characteristic length scale of 1 μm , time scale of 1 ms, and force scale of 10^{-7} dyn. The imposed pressure gradient is taken to be $p = -0.1$ for all channel widths. The resulting centerline velocity in the absence of a cell is 1.25, 1.8, or 2.45 mm/s, which are typical values for the microcirculation. The initial position of the center of mass is described by $\bar{y}_0$, the distance from the centerline $y = 0$ (Figure 1). Initial cell shapes are taken to be circles with a radius of 2.66 μm as to not influence migration. In this configuration, the elastic elements forming the cell boundary are compressed to a length less than their reference length [8]. In the initial stage of the motion, these elements rapidly elongate and the cell assumes a non-circular shape.

F. Description of Particle Motion

The lateral migration of a cell is described using the cell’s center of mass. To describe the cell’s orientation, the inertia tensor of the cell’s shape is computed. The orientation of a cell is then described as the angle between the major principal axis of the inertia tensor and the flow direction.

III. RESULTS

A. Computed cell shapes and motions

Figure 2 shows examples of cell shapes and motions. For $\bar{y}_0 = -2$ in a 10- μm Poiseuille flow (Figure 2 (a)), the cell migrates towards the centerline and equilibrates in a slightly asymmetric “parachute” shape. For $\bar{y}_0 = -2$ in a 12- μm Poiseuille flow, the cell initially tumbles before reaching a stable tank-treading motion with the center of mass at a distance of $-2.2 \mu\text{m}$ from the centerline (Figure 2 (b)). For $\bar{y}_0 = -4$ in a 14- μm Poiseuille flow, the cell initially tank-treads while slowly migrating away from the wall before eventually tumbling.

B. Analysis of cell trajectories

For channel widths ranging from 10- to 14- μm , Figure 3 shows time series plots for center of mass and orientation angle and phase-plane type plots for orientation angle against center of mass position. Trajectories in the phase-plane are not unique because the deformability of the cell leads to additional degrees of freedom.

For a 10- μm channel, cells migrate towards the center-line independent of initial position. This behavior is also found for an 8- μm channel [8].

For a 12- μm channel, the center of mass trajectories for initial positions $\bar{y}_0 = -1$ to -3 converge to a distance of -2.2 from the centerline. For $\bar{y}_0 = -1$ to -2 , initial tumbles result in migration towards the wall before a stable tank-treading motion is reached. In this case, a tumbling cell generates a lift directed towards the wall, in the opposite direction to that generated by cells closer to the wall [22, 23]. The phase-plane type plots in Figure 3

shows trajectories converging a fixed point where the center of mass position is $\bar{y}^* \approx -2.2$, and the orientation angle is $\theta^* \approx 0.12$.

For a 14- μm channel, the trajectories do not converge to a fixed point. For $\bar{y}_0 = -3.5$ and -4 , cells initially tank-tread while slowly migrating away from the wall before eventually tumbling. The cells spend the majority of their time tank-treading, but show occasional tumbles. As a result, trajectories in the phase-plane are mainly confined to a small region where large excursions occur when tumbles are executed. This is typical of intermittent behavior [24, 25] where one behavior, tank-treading, is periodically interrupted by another, tumbling.

C. Expanded Poiseuille Flow

An expanded Poiseuille flow profile is used (Figure 1 (b)) to distinguish the effects of the curvature of the flow profile [2, 3] from the effects of the finite width of the channel [26, 27]. The channel width is taken to be $2w_c = 20$, and the effective width of the underlying Poiseuille flow is $2w = 12$.

Results are presented in Figure 4 for $\bar{y}_0 = -3, -2.5$ and -2 which correspond to initial positions considered for the 12- μm channel shown in Figure 3. When the cell is placed at $\bar{y}_0 = -2.5$ or -3 , the cell migrates away from the wall and enters a tank-treading motion. For an initial condition slightly further from the wall ($\bar{y}_0 = -2$), the cell initially tumbles before settling in a tank-treading motion. The motions do not converge to the same position, as is evident in the center of mass plots (Figure 3).

IV. DISCUSSION

The results presented for a 12- μm Poiseuille flow show a focusing effect for red blood cells that depends on the ability to tank-tread near a wall. One well studied factor that determines the tank-treading of red blood cells is viscosity ratio [28]. The dimensionless suspending fluid viscosity corresponds to 1 cP, implying a viscosity ratio that would result in tumbling behavior in an unbounded shear flow. Therefore, other characteristics of the Poiseuille flow contribute to the tank-treading motion.

By examining different flow profiles, three key factors for focusing off-centerline in the 12- μm Poiseuille flow are found: initial proximity to a solid boundary, curvature of the flow, and width of the channel. If the cell is placed initially too far from a solid boundary, the cell migrates towards the centerline. If the cell is sufficiently close to the solid boundary, tumbling motions are inhibited, resulting in a tank-treading motion [23]. A cell placed in a shear flow near a boundary in a 20- μm channel would migrate and tumble [23]. Results from the expanded Poiseuille flow simulations indicate that the curvature of the flow has the effect of restricting the cell's motion to a region near the solid boundary. The last factor is the width of the domain, which focuses the tank-treading motions to a single position and orientation. The lack of focusing in the expanded Poiseuille flow demonstrate that curvature alone is not sufficient, and interactions with the opposite wall are necessary for focusing under the assumed conditions.

This predicted focusing effect appears to be analogous to the Segré-Silberberg effect, but significant differences exist from what is observed here. Ho and Leal [29] demonstrated that the Segré-Silberberg effect is a result of the balance of the effects of the wall and the curvature of the flow, resulting in a stable fixed point off-centerline and an unstable fixed point on the centerline. Here, it appears that the balance of wall effects and the curvature of the flow is again responsible for focusing of deformable particles, but the inclusion of deformability and lack of inertia allow for stable motion on the centerline.

Previous studies [10] have shown that when vesicles with relatively high internal viscosity are initially placed off the centerline in Poiseuille flow, the resulting tumbling motion suppresses migration to the centerline. The present results further show that this flow regime can lead to focusing of cells in eccentric positions when wall effects are present. Such an effect, which is analogous to that shown by Mortazavi and Tryggvason [15] for fluid drops, has not previously been demonstrated for red blood cells or other capsules or vesicles at zero Reynolds number.

The two-dimensional system used here represents a cross-section of a three-dimensional cell. The corresponding three-dimensional system is one with a rectangular channel where the rectangle's width matches the channel width, and the other dimension is large enough such that additional cell-wall interactions are not significant. In this case, the results of the two-dimensional model predict that a dilute, randomly dispersed suspension of red blood cells in a 12- μm channel would eventually migrate to the centerline, or focus in two positions off-centerline. This would result in three "sheets" of red blood cells in the rectangular 12- μm channel.

The present results show focusing in a 12- μm channel but not in a 10- or 14- μm channel. These results imply that the range of channel widths leading to focusing is narrow, no more than 4 μm . However, the existence of an intermittent regime [24, 25] in the 14- μm channel where tank-treading is interrupted with widely spaced tumbles suggests that a channel width of 14 μm is close to the maximum channel width at which focusing occurs. These predictions are based on the two-dimensional model cell. If such an effect occurs for three-dimensional cells, it may occur for a different range of channel widths. In a three-dimensional tube, red blood cells focusing off-centerline would result in an annulus of cells near the tube wall surrounding the cells that migrate towards the centerline.

In summary, these simulations show the possibility of focusing of flexible viscoelastic particles to off-center positions in Stokes flow. This phenomenon is found to be very sensitive to channel width. The results do not necessarily imply that such a phenomenon occurs for three-dimensional particles including red blood cells, in channel or tube flow. However, some analogous behaviors are evident in the three-dimensional simulations of Fedosov et al. [30]. Further theoretical and experimental studies are needed to test the existence in three-dimensional flows of the non-inertial focusing effect predicted by the present study.

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FIG. 1. Schematic diagrams of $\bar{y}_0$ for (a) Poiseuille flow and (b) expanded Poiseuille flow.

FIG. 2. Sample cell shapes taken at equally spaced times up to the maximum time indicated for (a) 10- μm Poiseuille flow with $\bar{y}_0 = -2$, (b) 12- μm Poiseuille flow with $\bar{y}_0 = -2$, and (c) 14- μm Poiseuille flow with $\bar{y}_0 = -4$.

FIG. 3. Results for 10-, 12-, and 14- μm Poiseuille flow. (a) Time variation of center of mass position. (b) Time variation of orientation angle. (c) Phase-plane type plots for orientation angle against center of mass position. Labeled points indicate (A) migration towards centerline, (B) focusing, (C) intermittent behavior.

FIG. 4.

Results for an expanded Poiseuille flow with a channel width $2w_c = 20$, and an effective width of the underlying Poiseuille flow $2w = 12$. (a) Time variation of center of mass position. (b) Time variation of orientation angle. (c) Phase-plane type plots for orientation angle against center of mass position. Labeled point indicate (D) stable tank-treading without focusing.