

Origin of red blood cell slippers in confined geometries

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One of the most intriguing characteristics of red blood cells is their ability to form asymmetric, rotating slipper states even in symmetric channel flows. Here we argue that the common association of these slipper states with the well-understood tank-treading in shear flow is incomplete. We use boundary-integral simulations for a systematic decomposition of the channel flow field into linear shear and quadratic curvature components. Our findings show that a fore-aft asymmetry induced by flow curvature is a plausible mechanism behind the formation of slipper shapes.

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Red blood cells (RBCs) are the most abundant cell type in mammals and humans. During their entire lifespan, they are exposed to flows inside blood vessels. In such flows, their extremely high deformability causes an amazingly rich dynamical variety that has fascinated physicists, physicians, and biologists for decades [1]. Besides their obvious physiological relevance, red blood cells represent a prototypical model system for an entire class of soft objects such as artificial vesicles or microcapsules, which have attracted substantial interest in the physics community over the last years. One of the most intriguing phenomena is the occurrence of dynamically rotating, highly asymmetric shapes in strongly confined microchannels. These so-called slippers have so far eluded a clear physical explanation.

To study the dynamics of soft objects in flow, the vast majority of research has focused on two simple yet prototypical flow fields: a linear shear flow and a quadratic Poiseuille flow. In linear shear flow, the velocity is uniaxially directed along a single axis, say x , and its magnitude depends linearly on a second axis orthogonal to x , say $u_x = -\gamma y$, with the shear rate γ . In biaxial Poiseuille flow such as the flow in cylindrical (blood) vessels, on the other hand, the flow features a quadratic dependence on the distance r from the central axis of the channel. In the Cartesian frame $r = \sqrt{y^2 + z^2}$ and therefore $u_x = U_0[1 - \alpha^2(y^2 + z^2)]$ with the flow curvature α . In synthetic microchannels with square or rectangular geometries, the flow profile is mathematically slightly more complex but shares the key characteristic of a curved flow with a simultaneous dependence on the y and z coordinates.

In linear shear flow, the two most important dynamics of RBCs—vesicles and capsules—are tumbling (or flipping) at low shear rates [2–9] and tank-treading at high shear rates [3–6,8,10–19]. At intermediate shear rates, various transitional regimes have been observed [9,20–27], while at very high shear rates RBCs exhibit so-called multilobe shapes [28,29] and finite-Reynolds effects [30]. In the tumbling regime, the RBC behaves essentially as a rigid body performing periodic flips with

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very little deformation. In the tank-treading regime, the RBC attains roughly the shape of an inclined ellipsoid whose membrane permanently rotates around the liquid interior, thus creating an important intracellular flow.

In Poiseuille flow, the two most important modes of motion are the croissant (or parachute) shape [31–42] and the slipper shape [31–38,40–46], together with some intermediate shapes [47]. Experiments have found the slippers to occur mainly at high velocities, and croissants at low and intermediate velocities [32,36,45,48,49]. Some studies [31,33] have in addition proposed the velocity lag between cell and mean flow as a possible cause for slipper formation. In the croissant mode, the RBC flows in the center of the channel with a stationary, symmetric state, while in the slipper mode the cell slightly oscillates around a stable off-centered position [45]. In addition, the membrane permanently rotates around the cell interior leading to an important intracellular flow. This observation has led researchers to interpret the slipper motion in Poiseuille flow as, essentially, a variant of the tank-treading regime in shear flow.

Here, we use a simplified RBC model to propose that—contrary to intuition—the slipper mode in Poiseuille flow is not associated with the tank-treading mode in linear shear flow. For this, we exploit the capability of boundary-integral simulations to impose arbitrary flow profiles without the need of confining walls. We find that the key ingredient necessary for slipper formation is the combination of symmetry-breaking due to a curved flow and a rotation due to a shear flow. Led by this insight, we then propose an explanation for the occurrence of slipper shapes as a “frustrated tumbling” mode different from the established “modified tank-treading” picture.

Methods. Fluid flow is modeled via the three-dimensional (3D) Stokes equation and solved with a boundary integral method (BIM) [50]. The RBC is discretized into 2048 triangles. The tolerance for the relative residue used by the GMRES solver is set to 10^{-5} . In the presence of channel walls, the computational domain is periodic. The channel is modeled via triangulated surfaces (2166 triangles) whose positions are maintained by a set of springs. Otherwise, an infinite domain is used. For further implementation details, see [36]; the computational cost on 32 CPU cores is maximally 1 day per data point.

The RBC is treated as an elastic membrane filled with a viscous hemoglobin solution. The ratio between interior and exterior (plasma) viscosity is defined as $\lambda = \frac{\mu_{\text{in}}}{\mu}$. For shear resistance, the Skalak law with a shear modulus $\kappa_s = 5 \times 10^{-6} \text{ Nm}^{-1}$ [51] is used. The reference shape for shear resistance is chosen as the discocyte shape for simplicity. In Fig. S3 of the Supplemental Material [52], we verify for a selected set of data points that a different reference shape does not affect our results. Additionally, the membrane is equipped with a bending rigidity described by the Helfrich law [53–55] with a bending modulus $\kappa_B = 3 \times 10^{-19} \text{ Nm}$ and a flat bending reference shape. To reduce parameter space, membrane viscosity was neglected. Volume conservation is ensured by rescaling the RBC and area conservation by setting the area dilatation modulus included in Skalak’s law to $\kappa_A = 100\kappa_s$. Despite its simplifications, this model has previously shown good agreement with experimental measurements [36].

To characterize the ratio between elastic and viscous effects, we introduce the Capillary number, which in shear flow is defined as

$$\text{Ca}_{\text{shear}} = \frac{\mu\gamma R_0}{\kappa_s} \quad (1)$$

with the effective cell radius $R_0 = \sqrt[3]{\frac{3V_{\text{cell}}}{4\pi}}$ and the shear rate γ .

In a Poiseuille flow, the shear rate γ is no longer uniform, thus requiring a redefinition of Ca. The velocity in a planar Poiseuille flow has the form

$$u_x = U_0(1 - \alpha^2 y^2) \quad (2)$$

with the curvature α , leading to an effective shear rate $\gamma_{\text{eff}} = du_x/dy \propto U_0\alpha^2 y$. Considering an RBC in the channel center, the shear rate at the outer edge is thus $\gamma_{\text{eff}} \sim U_0\alpha^2 R_0$. In a channel of width

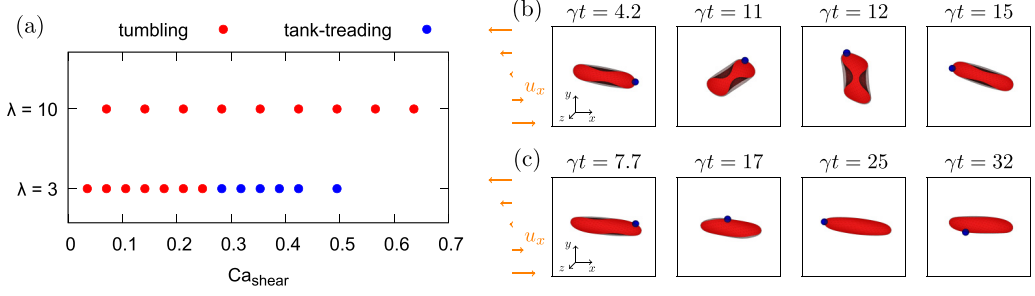


FIG. 1. RBC in pure shear flow. (a) At low shear rates the RBC tumbles, while at high shear rates a transition to tank-treading is observed for $\lambda = 3$. (b) Typical image sequence for tumbling ($Ca_{\text{shear}} = 0.070$, $\lambda = 3$), and (c) tank-treading ($Ca_{\text{shear}} = 0.46$, $\lambda = 3$). The blue dot serves to illustrate membrane rotation during tank-treading motion.

W , we have $\alpha = 1/(W/2)$, which finally leads to

$$Ca_{\text{pois}} = \frac{\mu \gamma_{\text{eff}} R_0}{\kappa_s} = \frac{\mu U_0 \alpha^2 R_0^2}{\kappa_s} = \frac{\mu U_0 \left(\frac{R_0}{W/2} \right)^2}{\kappa_s}. \quad (3)$$

A key ingredient of our work is to characterize cell behavior in a flow with fixed shear rate and curvature. In the presence of a flow curvature, this is hindered by the associated migration of the RBC [56] in the curvature plane, leading to changing shear rates. To suppress this migration, two different methods are employed. For the orthogonal superposition of shear and Poiseuille flow, a weak spring acting in the curvature plane is sufficient to push the cell back to the center. For the in-plane and biaxial superposition of these flows, the migration tendency is stronger and therefore the red blood cell is continuously shifted back to its original position.

Results. In recent studies [31–34, 36–38, 40, 43–46], experiments and simulations showed a significant proportion of slipper states for RBCs flowing in small microchannels. Besides microchannels with sharp corners, in some of these works [32, 34, 35, 38, 40, 43, 46] slippers were also found in cylindrical tubes, which corresponds closely to the *in vivo* geometry.

Our strategy to understand these shapes proceeds by starting from very simple flow geometries, followed by a stepwise increase in complexity until we reach our target geometry, the microchannel. As the correct value of the viscosity ratio λ representing the *in vivo* situation of red blood cells in blood plasma is not fully known [45, 57, 58] (and in fact most likely depends on cell age), we study two values: $\lambda = 3$ and $\lambda = 10$.

Pure shear flow. To set the stage, we start by studying our RBC model in a pure shear flow of the form

$$u_x = -\gamma y \quad (4)$$

whose strength is characterized fully by Ca_{shear} from Eq. (1). As shown in Fig. 1, we find the commonly observed tumbling state at low and the tank-treading state at high Ca numbers. We mention that in this work we denote as “tumbling” all states in which a constant cell shape rotates around its center point, which also includes nonellipsoidal shapes such as trilobes. The transition with a viscosity contrast of $\lambda = 3$ is located around $Ca_{\text{shear}} \approx 0.28$, in agreement with previous works, e.g., [17, 22, 29]. Again in agreement with previous observations, e.g., [59], the tank-treading state is not observed for $\lambda = 10$ even at very high shear rates up to $Ca_{\text{shear}} = 20$, which already hints at the different nature of tank-treading and slipper states since slippers *are* observed for $\lambda = 10$.

Orthogonal superposition of shear and Poiseuille flow. The pure shear flow of the previous paragraph is a valid approximation to the local flow in channels that are large compared to the RBC size, but it misses the important characteristic of flow curvature. The latter becomes particularly

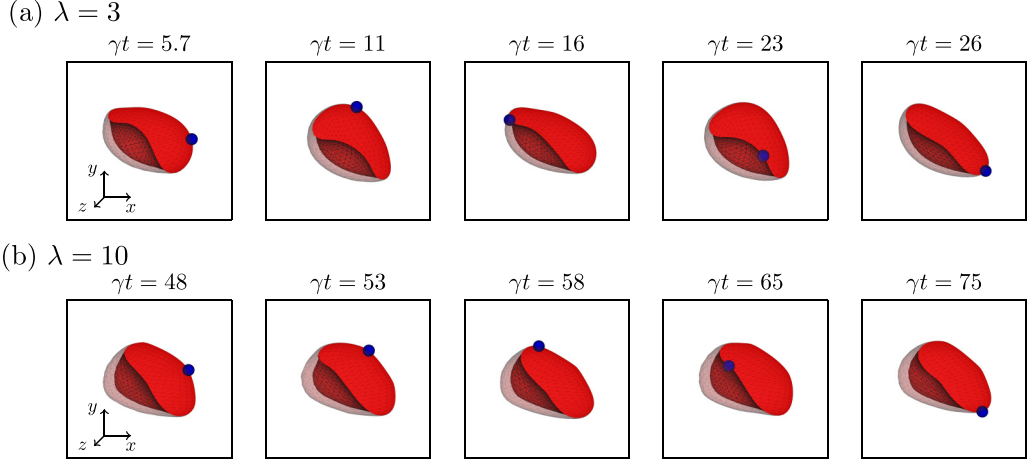


FIG. 2. RBC dynamics in orthogonal superposition of shear and Poiseuille flow (a) at $Ca_{\text{shear}} = 0.035$, $Ca_{\text{pois}} = 0.12$ for $\lambda = 3$, and (b) at $Ca_{\text{shear}} = 0.14$, $Ca_{\text{pois}} = 0.75$ for $\lambda = 10$. After some intermediate states, the RBC assumes a clear slipper state including membrane rotation, even though the considered shear rates would lead to tumbling in the absence of flow curvature as shown in Fig. 1.

important in small channels, which are the focus of our study. We exploit here the special capability of boundary-integral methods to impose truly infinite flows of arbitrary profiles without the necessity of physical walls. In this way, we amend the shear flow by superposing an additional Poiseuille flow profile. The curvature is chosen in the z -direction and thus stands orthogonal to the shear plane. The flow profile reads

$$u_x = -\gamma y + U_0(1 - \alpha^2 z^2). \quad (5)$$

This profile captures the key ingredients (shear and curvature) of the flow experienced by an off-centered cell in a rectangular microchannel, which is precisely the setup where slipper states are typically observed [36,45]. Hydrodynamic interactions with confining walls such as lift forces [56,60–62] are purposefully excluded here in order to bring out clearly the influence of the local flow profile as such. The key advantage of this flow profile is that it allows us to tune the shear strength in y and the flow curvature in z independently from each other. Accordingly, we characterize the flow profile by the two capillary numbers Ca_{shear} and Ca_{pois} defined above.

Figure 2 shows two examples for cell dynamics at different Ca_{shear} and different λ . In both situations, the cell attains a stable slipper state including the typical membrane rotation. This is rather surprising as the employed shear rates would, in the absence of flow curvature as in Fig. 1, fall deep into the tumbling regime. We further note that the investigated flow is unconfined and thus there are no walls that could prevent the tumbling motion. This leaves as the only explanation for slipper formation the additional flow curvature of the Poiseuille profile along the vorticity (z) direction of the shear flow.

To investigate this phenomenon more systematically, we create a phase diagram mapping the interplay between the shear component characterized by Ca_{shear} and the Poiseuille component characterized by Ca_{pois} in Fig. 3. Herein, the line $Ca_{\text{pois}} = 0$ corresponds to pure shear flow. For $\lambda = 3$ in Fig. 3(a) we find tumbling at low and tank-treading at high Ca_{shear} in agreement with Fig. 1. Upon addition of the second flow component by increasing Ca_{pois} , we observe that the tank-treading regime slightly grows towards lower Ca_{shear} . At around $Ca_{\text{pois}} = 0.05$, slippers start to appear. Interestingly, these slippers do not appear first at high Ca_{shear} as one would expect if slippers indeed corresponded to a variant of the tank-treading motion in pure shear flow. Instead, slippers first start to appear at low Ca_{shear} , but then very quickly and consistently occupy the entire Ca_{shear}

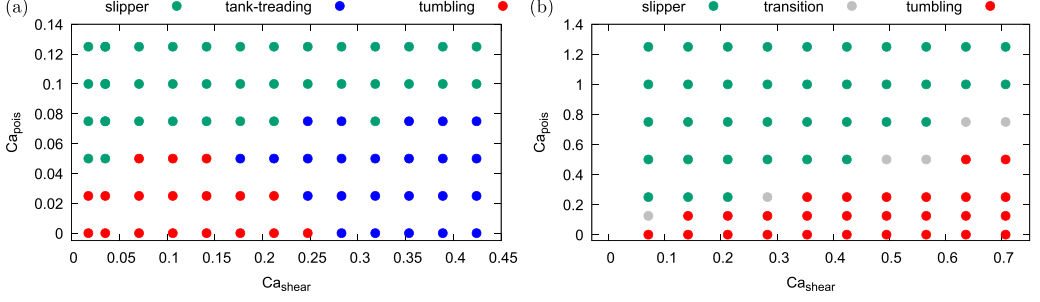


FIG. 3. Phase diagram for orthogonal superposition of shear and Poiseuille flow for (a) $\lambda = 3$ and (b) $\lambda = 10$. The occurrence of slippers upon increasing Ca_{pois} , even in regions where the shear component alone would lead to tumbling [$Ca_{\text{shear}} < 0.25$ in (a) and the entire Ca_{shear} range in (b)], demonstrates that the flow curvature is the key ingredient that causes the slipper state.

range. This supports our hypothesis that slippers in Poiseuille and tank-treading in shear flow are two distinct and unrelated modes of motion. Evidence for this hypothesis is even stronger when considering Fig. 3(b) for $\lambda = 10$. Here, upon increasing Ca_{pois} slippers appear consistently over the entire range of Ca_{shear} , even though there are no tank-treading states at all in pure shear flow.

In-plane superposition of shear and Poiseuille flow. Next, we ask whether the appearance of slippers is connected to the fact that the curvature and shear directions are orthogonal or whether a superposition of linear shear and Poiseuille flow in the same direction would be sufficient as well. The considered flow profile is thus

$$u_x = -\gamma y + U_0(1 - \alpha^2 y^2). \quad (6)$$

At $y = 0$, the derivative of the second term vanishes such that we obtain indeed a superposition of a pure shear and a pure Poiseuille, with no additional net shear.

The resulting phase diagram can again be drawn in the Ca_{shear} - Ca_{pois} -plane and is shown in Fig. 4(a) for $\lambda = 10$ and in the Supplemental Material [52] in Fig. S-1(a) for $\lambda = 3$. Comparing Fig. 3(b) for orthogonal superposition with Fig. 4(a) for in-plane superposition shows qualitatively the same trends. The addition of a small Poiseuille flow component leads to the appearance of slipper states at low Ca_{shear} . Increasing the Poiseuille flow strength makes the slipper region grow towards higher Ca_{shear} . Overall, the slipper region in the orthogonal superposition is, however, larger than for in-plane superposition, indicating that orthogonal curvature is more efficient in creating slippers than in-plane curvature. The physical reason for this observation will be discussed below. Again, the appearance of slippers at low Ca_{shear} and at $\lambda = 10$ contradicts the interpretation of slippers as a modified tank-treading mode.

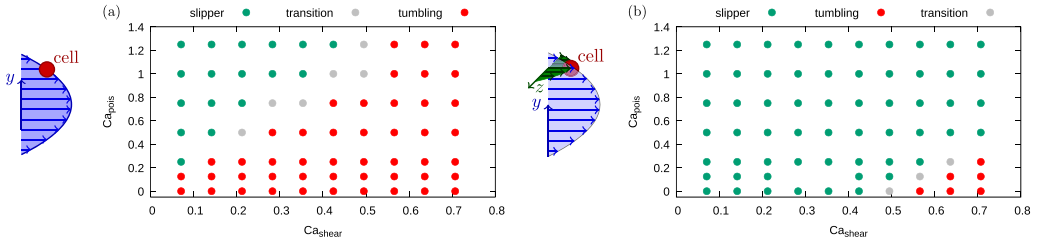


FIG. 4. (a) Phase diagrams for (a) in-plane superposition of shear and Poiseuille flow, and (b) biaxial superposition of shear and Poiseuille flow for $\lambda = 10$. In (b), $Ca_{\text{pois},y} = 1.25$ was fixed. In qualitative agreement with Fig. 3, the additional flow curvature triggers the appearance of the slipper state.

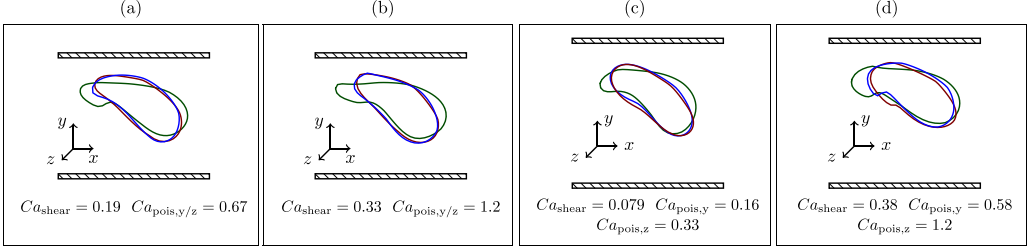


FIG. 5. Comparison of RBC shapes in our microchannel simulations (green) with shapes obtained by an orthogonal superposition of shear and Poiseuille flow (red) and with shapes obtained by a biaxial superposition of shear and Poiseuille flow (blue). The good agreement shows that our superposition approach is a sufficient representation of microchannel flow and that lift forces from confining walls are not essential for slipper formation. Parts (a) and (b) are in the square, and (c) and (d) in the rectangular microchannel. A similar picture for $\lambda = 3$ is provided as Fig. S-2 of the Supplemental Material [52].

Biaxial superposition of shear and Poiseuille flow. In a real microchannel, the flow is curved in the y - and z -directions. Since we observed in Figs. 3 and 4(a) that both curvatures independently lead to the creation of slipper states, it is natural to ask whether the effect would be amplified, i.e., whether the slipper region in the phase diagram would grow, if both curvatures were added simultaneously to the shear flow. We therefore study a system with the flow profile

$$u_x = \gamma y + U_{0,y}(1 - \alpha_y^2 y^2) + U_{0,z}(1 - \alpha_z^2 z^2). \quad (7)$$

This results in the appearance of three dimensionless numbers: Ca_{shear} , $Ca_{\text{pois},y}$, and $Ca_{\text{pois},z}$. The resulting phase plot for fixed $Ca_{\text{pois},y} = 1.25$ is shown in Fig. 4(b) for $\lambda = 10$ and in the Supplemental Material [52] in Fig. S-1(b) for $\lambda = 3$. Indeed, the slipper region is even larger than in the two cases before, where only a single curvature was added to the base shear flow. So far, all studied systems excluded the influence of confining walls. This influence will be considered next.

Microchannel flow. We finally study our target geometry, i.e., realistic microchannels, which includes hydrodynamic interaction with the walls. We consider a square channel with a side length $W = H = 9.6 \mu\text{m}$ as well as a rectangular channel with $W = 11.5 \mu\text{m}$ in the y -direction and $H = 8 \mu\text{m}$ in the z -direction. Such a channel was used in the recent experimental work of Recktenwald *et al.* [45] and, with slightly different dimensions, also in [36]. In contrast to the previous paragraph, shear and Poiseuille components can now no longer be tuned independently and only the maximum flow speed U_0 remains as a free parameter. Nevertheless, Ca_{pois} from Eq. (3) is well-defined. Ca_{shear} is also well-defined using the shear-rate obtained in the unperturbed flow profile at the coordinate of the cell. This allows a direct comparison of the RBC shapes in realistic microchannels with the shapes observed in the artificial flow fields studied above.

As has been shown previously in experiments and simulations [36,45], both slippers and croissants are frequently observed in this setup. Furthermore, numerical evidence shows that slipper states in nonsquare microchannels take off-centered positions in the long channel direction, here the y -direction, while remaining centered in the short direction, here the z -direction [63]. A selection of slipper shapes is shown in Fig. 5. Using the dimensionless numbers Ca_{shear} and Ca_{pois} , we can directly match slipper states in the microchannel with corresponding slipper states as they occur under the flow profiles from the previous paragraphs. Indeed, Fig. 5 shows that the shapes are similar. The slight differences stem from the absence of lift forces from the walls in the infinite flow profiles. To further underline the direct correspondence between the superposed flow fields studied above and the realistic microchannel flow, we compare the rotation periods, i.e., the time that it takes for the membrane to carry out one full rotation, measured in units of the inverse shear rate γ^{-1} . Referring to Fig. 5, the values are $T_{\text{biaxial}}/T_{\text{orthogonal}}/T_{\text{channel}} = 49/45/65$ for (a), $48/44/65$ for (b), $48/44/47$ for (c), and $52/47/57$ for (d). Together, these similarities demonstrate the validity

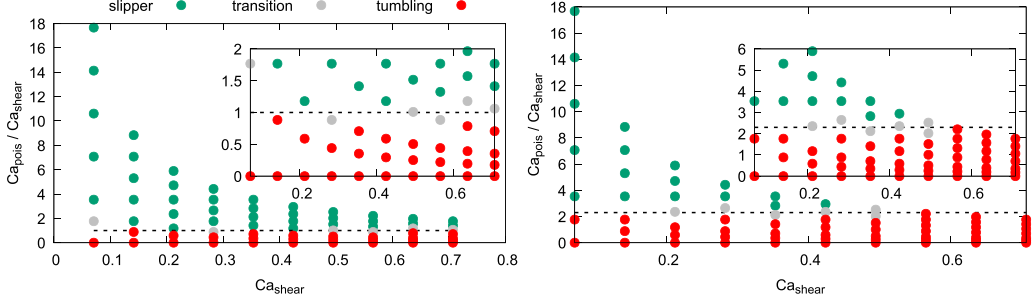


FIG. 6. (a) The phase diagram from Fig. 3(b) with a rescaled vertical axis shows that there is a universal transition point $(Ca_{\text{pois}}/Ca_{\text{shear}})_{\text{crit}} \approx 1$ for this system. (b) For the system in Fig. 4(a), a similar transition point is found; its value is at around 2.5.

of superposing a shear and Poiseuille profile(s) to mimic a true microchannel flow. They further highlight our key finding that flow curvature is sufficient to explain the occurrence of slipper states and that hydrodynamic interaction with channel walls is not essential.

Discussion and Conclusion. The transition from tumbling to tank-treading for vesicles, capsules, and red blood cells in shear flow is well understood [20,21,64]. For the transition from croissant/parachute to slipper in Poiseuille flow, the general explanation assumes first an instability of the croissant, leading to outward motion, which is then counterbalanced by the lift force from the confining wall [31,33,65]. Together, these two effects stabilize an off-center flow position where the local shear causes rotation of the membrane analogous to the tank-treading mode in shear flow. This line of argument, however, cannot be complete, as slippers in microchannels appear at (local) shear rates that are far below the tumbling-to-tank-treading threshold in shear flow. Even more, slipper states have been found at high viscosity contrasts where in shear flow no tank-treading motion at all is observed [36,45,59].

From our data in Figs. 3(b) and 4(a), we conclude that there exists, for each shear rate Ca_{shear} , a critical amount of additional flow curvature, embodied in Ca_{pois} , required to trigger the transition to the slipper state. It remains to be seen, however, whether there exists a universal transition point for each of the two considered systems. Indeed, if we rescale the vertical axis to $Ca_{\text{pois}}/Ca_{\text{shear}}$, the phase boundary becomes a nearly horizontal line independent of the shear rate, i.e., we find a critical transition ratio $(Ca_{\text{pois}}/Ca_{\text{shear}})_{\text{crit}}$. In Fig. 6 we show that this value is approximately 1 for orthogonal and approximately 2.5 for in-plane superposition of shear and Poiseuille flows.

Based on our systematic decomposition of flow fields into shear and curvature contributions, we are now in a position to propose a novel explanation for slipper formation. Its key ingredient is the effect of the flow curvature on the RBC shape. Hydrodynamic interactions between RBC and surrounding walls are not necessary for slipper formation. Consider first a tumbling RBC in shear flow. For a stable, periodic tumbling motion of an ellipsoid shape, it appears essential that the tumbling RBC possesses a plane of symmetry such that a 180° flip around an axis perpendicular to the shear plane leads to an identical state as shown in Fig. 7(a). Now consider an additional curved

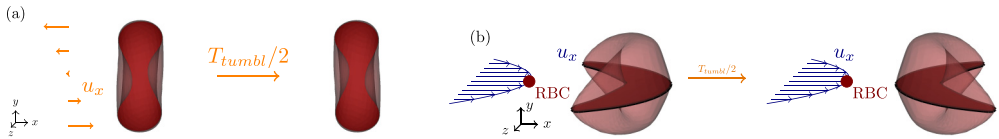


FIG. 7. (a) In pure tumbling motion, the RBC shape exhibits a plane of symmetry such that the initial shape is restored after half a tumbling period. (b) A curved flow (shown here in the z -direction) breaks the symmetry of the shape, thus preventing the tumbling motion.

flow in the z - or y -direction, which, in turn, causes curving of the particle in the same direction with the particle tip pointing in the direction of the flow, the x -direction. This curving breaks the original symmetry such that a 180° flip no longer leads to a symmetric situation as illustrated in Fig. 7(b). Instead, a (hypothetical) 180° flip would lead to a highly unstable situation with the tip pointing backwards. As a result, this symmetry breaking effectively prevents the regular tumbling motion and forces the cell to adapt to the conflicting influences of Poiseuille and shear flow by creating a new flow state, which is precisely the slipper. We therefore propose that the prevailing paradigm of the slipper shape should be modified, and that slippers should be viewed as a “frustrated tumbling” rather than a “modified tank-treading.”

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