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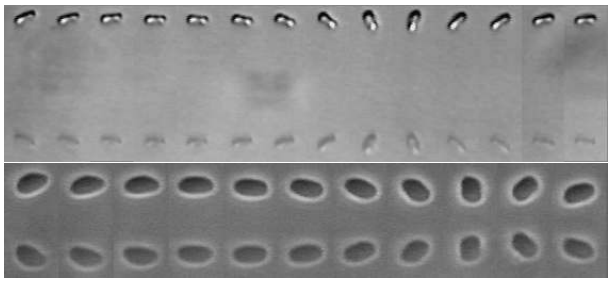

We describe the similarities and the specificities of the behaviour of individual soft particles, namely, drops, lipid vesicles and red blood cells subjected to a shear flow. We highlight that their motion depends in a non trivial way on the particle mechanical properties. We detail the effect of the presence of a wall with or without wall-particle attractive interaction from a biological perspective.

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Introduction

Blood circulation, microfluidic devices and emulsion processing bring into play soft micron-size particles like cells, vesicles and drops in creeping flows. We highlight the generic behaviour of these particles in shear flow and its specificities induced by the differences between the various particle structural properties. We focus on three situations relevant for blood circulation: particles in infinite medium, close to a wall (blood cells at a vascular endothelium) or adhered to a wall (leukocytes adhered to the endothelium).

Beyond their common features, like size and fluidity, fundamental differences exist among drops, vesicles and cells: drops and surfactant-covered drops present a viscous extensible interface; while vesicle and cell membranes are essentially incompressible[1], with no possible transport of molecules between the membrane and the inner volume, ensuring a constant membrane area. Cells exhibit more complicated mechanical properties. Red blood cells' (RBC) membrane, for instance, is underlined by a 2D visco-elastic spectrin network[2], which confers shear elasticity to their membrane and is responsible for their biconcave discocyte shape. Numerous theoretical works have studied the dynamics of particles with different mechanical properties [3-7]. The approach of the problem is non trivial since the shapes are not given a priori and the equations coupling the the membrane tension and the surrounding flow field are nonlinear. Experimental studies have been developed by several scientific communities coming from fields as diverse as fluid mechanics, soft matter and biorheology, and therefore, were not much compared to one another. Here, we describe behaviours that are common to drops, vesicles or RBCs before focussing on specific effects induced by the bending and elastic energy of the membrane and by its incompressibility.

Behaviour in unbounded shear flow

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The understanding of individual particles' behaviour in flow is a prerequisite to that of the rheology of suspensions. For instance, the deformability of RBCs plays a crucial role in the rheological properties of the whole blood, both at the largest scale of the arteries[8], and in the microcirculation through very small capillaries.

Shapes

A first striking feature is that drops[9], vesicles[10] and RBCs[11] can all exhibit ellipsoidal shapes in shear flow although drop shapes are governed by surface tension, vesicle shapes are determined by the bending rigidity of their membrane (it is easier to bend vesicle and cell membranes than to stretch them) and RBC shapes depend on shear elasticity. These ellipsoidal shapes are, however, reached under different shear rates (small for drops and vesicles, but high for RBCs) since surface tension and bending elasticity involve lower energy than shear elasticity. Moreover, RBCs deform without increasing their surface area whereas, upon increasing the flow strength, the drop stretches and breaks up.

Tanktreading drop-like motion in shear flow

A second striking point is that vesicles and RBCs characterized by a low ratio of their inner fluid viscosity to that of the suspending fluid ($c = \eta_i/\eta_o$), exhibit a typical tanktreading motion similar to that observed on drops: their membrane rotates around their centre of mass (Figure 1). This rotating motion transfers the tangential stresses of the flow to the inner fluid, which rotates and dissipates the work done by external flow, allowing the particles to maintain a stationary shape and a steady stationary orientation.

Transition: tumbling solid-like motion

In strong contrast to drops, above a critical value of the viscosity ratio, the motion of vesicles[10,12,] and RBCs[13] undergoes a transition towards an unsteady tumbling solid-like motion described, by analogy, with the flipping of a coin (Figure 1).

In order to elucidate this behaviour, Keller and Skalak[3] (KS) treated the particles as ellipsoids of fixed shape with a fluid membrane and used a simplified velocity field. They established the equation of evolution of the inclination angle θ of the particle with respect to the flow direction:

$$d\theta/dt = A + B \cos(2\theta), \qquad (1)$$

where $-2A$ is equal to the wall shear rate γ, and B is a function of γ, c and ν, the reduced volume defined by the ratio of the volume of the particle to the volume of the sphere with the same surface area. The first term on the right hand of equation (1) is a vorticity term equal to $-\gamma/2$, while the second term is an extensional term at 45° with the flow direction. Equation (1) predicts tanktreading ($-A/B < 1$), tumbling ($-A/B > 1$), and a critical shear rate which depends on c and ν. Theoretical predictions show a rather good qualitative agreement when compared to the observations (Figure 2) of the time evolution of θ measured on tumbling vesicles[12] and RBCs[14]. A good quantitative agreement of the critical shear rate is also found for vesicles[12] (Figure 2c). However, for RBCs, the model does not capture the observed shear-rate dependency of the tanktreading-tumbling transition, and predicts shear rate at the transition in complete disagreement with observations[15]. The model also fails to describe the behaviour of vesicles when they deform in the flow[12]. These discrepancies are due to the shear elasticity of the RBCs' membrane and to vesicles' deformability, we now discuss..

Effect of membrane shear elasticity

We recently showed that RBCs in shear flow present a motion more complex than that described by KS. A typical behaviour[15] is illustrated in Figure 3. For high values of the shear stress ($\eta_o \gamma$), RBCs present a quasi steady tanktreading motion but when $\eta_o \gamma$ is decreased their inclination oscillates about a mean angle down to a critical $\eta_o \gamma_c$, for which RBCs tumble at least once. This swinging regime is characterized by a quasi-nondeformed cell shape and an oscillation period of the inclination angle equal to half the tanktreading period. The swinging/tumbling transition is induced by tuning down (or up) γ.

Swinging and shear-stress triggered transition are not observed on purely viscous vesicles but swinging has, however, been detected on elastic capsules in shear flow[16], when they were slightly non spherical at rest. These features are a signature of the membrane shear elasticity. Indeed, if one assumes that the unstrained RBC shape is biconcave, the local elements of the elastic membrane are not equivalent : for instance, during tanktreading, the elements which form the rim at rest rotate about the stationary cell shape to reach the dimples after rotation and vice and versa. They are then locally strained and store elastic energy (Figure 4). After a 180° rotation, the elements retrieve their initial shape and are no more strained, thus resulting in a periodic storage of energy. We described this effect by extending the KS model[15]: when writing that the rate of dissipation of energy in the cell equals the rate at which work is done by the external fluid on the cell, we added the elastic power stored in the periodic elastic membrane strain to the cell viscous energy dissipation. The modified model indeed predicts time oscillations (figure 5), and it captures the trends of the γ variations of the amplitude and period of oscillations, as well as the motion transition for decreasing values of the shear stress (Figure 3). We emphasize that the fit by such a model of the characteristics of swinging and tumbling-tanktreading transition on individual flowing RBCs allows the determination of internal viscosity, membrane viscosity and shear modulus of each cell. Therefore, this analytical model, which still has to be refined, or alternatively, a numerical approach[17] hold promises for applications in non-invasive cellular-scale diagnostic in clinical hemorheology..

Effect of vesicle deformability

Vesicles are floppy objects whose shape may vary during motion in the flow. In the tumbling regime, they may tremble or successively present ellipsoidal and spherical shapes, which strongly affect the flipping motion[12,18]. This effect, although not relevant for cells which are more rigid, has received recent attention[5]. It can be understood by considering that the variation of the tumbling angle with time induces a variation

of the stretching ratio of the deformed vesicle since hydrodynamic pressure induces stretching along the +45° direction and compression along the –45° direction, where interior flow relaxation can lead to nearly vanishing membrane tension (in case of low internal viscosity) and hence strong shape fluctuations and/or shape relaxation into a sphere.

Presence of a wall: lateral drift

The presence of a wall is a situation most relevant to blood physiology, especially for blood cells circulating in arterioles or venules. Indeed, a RBC depleted region near the capillary walls has been long-reported[11,19] originating from the impossibility for RBCs to approach the endothelium walls, while oppositely, white blood cells can approach the endothelium and be captured onto its surface.

Migration from the wall is known for deformable drops[20] and RBCs[11,19] since the 1960s and has been recently observed on giant lipid vesicles[21,22] (figure 6). It has been explained in terms of modifications of the flow field induced by the asymmetric shape of the object and the wall[23,24]. The drift velocity away from the surface in absence of external force has been theoretically predicted[24]. No lift force is observed on spherical objects.

The associated lift force Fl is a biological issue since it may counterbalance the adhesion force experienced by leukocytes at their approach to the endothelium. We used giant unilamellar vesicles to determine the variation of the lift force with the aspect ratio, the vesicle radius, the distance to the substrate and the shear rate[21]. These vesicles (closed lipid bilayer membrane) were filled with sucrose solutions of controlled density[25], which allowed to vary ν by deflating/inflating the vesicles via regulating the outer osmotic pressure. Flowing vesicles were found to unbind from the substrate above a critical value of γ and hover at a distance h from the substrate: h self-adjusts so that the hydrodynamic lift exactly counterbalances the vesicle buoyancy. In our experiments, the lift force Fl ranged from 0.2 to 150pN and wrote as:

$$Fl = f(\nu)\, \eta_o\, \gamma\, R^3/h \qquad (2)$$

where f was determined experimentally.

By using Eq. (2), we estimated the lift force acting blood cells in post-capillary venules, where the wall shear stresses range from 0.2 to 1 Pa. For h = 350 nm (typical size of leukocytes microvilli[26]), Fl ranges from 31 to 155 pN for RBCs (ν = 0.7). It is equal to 0 for spherical leukocytes while it ranges from 46 to 230 pN if the cell is slightly deformed (ν = 0.95). Hydrodynamically speaking, flowing leukocytes must therefore imperatively preserve their spherical shape to approach vessel walls. Then, selectins binders fast form and break molecular bridges with the cell, preventing its deformation, allowing its capture and slowing down and permitting progressive elimination of the lubrication layer at the vessel surface. When an intimate cell-wall contact occurs, the cell no longer experiences the lift force. It can strongly bind to the endothelium and deform. Particles adhered to the wall

Particles adhered to the wall

When a soft particle is strongly adhered to the wall in shear flow a new question arises: does the particle present a surface/volume flow? Or, in biological terms: are cell membranar adhesion receptors able to flow towards the cell adhesion line with the substrate and enhance cell adhesion?

We experimentally showed the existence of a surface flow on giant lipid vesicles[28]. It is divided into two symmetric quadrants with two stagnation points on each vesicle side (Figure 7). The surface streamlines avoid the motionless contact zone thus limiting the friction between the cell and the substrate. As a consequence, the membrane is strongly sheared since the rotational velocity on streamlines close to the contact zone is much smaller than that close to the stagnation points.

For cells, the cytoskeleton prevents the surface flow of micron-size defects[29]. It could, however, allow molecular surface flow among the membrane proteins anchoring the underlying cytoskeleton and thus favouring the recruitment in the contact zone of the adhesion receptors of the cell membrane. This point has still to be investigated.

Conclusions

The behaviour of soft particles in flow present specific features which strongly and non-trivially depend on the particles' shape and mechanical properties. These specificities must be accounted for when one considers cells in a flow, since they can be exploited to characterize individual cell mechanics (swinging), and because they involve relevant forces or flows. A lot of work has still to be done in the direction of more complex biomimetic vesicles[30] and cells (for instance tumor cells at the origin of metastasis), towards the effect of interactions between cells (high cell concentration in the blood flow) or to study flows that mimic blood microcirculation through micron-size capillary networks[31].

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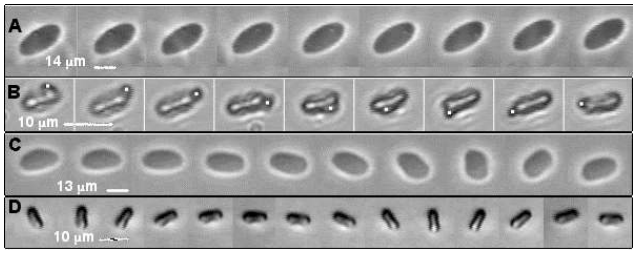

Figure 1 : Vesicles and red blood cells in shear flow. A : tanktreading vesicle, viscosity ratio $c = \eta_i/\eta_o = 1$; B : rotation of a bead (diameter 1 µm) stuck on the membrane of a tanktreading RBC with c = 1/47, shear rate : 6 s^{-1}; C : tumbling vesicle with c =8 ; D : tumbling RBC with c = 1/47, shear rate : 0.8 s^{-1}

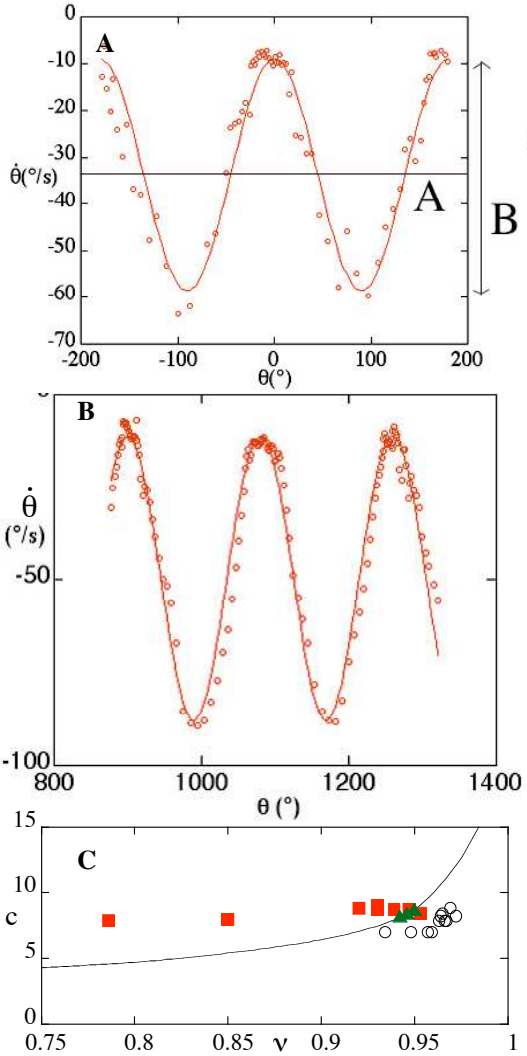

Figure 2 : Tumbling of vesicles and RBCs. Variation of the angular velocity dθ/dt of the inclination of a vesicle (A) and of a RBC (B) versus the inclination angle θ; C : regimes of motion of vesicle (■) : tumbling, (O) : tanktreading, (▲) : transition. The solid line is the tumbling /tanktreading transition line given by the KS model.

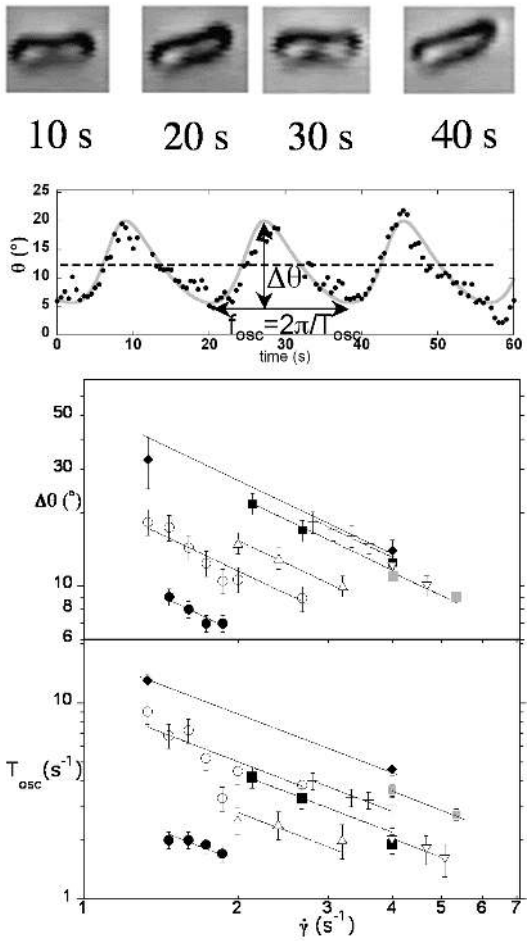

Figure 3 : RBC motion in shear flow. A : swinging RBC, c=1/47, shear rate = 1.33 s^{-1} ; B : Orientation versus the time (c= 1/47, shear rate = 0.8 s^{-1}) ; C : Experimental variations of the amplitude and period of oscillations on individual RBCs, (O) , (●) : c=1/22 ; (■), (□) : c=1/31 ; (Δ), (+), (♦), (∇) : c=1/47. Solid lines are obtained by KS modified model.

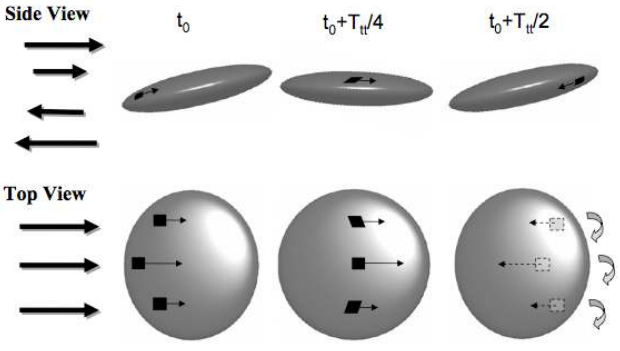

Figure 4: local strain of elastic RBC membrane elements during the rotation of the membrane when the RBC tanktreads

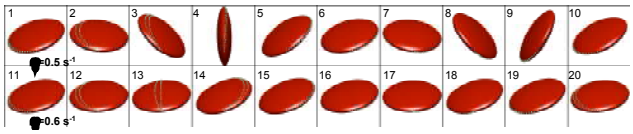

Figure 5: RBC motion and transition for two shear rates, as computed by using the modified KS model

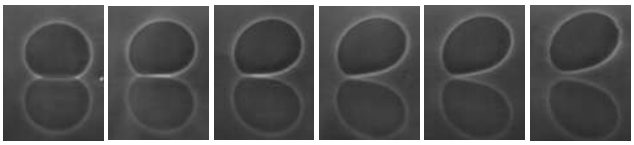

Figure 6: Unbinding of a vesicle in a shear flow. The lowest image is the reflection on the substrate. From left to right, each picture is taken at increasing shear rates: 0, 0.09, 0.14, 0.23, 0.32, 0.36 s^{-1}, R=36, 9 μm, ν = 0.98

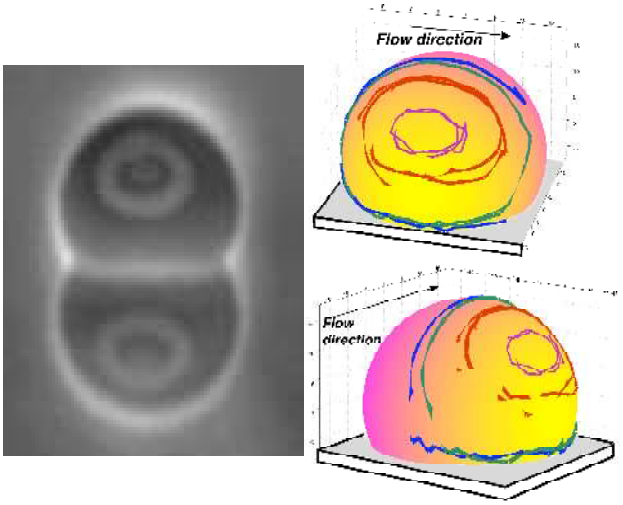

Figure 7: Marker trajectories on the surface of a vesicle adhered to a substrate in a shear flow. Left : vesicle (R = 10 μm), its reflection on the substrate and the trajectories of two markers. One is on at stagnation point, the other one rotates on the membrane. Right : streamline reconstruction on a vesicle (R=17.5 μm)