Abstract. Blood flow is dictated by the dynamics of red blood cells (RBCs), which constitute by far the major component. RBCs are made of a two dimensional fluid bilayer of phospholipids, having underneath a network of proteins conferring to them shear elasticity, and they possess many membrane and transmembrane proteins (like ion channels). Simplified systems, like vesicles (made of a pure bilayer of phospholipid) and capsules (made of an extensible polymer shell) are used as models for RBCs. Both systems reproduce several features known for RBCs under flow. Their interest lies, besides some simplicity, in the fact that they can be fabricated in the laboratory, and their properties (size, stiffness, internal content....) can be varied in a wide range allowing thus to explore a quite significant parameter space that is essential to test predictions and discriminate between different models. We shall review the main recent achievement in this field, both for a single entity, collective effects and the impact on rheology.

1. Introduction
Blood is a complex fluid that is primarily composed of red blood cells (RBCs), which occupy (in a healthy human body), about 45% of the blood volume. The rest consists of plasma, while the other blood elements (white blood cells, platelets, etc.) take up less than 1% of the total blood volume.

The descriptions of blood flow properties escape the traditional laws for simple fluids. The complex character results from an intimate coupling between the shape of RBCs and the ambient plasma, which leads to a rich set of RBC morphologies in the blood circulatory system. Understanding the selection of shapes and dynamics among a large manifold of possibilities, the collective effects, the spatiotemporal organizations, is a challenging problem. This type of complexity is a characteristic property of non-equilibrium dissipative systems for which general thermodynamic principles, such as minimization of energy, maximization of entropy, etc., cannot be applied.

During the 70’s and 80’s a large number of studies were devoted to finding the equilibrium shape of a RBC. Helfrich [1] introduced simple geometrical models in which he assumed that most of the energy is stored in bending modes of the cell membrane. He proposed that the energy of the cell is a quadratic functional of the mean membrane curvature $H$, and the shape of the cell is obtained by minimizing the curvature energy subject to two constraints: the total area is constant (the local area, and thus the total one, is fixed –the membrane is viewed as a two dimensional incompressible fluid), and the enclosed volume is also constant, the internal fluid being incompressible. The two constraints are imposed via two Lagrange multipliers $\lambda_1$...
and $\lambda_2$, so that the total "free-energy" to be minimized is

$$F = \frac{\kappa}{2} \int H^2 dA + \lambda_1 \int dA + \lambda_2 \int dV$$

(1)

where the first two integral are performed over the total surface, the last one over the enclosed volume, $\kappa$ is the membrane bending rigidity, having the dimension of an energy. The curvature energy (the first term) is invariant under an increase of the absolute size of the cell (if lengths $(x, y, z)$ are multiplied by a constant $\mu$ –a homothety–, this implies that $dA \to \mu^2 dA$ and $H^2 \to \mu^{-2} H^2$, so that the energy is invariant). This implies that the size itself does not matter, but only the swelling ratio, that tells us how much is the shape close to, or far from, a sphere. The swelling ratio, called also the reduced volume, is defined as the ratio of the actual volume $V$ over that of a sphere having the same area $A$ as the RBC:

$$\nu = \frac{V}{(4\pi/3)} \left[ \frac{A}{4\pi} \right]^{3/2}$$

(2)

For a sphere $\nu = 1$, otherwise $\nu < 1$. For a human RBC $\nu \simeq 0.65$. This model was successful in predicting the biconcave shape of the RBC, but also in predicting many other shapes corresponding to different values of $\nu$. RBCs have been mimicked by vesicles (the membrane of which is made of a bilayer of phospholipids, unlike RBCs, which in addition, possess proteins networks and protein channels, etc., see late) that could be fabricated in the laboratory, and where the reduced volume could be varied at will in order to test the prediction of the model. A quite good agreement could be found between predictions and experiments, provided that the model be enriched, like introducing, for example, a spontaneous curvature $H_0$ (where $H$ in (1) had to be substituted by $H - H_0$, meaning that an open membrane would have minimal curvature energy when $H = H_0$). The problem acquires now two parameters, $\nu$ and $H_0$, and the variety of shapes increases quite dramatically. The problem of equilibrium shapes by using the Helfrich model and its variants is now well understood both experimentally and theoretically (see [2] for a review).

The end of 90’s has known the emergence of a new activity, namely the behaviours of RBCs and vesicles under nonequilibrium conditions (basically under imposed flows), albeit some sparse works appeared already in the 80’s without active research at the international level. While by the end 90’s only few groups (basically in Europe) were active in this field, the advent of the new century has known an unbelievable upsurge of interest in various communities, physics, mechanics, mechanical engineering and applied mathematics, everywhere over the world, with a central activity in Europe, USA and Asia. The number of papers that has been devoted to this field since the end of 1990 may be estimated to few hundreds. Therefore this review can not cover all these progresses, but will focus on some aspects, namely vesicles, capsules and RBCs under shear and Poiseuille flows, and only say few rapid words about rheology of a dilute suspension, and collective effects of RBCs.

2. RBC properties and introduction of the biomimetic systems, vesicles and capsules

Healthy human RBC at rest has a biconcave shape that minimizes the Helfrich energy. Its size if of about few $\mu$m in length, and its membrane is made of a phospholipid bilayer, which is fluid at physiological temperature. Besides phospholipid molecules, the membrane possesses a spectrin network (also called the cytoskeleton) made of proteins that confer to RBC plane shear elasticity (figure 1). In addition, the membrane of RBC has several membrane and transmembrane proteins having different roles and functions (like ion channels,...). For mechanical properties suffices it to say here that the RBC membrane has a visco-elastic behaviors. The interior
of the RBC is made of an aqueous solution containing hemoglobin (and other species, like ATP-adenosine triphosphate) that is responsible for oxygen transport from lungs towards the microvasculature (arterioles, veinules and capillaries) where gas exchange takes place. The hemoglobin solution is a newtonian fluid. The hemoglobin solution has, at physiological temperature, a viscosity which is of about 5 times that of the plasma (its viscosity is close to that of water), but this viscosity is quite temperature-dependent.

A vesicles is a closed membrane which is made, like RBC, of a purely phospholipid bilayer, which is fluid at physiological as well as at room temperatures. It has become now quite standard to fabricate them in the research laboratories, with various sizes (their typical radius ranges from few µm to about 100 µm). Their bending rigidity is of about a fraction of eV (and is close to that of the RBCs). They can be swelled or emptied thanks to osmosis, and thus their reduced volume ν can be changed. Their internal content can be varied (polymer solutions in order to act on the internal viscosity, and so on). In particular for ν = 0.65 the vesicles exhibits a biconcave shape which is similar to that of a human RBC. Different types of phospholipids can also be used, in order to act, for example, on the bending rigidity. Vesicles share with RBCs an important property, namely, their membrane area is inextensible.

Finally, capsules are quasi-spherical shells made of polymers. They can be obtained thanks to interfacial polymerization of a liquid drop. This leads to approximately spherical particles enclosed by a thin polymerized membrane with mechanical properties that depend on the fabrication process. For biological applications (as carrier of active substances, for example) the typical membranes that are used or natural or synthetic polymers such as poly-L-lysine, alginate or polyacrylates. Their membrane is extensible, unlike vesicles and RBCs, in turn they are endowed with shear elasticity, mimicking the cytoskeleton of the RBCs. Their sizes can be quite diverse (say from a fraction of µm up to few mm; the later size is quite familiar in everyday life, the pharmaceutical capsule). The mechanics of a capsule belongs to the class of nonlinear elasticity [3].

3. Basic modeling of RBCs and their biomimetic counterparts under flow
In vivo the Reynolds number at the scale of the RBC is often small enough (except in arterioles and at some sites of aneurysms [4]) so that the inertia is often negligible. Experiments on vesicles on RBCs have been so far confined to the small Reynolds number limit (but access to higher Reynolds numbers is by now quite feasible). The fluid inside and outside the cell is thus described by the Stokes equations

\[ \eta \Delta u - \nabla P = 0 \]  

(3)
\[ \nabla \cdot \mathbf{u} = 0 \]  

(4)

where \( \mathbf{u} \) is the velocity field and \( P \) is the pressure. The quantities associated with the internal fluid are denoted with a prime. For example, the viscosity of the internal fluid (which is in general different from that of the external fluid) will be denoted as \( \eta' \). At the membrane we have the following boundary conditions:

- Continuity of the velocity field
  \[ \mathbf{u} = \mathbf{u}' \]  
  (5)

The continuity of the normal component is a consequence of the mass conservation, while the tangential velocity continuity follows from the assumption of no-slip condition.

- Equality of the fluid velocity and the membrane one, \( \mathbf{u}_m \)
  \[ \mathbf{u} = \mathbf{u}' = \mathbf{u}_m \]  
  (6)

This is valid under the assumption that the membrane is not permeable to water flow (which is the case once the osmotic equilibrium is achieved). Note that the knowledge of the normal membrane velocity (which coincides with that of the adjacent fluid) is sufficient in order to determine the evolution of the membrane. However, if one is interested in the fluid motion along the membrane (the so-called tank-treading motion), then we have to determine the adjacent fluid tangential velocity. To that end we impose that the tangential membrane velocity coincide with that of the adjacent fluid (the no-slip condition).

- Continuity of the stress
  \[ \sigma \cdot \mathbf{n} - \sigma' \cdot \mathbf{n} + \mathbf{f} = 0 \]  
  (7)

where \( \sigma = -P \mathbf{I} + \eta (\nabla \mathbf{u} + \nabla \mathbf{u}^T) \) is the stress tensor, with the superscript ‘\( T \)’ designating the transpose and \( \mathbf{f} \) is the membrane force. This force is composed of two contributions: the bending force and the membrane in-plane elasticity (for example membrane shear elasticity), that we shall introduce separately.

**Bending force** \( \mathbf{f}_b \)

The bending force, which can be obtained from the functional derivative of the energy (1), and \( \mathbf{n} \) is the normal vector pointing towards the exterior of the cell. Before writing this expression two remarks are in order: (i) the incompressibility condition in (4) guarantees, in principle, the conservation of the enclosed volume; the Lagrange multiplier \( \lambda_2 \) can thus be removed from (1), the pressure field \( P \) plays now the role of the Lagrange multiplier. (ii) Under flow the stresses are inhomogeneous along the membrane, so that we need to impose local membrane incompressibility, and not only the global one. In other words, the global Lagrange multiplier must be replaced by a local one, denoted hereafter as \( \zeta \), that plays on the membrane the same role played by the pressure field in the bulk (the membrane is a two dimensional incompressible fluid). The functional derivative of the free energy provides us with the membrane force \([1, 5]\) (a simple derivation can be found in two dimension in \[6\])

\[ \mathbf{f}_b = \left[ k_c \left( \frac{1}{2} (H - H_0) [4K - H(H + H_0)] - \Delta_s H \right) + H \zeta \right] \mathbf{n} + \nabla_s \zeta \]  

(8)

where \( H \) is the mean curvature, \( K \) the Gaussian curvature and \( \Delta_s \) is the surface Laplacian (known also as the Laplace-Beltrami operator) and they can all be written in terms of the normal vector

\[ H = \nabla_s \cdot \mathbf{n} = \nabla \cdot \mathbf{n} \quad \text{and} \quad 2K = H^2 - \nabla \mathbf{n} : \nabla \mathbf{n}^T. \]  

(9)

The surface gradient, the surface divergence and the Laplace-Beltrami operator are respectively expressed by:
\(\nabla_s f = (I - n \otimes n) \nabla f = \nabla f - (n \nabla f) \cdot n,\)  
(10)

\(\nabla_s \cdot v = (I - n \otimes n) : \nabla v = \nabla v - ((\nabla v) \cdot n) \cdot n,\)  
(11)

\(\Delta_s f = \nabla_s \cdot (\nabla_s f).\)  
(12)

\(f\) and \(v\) are scalar and vector fields, respectively.

- The Lagrange multiplier \(\zeta\) is determined from the requirement that the surface divergence of the velocity field is zero

\(\nabla_s \cdot u = 0\)  
(13)

This condition will be used when modeling a RBC or a vesicle (which are inextensible), but not for extensible capsules, of course. One can alternatively impose quasi-incompressibility by choosing a large membrane tension, as done in some numerical calculation [7]. If a cytoskeleton is to be taken into account, the associated force has to be added to the membrane bending force. Since several preliminaries are needed, this force will be introduced separately in the next section.

- Finally, boundary conditions on the external domain (containing all the suspended entities) must be specified. In an unbounded domain, the velocity field at infinity must be equal to the imposed one (e.g. linear shear flow, or Poiseuille flow...). If the domain is finite, say a tube, or a cube, usually the boundaries are taken to be rigid, and the field is assumed to vanish on the boundaries. Of course, in the human body, the blood vessels are flexible, and for those problems we have to specify the dynamics of the blood vessel wall. This question will not be considered in this short review.

**Elastic force \(f_e\)**

Consider a small patch of a membrane and try to write down how that patch will act on its environment (i.e. the membrane materials). Like in usual bulk elasticity, due to the short range interaction, the patch interact with its environment only via the contour of the patch. This means that the force must be a divergence of a second-order tensor

\(f_e = \nabla_s \cdot \tau\)  
(14)

where \(\tau\) is the stress tensor defined in the plane of the membrane \(^1\). It is interesting to note that also the bending force in (9) can also be written as a surface divergence of a second-order tensor \(\tau_b\), given by

\[\tau_b = -\kappa \left( -\frac{1}{2} H^2 (I - n \otimes n) + H \nabla_s \otimes n - n \otimes \nabla_s H \right) + (I - n \otimes n) \zeta\]  
(15)

It can be shown, in the theory of elasticity of large deformations, that

\[\tau = \frac{1}{J_S} F^S \frac{\partial W_s}{\partial E^S} F^{ST}\]  
(16)

where \(W_s\) is the surface strain energy function, \(F^S = (I - n \otimes n).F.G(I - n^R \otimes n^R)\) with \(F\) is the usual deformation tensor (if the reference configuration is labeled as \(x^R\), and the actual one as \(x(x^R, t)\),

\(^1\) Integrating (15 on the patch of area \(A\) and using the Gauss theorem on a curved surface, one has \(\int_A \nabla_s \cdot \tau = \oint_L \tau m + \int_A 2H \tau n\), where \(L\) is the contour delimiting the patch, \(m\) is the normal to the contour. If the stress tensor \(\tau\) is defined on the tangent plane, then \(\tau n = 0\), and only the contour contribution remains, in accord with the Cauchy principle of elasticity.
\[
 \frac{\partial \mathbf{x}}{\partial x} / x^R
\]
and \( E^S \) is the Green-Lagrange tensor defined as
\[
 E^S = \frac{1}{2} \left( \mathbf{F}^T \mathbf{F}^T - \mathbf{I} + n^R \otimes n^R \right)
\]
(that coincides with the usual two dimensional strain tensor in the limit of linear elasticity), and \( J^S = \text{Det}(\mathbf{F}^S) \). In order to obtain the explicit form of the force, one needs to introduce an explicit model for the energy \( W_s \). Like the Helfrich energy which depends on invariants (the mean curvature is nothing but the trace of the tensor \( \nabla_s \mathbf{n} \)), this energy must depend on invariant only. Two commonly used invariants are
\[
 I_1 = 2 \text{Trace}(\mathbf{F}^S), \quad I_2 = J^2_s - 1
\]
Thus \( W_s \) depends on these two invariants, \( W_s(I_1, I_2) \). This is true as long as one considers that the membrane is an isotropic medium. As stated above the elasticity of RBCs is ensured by a protein network (spectrin). This network is quite disordered. From one elementary cell of the network to another the branches of spectrin exhibits all possible orientations, and therefore one expects the isotropy assumption to make sense. The widely used model model for the RBC and capsules is that of Skalak et al. \[8\]
\[
 W_s = \frac{B}{4} \left[ \frac{1}{2} I_1^2 + I_1 - I_2 \right] + \frac{C}{8} I_2
\]
where \( B \) and \( C \) are parameter constant estimated to \( B \simeq 0.005 \text{ dyn/cm} \) and \( C \simeq 100 \text{ dyn/cm} \). The large magnitude of \( C \) compared to that of \( B \) ensures that a small deviation of \( I_2 \) from unity generates large tensions. Consequently the membrane is nearly incompressible. The idea is to inject (18) into (16) in order to obtain the force (15) that has to be added inserted into (7) where \( \mathbf{f} = \mathbf{f}_b + \mathbf{f}_e \). The above set of equations is complete and describe dynamics of vesicles (fluid membranes; no shear elasticity), or a RBC and a capsule if \( \mathbf{f}_e \) is taken into account.

4. Different methods of solutions
There has been in the literature several methods used to solve the above set of equations. The analytical method is confined to situations where the shape is close to a sphere, and where reductive perturbation methods (transformation of the set of PDE’s into nonlinear ODE’s) become possible. This has been successful in studying a single vesicle \[9, 10, 11, 12, 13\], compressible capsule \[14, 15\], incompressible capsule \[16, 17\] under unbounded shear and Poiseuille flows. Pairs interactions has been also studied along these lines \[18\]. The analytical method has allowed to gain some interesting insight into the phenomena. Besides these situations which are confined to quasi-spherical shapes, all the other studies are based on numerical simulations. The first well studied method is the so-called boundary integral one, based on the use of the Green’s function techniques (thanks to the linearity of the Stokes equations) \[19\]. This method has been used for vesicles in 2D \[20, 21\], and 3D \[22, 7\] and for capsules \[23\]. The advantage of this method is the fact that there is no need to solve for the fluid domain, and the whole cell dynamics is encoded in the membrane itself. This is done at a certain price, namely nonlocality: in order to move one membrane point, we must have information on the location of all the other points, so that the complexity of the method (in terms of numerical schemes) is of order \( N^2 \), \( N \) being the number of discretization points on the membranes (and boundaries, if any). Using fast multipole methods, one can lower the complexity of the method down to \( N \) \[24, 25, 26\].

The other class of methods consists in either meshing the fluid domains (finite differences, finite elements), or using spectral methods, and solve the fluid equations subjected to boundary conditions. Then the cell is considered to be immersed in that domain (the associated method is called the immersed boundary method). The determination of the velocity field of the membrane is performed thanks to an interpolation from neighboring lattice points where the velocity field is computed. Once this step is done, the membrane point is displaced by that velocity, and so on.
In this problem the membrane is considered in the Lagrangian sense, it is explicitly displaced. The immersed method is quite old [27, 28], but has been used only recently for studying vesicles and capsules [29, 30, 31]. In the above situations the membrane is treated in the continuum formulation, and membrane forces are then discretized. Other alternatives have treated the cell membrane as made of beads connected with springs having stretching and bending stiffness [32, 33].

Other quite popular methods that have been adapted to vesicles, and cells in general, is the phase-field [34, 35, 36, 37, 38] and the level set methods [39, 4] where the membrane is implicitly defined via the introduction of a scalar field (the phase field or the level set function), and where all geometrical properties (like mean curvature, normal, etc...) can be expressed in terms of this field. This method is fully eulerian, and has been used for vesicles, but not yet, to our knowledge, when membrane shear elasticity is included. The fluid/structure coupling is then solved either by finite differences [40], in Fourier space [35], or using the finite element methods [39, 4].

Finally, there are methods which consist not in solving the fluid equations directly, but just by mimicking them via kinetic equations. In this category, one can cite three kinds of methods (i) DPD (dissipative particle dynamics), which is akin to molecular dynamics, consists in viewing fluid particles as "atoms" or "molecules" to which basic Newton laws are applied with pairwise interactions. Despite the simplicity of the implementation method in MD, it sets a severe limitation on the size and time scales that can be handled in practice. In order to circumvent this limitation, DPD has been introduced and can be viewed as a coarse-grained method where each "particle" represents a cluster of atoms or molecules and as a result of internal degree of freedoms associated with each "particle, the particle-particle interaction includes a random and dissipative contribution [41, 42, 43]. The cell membrane is simulated by a particles interconnected with spring in the triangulated network. The particle-particle interaction are relatively soft (in comparison to real atom-atom interaction where Lennard-Jones potentials are used) and this makes the DPD method to be computationally highly efficient. However, this method might induce unacceptable errors if the degree of coarse-graining is not adequately chosen. Note also that this method, while used recently to simulate concentrated suspensions [44], has not yet been quantitatively used for the simple case of a vesicle (or RBCs) under a linear shear flow, as described in the following. (ii) Multiparticle collision dynamics (MPCD). It is a particle-based mesoscale simulation technique which incorporates thermal fluctuations and hydrodynamic interactions. Coupling of embedded particles to the coarse-grained solvent is achieved through molecular dynamics [45, 46, 47, 48, 49, 50]. This method has been used to vesicles or capsules [51, 52, 53]. This method is costly and some serious discrepancies with the boundary integral method (that uses directly the Stokes equations) have been pointed out for vesicles under a linear shear flow [7]. More precisely, in Ref.[51] it was reported that under a shear flow the period of tumbling times the shear rate varies by about a factor ten in a certain range of variation of shear rate, while in Ref. [7] only a very weak variation (of about 10%) was found. (iii) Lattice-Boltzmann method (LBM) consists in viewing the fluid as a set of particles leaving on lattice. In the spirit of the LBM, a fluid is seen as a cluster of pseudofluid particles that can collide with each other when they spread under the influence of external applied forces. Advantages of the LB method are its relative ease of implementation together with its versatile adaptability to quite arbitrary geometries. The LBM method is a hydrodynamics solver, and the cell is treated in an immersed boundary method, as discussed above [54, 55, 56, 57]. Here again, despite its use for concentrated suspensions, no quantitative phase diagram even in a simple situation (linear shear flow) has been reported yet.
5. Type of flows and definition of dimensionless parameters

In what follows we shall review the problem of a vesicle under a linear shear flow and a planar or cylindrical Poiseuille flows. The behavior in a Couette flow will not be discussed, despite the fact that it reveals some interesting features [58]. These flows are defined as

\[ v_{0x} = \dot{\gamma} y, \quad v_{0x} = v_{\text{max}} \left[ 1 - \frac{y^2}{(w/2)^2} \right], \quad v_{0z} = v_{\text{max}} \left[ 1 - \frac{r^2}{(w/2)^2} \right] \] (19)

where \( \dot{\gamma} \) is the shear rate, and the other velocity components are zero. These flows could be viewed as unbounded or bounded. In the latter case, and in the case of a linear shear flow we have \( \dot{\gamma} = \frac{V_0}{w} \) where, for example, the lower plate at \( y = -w/2 \) is fixed (the full velocity field vanishes there), while the upper one moves with velocity \( V_0 \) (the full velocity field is equal there to \( V_0 \)). For a Poiseuille flow, the typical shear rate will be taken to be that at the wall, for example in the planar Poiseuille flow it is equal to \( \dot{\gamma} = 4V_{\text{max}}/w \). In the unbounded regime and for a linear shear flow \( \dot{\gamma} \) is a parameter specifying the shear rate. In the case of an unbounded Poiseuille flow the absolute value of the velocity does not matter (due to Galilean invariance), but only the curvature of the flow, which is \( \alpha = 8V_{\text{max}}/w^2 \) (of course neither \( V_{\text{max}} \) nor \( w \) have a physical sense, but only \( \alpha \)).

The full problem possesses several dimensionless numbers. We use \( R \) (radius of the cell corresponding to a spherical shape having the same area \( A \) as the real shape) as unit of length, \( 1/\dot{\gamma} \) as unit of time (in the case of a Poiseuille flow we use the shear rate at the wall, be it fictitious –unbounded flow– or real), so that the velocity unit is \( U = \dot{\gamma} R \). For the pressure field we use \( \eta U/R_0 \). The dimensionless numbers are

- the so-called Capillary number (in analogy with drops) measuring the flow strength over the bending energy of the membrane
  \[ C_\kappa = \frac{\eta R^3 \dot{\gamma}}{\kappa} = \dot{\gamma} \tau_\kappa \] (20)
  where \( \tau_\kappa \) is the time scale of relaxation of bending modes. Typical values of \( \kappa \) for vesicles is \( 10^{-19} \text{J} \). Recent measurement [59] on RBCs provides a bending rigidity of about \( 3 \times 10^{-19} \text{J} \).
- The capillary numbers associated with membrane plane-elasticity (shear and stretching)
  \[ C_s = \frac{\eta R \dot{\gamma}}{B} = \dot{\gamma} \tau_s, \quad C_e = \frac{\eta R \dot{\gamma}}{C} = \dot{\gamma} \tau_e \] (21)
  where \( \tau_s \) and \( \tau_e \) are time scales of relaxation of shearing and extensional/compressional modes.
- The degree of confinement
  \[ C_n = \frac{2R}{w} \] (22)
- The viscosity contrast measuring the ratio between the viscosity of the internal fluid, \( \eta' \), to that of the external one \( \eta \)
  \[ \lambda = \frac{\eta'}{\eta} \] (23)
- The reduced volume
  \[ \nu = \frac{V/(4\pi/3)}{[A/(4\pi)]^{3/2}} \] (24)
  which is the ratio of the actual area enclosed by the vesicles over the that of a circle having the same perimeter.
Using the values of parameters given above, taking for the typical radius of a human RBC $R \sim 3 \mu m$ and using the plasma viscosity (close to that of water), we find for the capillary numbers (in c.g.s units):

\[ C_c \sim 0.1 \dot{\gamma}, \quad C_s \sim 10^{-3} \dot{\gamma}, \quad C_e \sim 10^{-5} \dot{\gamma}. \]

The small prefactor in $C_e$ means that the relaxation time for extensional mode is of about $10^{-5} \text{s.}$, for shearing mode it is of about $10^{-3} \text{s.}$, and for bending mode $0.1 \text{s.}$ So the highest time scale seems to be the one associated with the bending mode, the most relevant one, in principle. This time scale is consistent with the study of Tomaiuolo and Guido in start-up shape dynamics of RBCs in microcapillary flow [60], where it is found that the time needed for a RBC to adapt a stationary shape after application of a flow is of the order of $0.1 \text{s.}$

6. A vesicle, capsule and RBC under linear shear flow in an unbounded geometry

6.1. Vesicles

This is the simplest situation where the system is made of only a fluid membrane. Vesicles have revealed several types of motions under this type of flow, and the full phase diagram was given recently [7] by means of numerical simulations using the boundary integral formulation in three dimensions. Analytical [11, 12, 61] and semi-analytical [51] determinations of the phase diagram were made. If the shear flow is unbounded $C_n = 0$. Furthermore for a fluid membrane only the capillary number $C_c$ enters into play. For a fixed $\nu$ the parameter space is thus two-dimensional ($C_c$ and $\lambda$). At small enough $C_c$ (see figure 2) the motion is of tank-treading (TT) type, where the angle between the main axis of the vesicle and the flow direction remains constant in the course of time, while the membrane (which is fluid) undergoes a tank-treading motion. Upon increasing $\lambda$, the TT motion undergoes a saddle-node bifurcation towards tumbling (TB). If $C_c$ is not too small the TT motion becomes unstable via a Hopf bifurcation and an intermediate regime takes place, namely vacillating-breathing (VB) mode: the long axis does not make full rotation (unlike TB), but rather oscillates around the flow direction, while the shape undergoes breathing-like motion. The existence of this type of mode was predicted analytically [9]. The VB mode was called later, unfortunately, swinging [51] or trembling [11], and this has caused some semantic confusion in the literature. Upon increasing $\lambda$ the VB mode becomes a TB mode; the angle of oscillation increases gradually until it reaches $\pi/2$ in total amplitude, where TB prevails. At higher $\lambda$, TB undergoes kayaking (a denomination already used before for ellipsoids, liquid crystals; the terminology ”spinning” was also used in the case of vesicles [62]), where the main axis describes a cone about the perpendicular to the plane of the shear flow. For $\nu = 0.95$ the full numerical simulation has been captured by analytical theory [61] (using the quasispherical assumption, which is legitimate for small enough $\nu$). By varying $\nu$ the phase diagram keeps the same kind of shape [7]. Experiments have been performed and have reported that there is a qualitative agreements with the theory and numerical simulation [63, 64]. However, experiments reported that the phase diagram could be described by only two dimensionless parameters, related to the above ones by

\[ \Lambda = \frac{4\sqrt{\Delta}}{\sqrt{30\pi}} (1 + \frac{23\lambda}{32}), \quad S = \frac{7\pi}{3\sqrt{3\Delta}} C_a \quad (25) \]

with $\Delta = 4\pi(\nu^{-2/3} - 1)$, called the excess area with respect to a sphere (for a sphere $\nu = 1$ and thus $\Delta = 0$). Simulation as well as advanced analytical theory [61] showed that was not possible, three independent parameters seem necessary ($C_a, \lambda, \nu$) (or $\Lambda, S, \Delta$)). This has been confirmed by another simulation result [65].

6.2. Capsules and RBCs

Recent analytical calculations on inextensible capsules (using linear elasticity for the membrane, for the sake of simplicity) have been proposed, and they led to some interesting phenomena.
Figure 2. The phase diagram of a vesicle in a shear flow showing the various kinds of motions obtained numerically in three dimensions [7]. Shown is also a comparison with the analytical theory by Farutin et al.[13].

Besides the TT, VB and TB modes reported above, the shear elasticity introduces two main new effects: (i) if there is no viscosity contrast, under a weak enough flow (where a fluid vesicle would always exhibits TT), the capsule undergoes TB. The weak flow can not overcome the cytoskeleton pinning, since any motion of the network (considered to be relaxed in its reference state) will have to shear the network since the cytoskeleton has to accommodate, if it had to undergo TT, the cell geometry. Therefore the membrane undergoes a TB motion, at the price of keeping the cytoskeleton close to its equilibrium configuration. Beyond a critical value of shear rate, the shear stress can overcome the resistance to network deformation, and the membrane shows a TT motion. (ii) In the TT motion, when a material point (an thus the cytoskeleton) moves, it remembers, so to speak, its original configuration after a half turn (for an ellipsoid, for example, after \( \pi \) rotation the shape is the same), and attempts to go back to that unstressed reference state. This attempt of relaxation (the associated time scale is fixed by the cytoskeleton dynamics) causes small oscillations of the angle between the main axis of the TT cell. These small oscillations were named swinging (SW), not to be confused with Vb where the oscillation is quite large accompanied with breathing. This kind of motion was reported experimentally in [66, 67]. If the viscosity contrast increases further and further, approaching the TB regime, the cell undergoes a motion which is very close to VB mode (ample amplitude breathing, while the main axis makes oscillation about the flow direction). A theoretical study was first undertaken by assuming that the cell has a fixed shape (following the seminal work of Keller and Skalak [68]) by adding the contribution due to the cytoskeleton [69] that has been successful in accounting for some of the motion of the RBC (especially SW). Later studies [16, 17] have relaxed the assumption of a fixed shape by following a previous study on vesicles [9]. The motions like SW was recovered, and the studies showed that the VB mode still manifests itself with ample amplitude. These studies have also pointed out that the so-called intermittent motion (SW interrupted by TB and so on) reported in Refs. [69, 67] was an artefact of the model (fixed shape), and that this motion disappears if the shape is free to evolve. This result [16, 17] is consistent with numerical simulations which showed no intermittency [70, 71, 72].
6.3. Impact on rheology

A natural question is how do the various types of dynamics described above affect rheology. This question was addressed first theoretically in the dilute regime for the vesicle system [9, 73, 10]. A first unexpected result is that the effective viscosity, in the TT regime, decreases upon increasing the viscosity contrast \( \lambda \). More precisely, if we define the effective dimensionless viscosity as
\[
\eta_{\text{eff}} = \frac{(\eta_s - \eta)}{(\eta \phi)},
\]
where \( \eta_s \) is the viscosity of the suspension, \( \eta \) that of the suspending fluid and \( \phi \) the volume fraction, it was found in the quasi-spherical regime that [9]
\[
\eta_{\text{eff}} = 1 + \frac{5}{2} \phi - \frac{23\lambda + 32}{16\pi} \Delta
\]
where recall that \( \Delta \) is the excess area from a sphere (it vanishes for a sphere, in that case a vesicle behaves like a rigid particle, and we recover the Einstein result). This result is valid for small enough \( \phi \) (say few %). We see that \( \eta_{\text{eff}} \) decreases with \( \lambda \), which is a completely opposite result to that of Taylor for emulsion
\[
\eta_{\text{eff}} = 1 + \phi \frac{5\lambda/2 + 1}{\lambda + 1}
\]
which increases with \( \lambda \). A brief explanation is presented in [9], and a more extensive discussion is given in [74]. This results is valid in the TT regime only. Further increase of \( \lambda \) induces a transition from TT to VB or TB. In the TB regime the viscosity increases with \( \lambda \) [12]. In other words \( \eta_{\text{eff}} \) decreases in the TT regime and increases in the TB regime as \( \lambda \) is varied, meaning that \( \eta_{\text{eff}} \) exhibits a minimum at the TT-TB transition. This result was confirmed by numerical simulation in 2D [74] and in 3D [65]. It is interesting to note that the overall features of equation (26), which is derived in 3D, is also captured in 2D simulations. This points to the nontrivial fact that the 2D assumption is quite realistic in modeling rheology in the dilute regime. The same trend is found in the simulations of capsules [75]. Experiments have been performed on vesicles [76, 77] and RBCs suspensions [76]. The experiments in [76] show exactly the same trend. Other experiments in [77] arrived to the same conclusion as long as \( \lambda \) is of order of, or bigger, than 1. It was reported in that experiment that in the small \( \lambda \) regime, \( \eta_{\text{eff}} \) decreases with \( \lambda \) (as in the Taylor problem). This last result is not, so far, supported by numerical simulations nor by the experiments made in Ref.[76]. Another fact is that experiments on rheology of vesicle suspensions [76] have been performed for higher volume fractions (up to 12%) where hydrodynamic interactions can no longer be ignored. Nevertheless, the effective viscosity exhibits the same qualitative features as that obtained analytically [12] and numerically [74, 65]: it decreases with the viscosity contrast in the TT regime, goes through a minimum in the vicinity of the TT to TB bifurcation, and then increases in the TB regime (recall that expression .(26) is valid in the TT regime only).

7. Vesicles under a Poiseuille flow

7.1. Cross-streamline migration

The notion of lift force is an important field of research in mechanics. A spinning sphere is known to undergo a lift force due to inertia [78]. In the Stokes regime (relevant to blood flow), a spinning sphere does not feel any lift force due to the reversibility of the Stokes equation upon time reversal. However, a cell under shear flow is deformed and acquires an upstream/downstream asymmetry that destroys some symmetry (Stokes flow with boundary condition on a free surface, the cell one) under time reversal, that may gives rise to a lift force. As a consequence of thus in a Poiseuille flow (even in un unbounded geometry) a cell has the ability to exhibit cross-streamline migration. This mechanism is responsible (in part) for the Fahraeus-Linquvist effect (reported in 1931)(see [79]). Indeed, measurements in vitro show a quite counterintuitive effect: the apparent
blood viscosity decreases upon decreasing the channel diameter $D$, until a typical value of $D$ of about few micrometers; in other words the more the blood is squeezed, the easiest it flows! It is only when $D$ becomes of the order of the RBC diameter that the apparent viscosity shows a sudden increase. The Fahraeus-Lindqvist effect is explained by the existence of a depletion layer (a layer which is free of RBCs) near the wall boundaries. The cell-free layer is due to (i) a lift force caused by the wall, and its origin is of purely viscous nature (unlike macroscopic lift –e.g. on a ball or airplane—which is due to inertia), (ii) a cross-streamline migration associated with the shear gradient of the Poiseuille flow. These two lift forces have been analyzed in the case of a single particle (namely a vesicle or capsule representing a model for the RBC) both theoretically [80, 20, 81, 6, 82, 10] and experimentally [83, 84, 85]. It was initially found numerically that a vesicles which is placed away from the centerline of the Poiseuille flow migrates towards the center, as shown in figure 3. It was suggested [6] that the migration velocity scales as

$$v_{\text{migration}} \sim \alpha f(C_\gamma(y))$$

(28)

where $\alpha$ is the curvature of the Poiseuille flow and $f$ is a universal function of the capillary number, where $C_\gamma(y)$ is the local capillary number in which $\gamma$ is replaced by the local gradient of the Poiseuille flow. Using the small deformation theory for vesicles [86] it was found that far away from the center the migration velocity is constant and is given by

$$v_{\text{migration}} \sim \alpha \Delta^{1/2} R^2$$

(29)

and does not depend on membrane rigidity. The prefactor is a complicated function of the viscosity ratio $\lambda$. Experiments on vesicles have analyzed the migration in a microfluidic channel and it was shown that the vesicle always migrates towards the center [85]. However, in a very weak flow (much weaker than usual flows in experiments), it has been shown that a quasispherical vesicle can migrate outwards [87].

7.2. Symmetry-breaking: slipper

A longstanding puzzle in blood microcirculation is the understanding of why do RBCs adopt an asymmetric shape (called a slipper) in microcirculation, despite a symmetric flow. In vivo the volume fraction of RBCs in the microvasculature (also called hematocrit) is of about 20% (unlike in macrocirculation where the hematocrit is of about 45%), so that RBCs are in a close contact with each other. The first comprehensive experimental report on the slipper phenomenon is that of Skalak and Branemark[88] (who studied a cluster of cells), followed by another experimental study by Gaetgengs et al. [89]. Subsequent studies on single RBCs exhibiting a slipper shape in a glass tube were briefly reported by Secomb et al. [90], and analyzed in more detail by Guido and Tomaiuolo [91]. This problem was revisited more recently [92, 93].
A first theory, using a lubrication approximation was proposed by Secomb and co-workers [94], and the slipper shape was later observed in numerical simulations by Pozrikidis [95]. Two dimensional simulations were considered more recently by Secomb et al. [90], who reported on the slipper shape. Recently, considering [96] an unbounded parabolic velocity profile, the slipper shape was shown to be an intrinsic configuration resulting from the instability of the symmetric (parachute) shape.

More recently [97] the study of the slipper in the presence of bounding walls has been considered. The walls did not destroy the branch of solution found in the unbounded geometry [96]. However the presence of walls has led to an unexpected complexity. Five distinct morphologies and dynamics are identified, depending on flow and structural parameters. The viscosity contrast has been set to unity and the reduced area $\nu = 0.6$ (close to that of the Human RBC), and the two other parameters $C_\kappa$ and $C_n$ have been varied. The shape and dynamics phase diagram is presented in figure 4 where there are 5 distinct regions with different types of shapes. For a weak and strong confinement, there is always a slipper solution, the intermediate confinement shows either a symmetric parachute shape, or a motion of flagella type, that has been called "snaking". Figure 5 shows a snapshot of the snaking motion (figure 5). The snaking may be either centered (the center of mass undergoes oscillation with a mean value equal to zero), or non-centered (the mean value of the center of mass is different from zero).

The phase diagram shown in Fig. 4 says that for a given confinement $C_n$, the transition from the parachute shape to a slipper one always occurs upon decreasing the flow strength (which corresponds to decreasing $C_\kappa$). Experiments are sparse [92, 91, 93], but there is a consensus that the occurrence of the slipper occurs upon increasing the flow strength, which is in contradiction with the phase diagram shown in Fig. 4. We have attempted to understand this major discrepancy, and came to the conclusion that the viscosity contrast plays a major role. RBCs in vivo have a viscosity contrast of about $\lambda \approx 5$, and this ratio depends on temperature. It has been found very recently [98] that introduction of a viscosity contrast leads to new branches of slipper solutions that corresponds to a transition from parachute to slipper upon increasing the flow strength, in accord with the experiments.

Figure 4. The phase diagram of a vesicle in a Poiseuille flow showing 5 distinct regions.
8. Some collective motions in a Poiseuille flow

Experiments on RBCs suspensions are known to form rouleaux at low enough shear rate, and are destructed upon increasing flow strength. The rouleaux formation is mediated by the so-called depletion forces (osmosis-type of attraction) caused by plasma proteins (fibrinogen and $\beta$-globuline)[99]. Actually, numerical simulations of RBCs in a channel flow (in the absence of any interaction mimicking the depletion force) form clusters of purely hydrodynamical origin [100, 101]. The cluster formation has been analyzed in details experimentally [102]. The analysis of the flow field around a cell show that the Poiseuille flow is modified by the cell which creates converging vortices at the front (aspiring thus a cell ahead of it; see figure 6) and diverging at the rear, avoiding thus cells to come too close to each other. The size of the cluster is a function of the flow rate [101]. It is shown that for a given flow rate there exists a maximum cluster size, so that if the initial formed cluster is too large, it will expel one or few cells ahead in order to bring down the size of the cluster to the marginally stable one. Many other other collective phenomena are currently studied and will give rise to publications in the next few months.

9. Conclusion

This review was intended to present a brief description of some aspects of the field of vesicles, capsules and RBC dynamics under flow, and to show the impressive upsurge of interest in the past few years. This short review does not pretend to have covered all phenomena studied recently in this field, but at least it provides a large scale picture of the recently realized and ongoing research in this field. We are at the prelude of being able to simulate with realistic models a large number of cells (with blood sample of few centiliters) thanks to the progress of computational science (parallel, GPU –Graphic Processing Units – domain decomposition theories, highly performing finite element libraries...). My personal guess is that it will be possible to simulate a real blood flow in a real architecture in animals (like mouse) within the next ten to twenty years, which will then open the way to simulation of the circulatory system of the human body. This field will surely grow rapidly further and further and the next research generation will be mainly directed towards implication in health problems and care: physical factors impacting cardiovascular diseases and relation to blood flow, pressure waves and relation to blood tension, capillary rarefaction, thrombosis, aneurysms, the role of endothelium, coupling to arterial mechanics, the role of glycocalyx (a polymer brush covering the interior of blood vessels), the lab-on-chip technologies (blood diagnosis, blood sorting out...), and so on.
Figure 6. The induced flow field pattern in the comoving frame showing converging vorticies ahead and diverging ones at the rear. This explains the origin of clustering.

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