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Recent progress in the physics of microfluidics and related biotechnological applications

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Since the mid-nineties, the physical understanding of microfluidic flows has reached a level sufficiently elaborate for envisaging applications in all sorts of domains. As the domain expanded, the existence of new situations where fluid dynamics at small or moderate Reynolds numbers combines with confinement, interfaces, transport, particles along with disordered substrates raised new challenges. The present review is restricted to three domains in which progress in the physical description has been made recently (droplet-based, inertial and paper-based microfluidics) and for which biotechnological applications are foreseeable.

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Introduction

Since the mid-nineties, the physical understanding of microfluidic flows has reached a level sufficiently elaborate for envisaging applications in all sorts of domains. Today, several comprehensive reviews and books, discussing the physical aspects of microfluidics, are available [1–11]. They include descriptions of the scaling laws that govern the balances of forces at the microscale, along with discussions of the properties of low Reynolds number flows (i.e. flows where viscosity dominates over inertia), diffusion, capillarity, electrokinetics, that is, notions that must be grasped to understand the fluid behavior in complex geometries in microfluidic devices, design efficient mixing devices, exploit microdroplets, or achieve efficient separation. The current designs of microfluidic chips take into consideration that Reynolds numbers are low (I will discuss important exceptions later), Peclet numbers (i.e. the ratio of the advection to the diffusion terms) are large and capillary numbers (i.e. the ratio of viscous over capillary forces) are small. There is no more serious attempt to exploit Venturi or Coanda effect in standard lab-on-a-chips, where small Reynolds numbers prevail. It is accepted that diffusion is often unacceptably slow to mix reactants, and that bubbles are difficult to remove when wettability conditions are unfavorable, both phenomena substantiating the scaling laws that govern microfluidics.

Still the physics of microfluidics faces challenging problems and the objective of the review is to present three topics for which physical understanding has progressed, and for which biotechnological applications are foreseeable. The topics are:

- Droplet-based microfluidics
- Inertial microfluidics
- Paper-based microfluidics

The list is far from exhaustive. The physical understanding has also progressed in areas such as electrohydrodynamics in nanotubes [12], hydrodynamics over superhydrophobic surfaces [13,14], microfluidic self assembly [15], microfluidic swimmers, confined nucleation [16] to mention but a few. The limited number of contributions I mention here, imposed by space limitations, is based on the strength of the expansion of the domain in which they pertain, the simplicity of the situations they address and their link to biotechnological applications. Although the selection of papers I made does not completely exclude some level of arbitrariness, I hope it reflects the actual evolution of the field, as viewed from a physicist's prospective.

Droplet-based microfluidics

Droplet-based microfluidics operates with liquids encapsulated and conveyed in droplets, as opposed to single phase microfluidics, where fluids are confined and transported directly in microchannels. The development of the domain has been fostered by a series of contributions, made in the years 2000–2003, that demonstrated droplet generation [17,18], internal mixing [19], screening capabilities underlining the importance of wetting conditions [20], or the interplay between viscous and capillary forces in droplet generation [21] and breakup [22]. Contributions are numerous — they are reviewed in Refs [23,24•,25]. This early period was followed by a boost of biotechnological applications. Droplet-based microfluidics is today an important branch of microfluidics.

From a physical standpoint, droplet-based microfluidics rests on the control of interfaces in movement. It thus

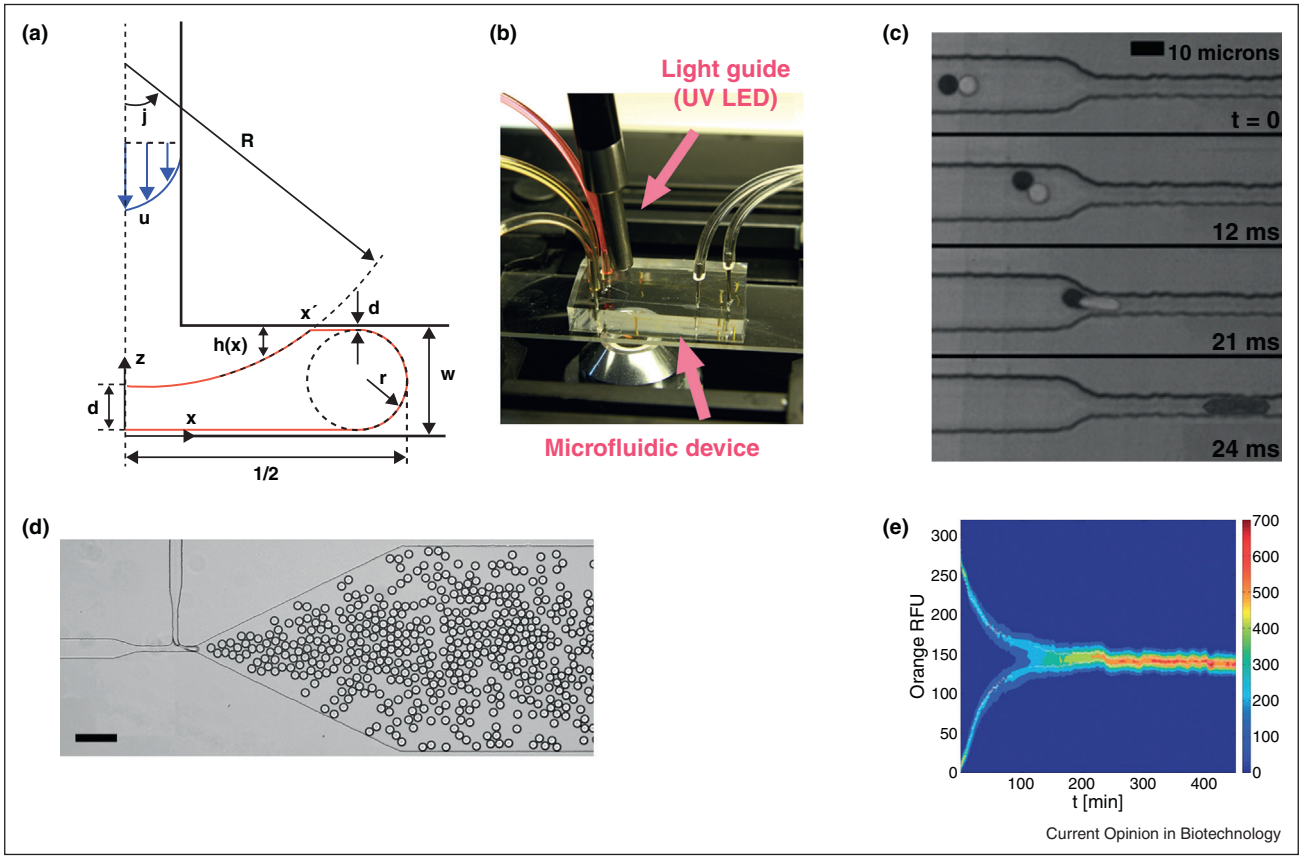
involves subtle nonlinear dynamical phenomena [26•] that embrace a continuum of scales ranging from the microchannel width (100 μm) to nanometric scales [27]. A range of five orders of magnitudes within which nonlinear couplings play crucial roles! Many results established by the fluid dynamics community over the last century addressed, for the sake of simplicity, unbounded geometries. By contrast, microfluidics is inherently associated to the presence of a confinement. The coupling between droplet dynamics and confinement, often in unusual geometries, raises new issues, and stimulates the development of novel phenomenologies or theories, at the risk, perhaps, of opening a Pandora box.

Concerning droplet breakup in T-junctions, an analytical theory [28] was proposed and experimentally confirmed [29] a few years ago. More recently, the regime of obstructing droplets has been solved [30]. We thus now have established analytical approaches to the problem of droplet breakup in T-junctions which cover situations of practical interest.

Reducing the droplet sizes down to the colloidal range (1 μm, 1 pl) was demonstrated in the last few years [31]. Applications in the field of targeted drug delivery have been demonstrated [32]. Recently, it was shown that these colloidal droplets can be manipulated in a way similar to microdroplets of standard sizes [33], the physics of miniaturization offering advantages in some cases. In this work, fusion, sorting, internal mixing, PCR were demonstrated for droplets of 2 μm size. Interestingly, mixing times in the order of 100 μs were obtained, opening new possibilities to study fast kinetic phenomena.

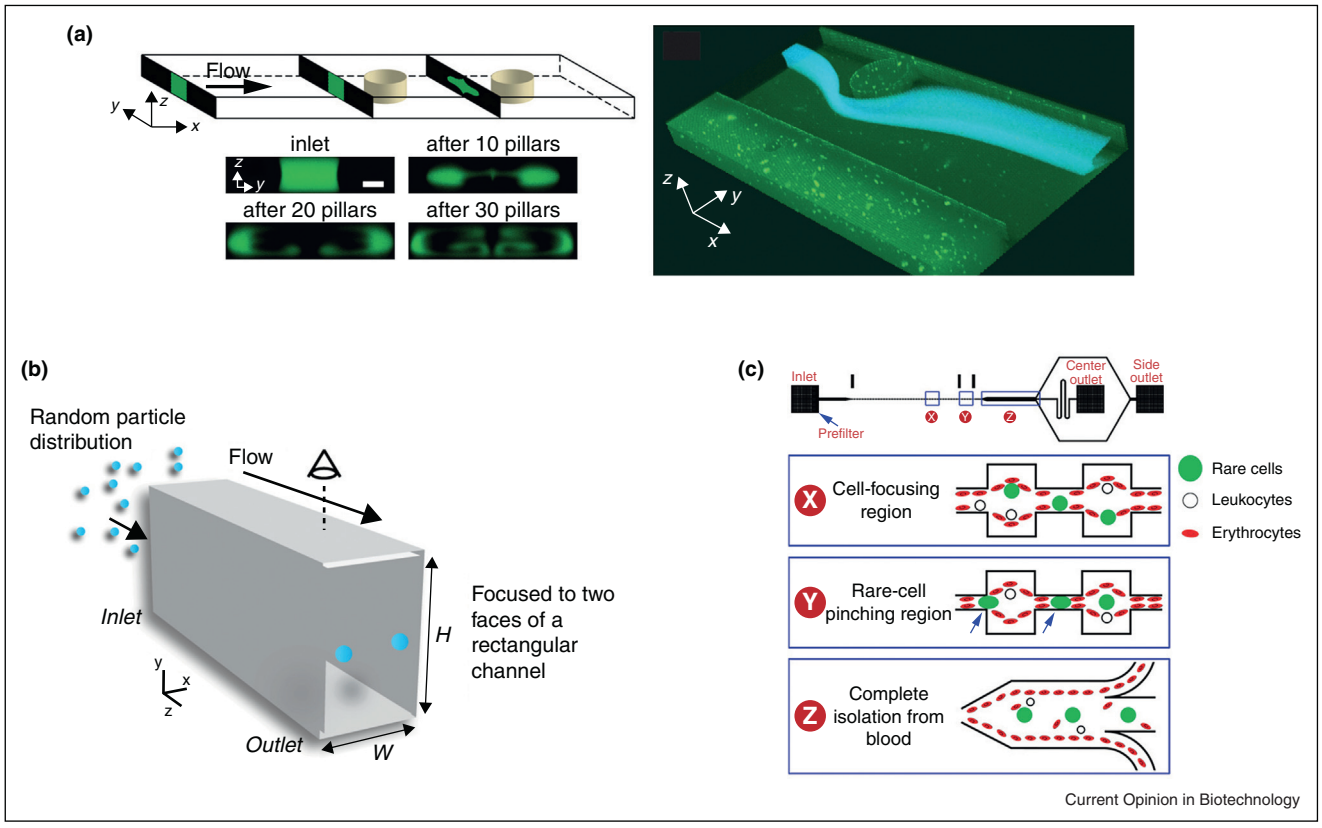
New combinations between droplets and external excitations have been reported: combining droplets with light

Figure 1



(a) Sketch of a droplet arrived in a T-junction, obstructing the channels, and forced to elongate in the presence of the external phase. The critical part of the problem is the dynamics of the wedge, parameterized geometrically. Reprinted figure with permission from [30]. Copyright 2013 American Chemical Society. **(b)** Picture of a system using light to quench mixing. Reprinted with permission from [35]. **(c)** Coalescence of 2 fl droplets, 2 μm in diameter, forced in a restriction, and subjected to an AC electric field. Reprinted with permission from Marie Leman MMN Laboratory ESPCI Paris. **(d)** Populations of droplets developing complex chaotic dynamics. Reprinted with permission [40]. Copyright 2013 Physics Reports Journal. **(e)** Dynamics of the transfers of surfactant between two droplets. Reprinted with permission from [45]. Copyright 2013 RCS.

Figure 2



(a) (Left) Evolution of a blob of fluorescent tracer passing after series of pillars; (right) evolution of a set of streamlines passing along of a single pillar, showing the irreversible transformation of their structure, indicating moderate Reynolds numbers. Reprinted figure with permission from [58]. Copyright 2013 Nature Publishing Group. **(b)** From disorder to order: a random distribution of particles transforms into an ordered organization, under the subtle action of lift forces and wall interactions. Reprinted figure with permission from [57]. Copyright (2013) by the American Physical Society. **(c)** Biotechnological application of the ordering effect of inertia forces to the sorting of rare cells. Reprinted with permission from [56]. Copyright 2013 RCS.

gave rise to novel techniques of droplet handling [34]. Recently, it has been shown that with the appropriate physico-chemistry and flow pattern, light may trigger mixing externally [35].

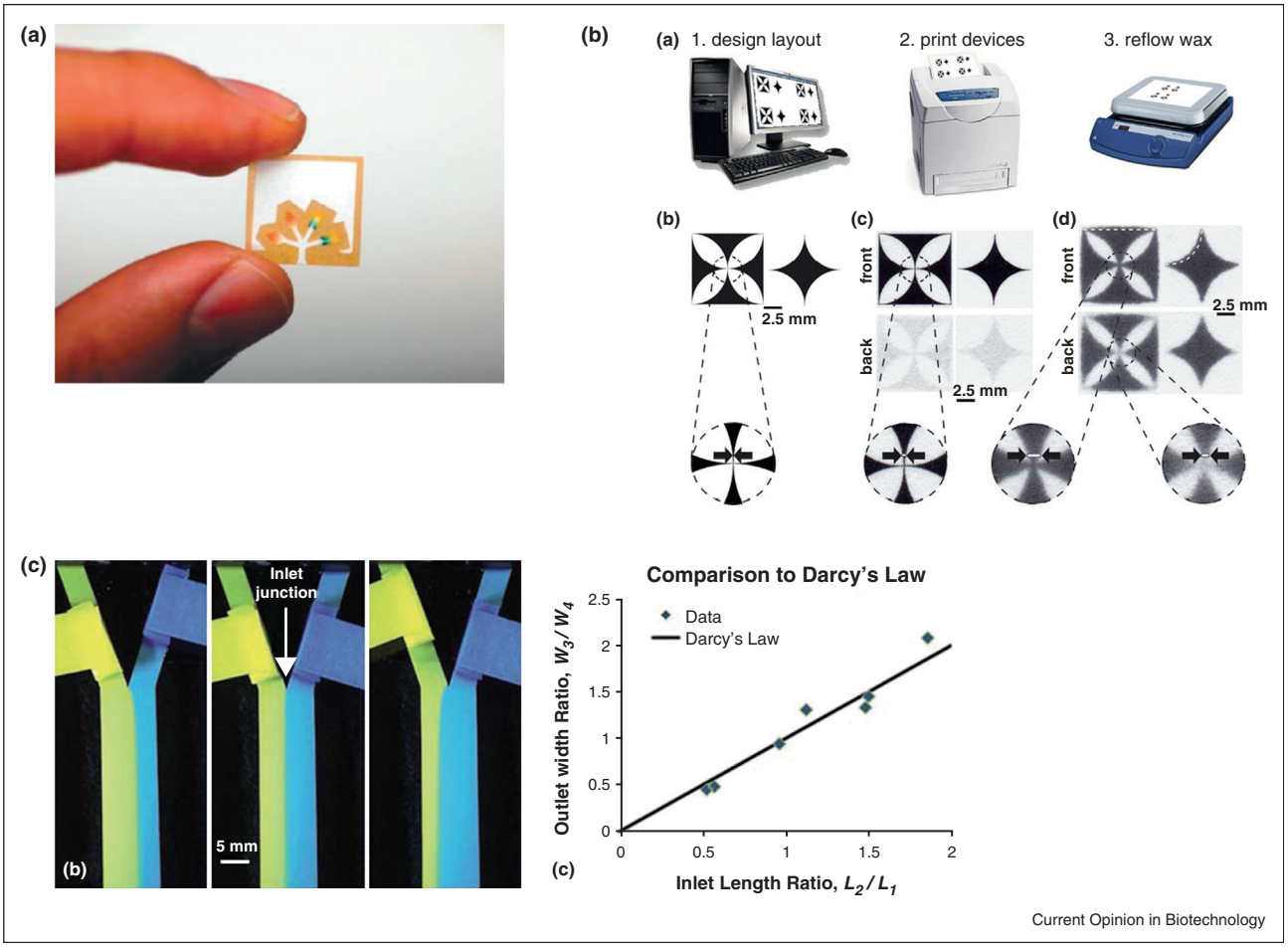
New ideas for handling droplets have recently been proposed. In one of them, a thermal gradient induces channel height deformations, which, coupled to capillarity, force the droplets to move toward the low temperature regions [36,37] (a direction opposite to thermocapillarity). This method offers advantages as compared to electrowetting, in terms of simplicity of microfabrication (and therefore cost), contamination (reduced by the presence of a lubricating film between the droplet and the wall). Another approach exploiting height gradients has been reported [38,39].

A topic in which progress has been made recently concerns the dynamics of droplet populations driven through Hele Shaw cells. A recent review summarizes the work done on the subject until 2012 [40]. In such systems, the droplet motion induces dipolar motions, which mediate $1/r^2$ dipolar interactions and give rise to rich dynamical behavior. Phonons [41], and shock waves [42] have been observed and described theoretically. More recently, dynamical clustering, shocks [40], and jamming [43] have been reported.

Finally, the role of the surfactants has been recently analyzed in a more systematic manner [44,45]. Surfactants are exceedingly important in droplet-based microfluidics since they control the emulsion stability and the droplet-wall interactions. Ref [43] shows how the surfactant concentration equilibrates in a monodisperse emulsion. Albumin is shown to reduce the exchanges by modifying the solubility, rather than providing a physical barrier. This hypothesis, usually adopted in the field, probably needs being revisited.

In the field of droplet-based microfluidics, the capability of producing monodisperse multiple emulsions with controlled structures is unique (see Ref [46] for a recent

Figure 3



(a) Pioneering work. Reprinted with permission from [61]. Copyright 2013 American Chemical Society. **(b)** Reprinted with permission from [60]. Copyright 2013 American Chemical Society. **(c)** Reprinted with permission from [64]. Copyright 2013 RCS.

review). Owing to the complexity of the situations, the physics in this domain has made little progress. Much remains to be done in this area (Figure 1).

Inertial microfluidics

Under standard conditions, microfluidic Reynolds numbers do not exceed 0.1 and therefore can be considered as sufficiently small for Stokes approximation to apply. Stokes limit imposes time reversibility and unicity of the solutions, which precludes vortex shedding and guarantees flow stability. These properties have enabled microfluidic technology to reach an exquisite level of flow control. Nonetheless, recently, a few investigators [47••] advantageously exploited inertial forces, still keeping flow under control. Note that the requested Reynolds numbers being on the order of 10, the requested speeds and inlet pressures are on the order of meters per second and bars. One important outcome of this approach is related to particle arrangement and mixing under high throughput conditions. As was discovered in the early sixties [48,49], the combination of lift forces and particle/wall interactions gives rise to equilibrium locations at which particles get trapped as they move downstream. The phenomenon is subtle and is currently discussed in the literature [50–53]. Starting with an ensemble of particle randomly dispersed in space, one ends up with an ordered pattern both cross-stream and streamwise. It is remarkable that inertial forces bring the system from disorder to order, acting somehow against the second principle. Application of these ideas has been shown for single cell encapsulation [54], where Poisson distributions can be escaped and the yield improved. Other applications concern the separation of platelets from blood [55], the separation of rare blood cells [56], and more recently, the sorting of particles and cells of different shapes [57]. In 2013, it has been shown that inertial microfluidics provides the capability to shape the streamlines under excellent

control [58••]. The idea is to exploit time irreversibility induced by the presence of inertia. Unlike the fluid motion that reverses upon passing an obstacle, flow with finite inertia is accompanied by a net deformation of fluid streams. After passing several obstacles, the effect adds up and eventually, it becomes possible to 'sculpt' the flow pattern in a way entirely controlled by the geometry. Predicting the flow patterns requires solving the full Navier–Stokes equations, which may prove time-consuming, but the authors provided intuitive methods for anticipating the result (Figure 2).

Paper-based microfluidics

The advantages of paper microfluidics are the extremely low cost, the compatibility with biological applications, the absence of pumping the ubiquity of the material and the absence of waste (by burning). These networks could resemble a microfluidic chip, except that there is no bottom or roof. If capillarity was neglected, pressure would be homogeneous. In fact, the pressure gradients are induced by capillarity and thereby by the flow itself, not by a pump; this makes a crucial dynamical difference with 'ordinary' microfluidics. Since a first set of pioneering papers from Whiteside's group [59–61] a fast expansion occurred in this area. Somehow provocatively, paper technology is sometimes called 'Microfluidics 2.0' (See http://www.mf20.org).

Paper is made by dewatering a suspension of wood fibers starting from very low content of solids [62]. Its network structure can be 'mimicked by cooking a portion of spaghetti and pouring it on a plate, to form a planar assembly of fibers that lie roughly horizontal.' [62]. Papers are naturally hydrophilic, but chemically treated hydrophobic papers are also commercially available. Since wood fiber is hygroscopic, paper swells as water imbibes it. At the moment, the understanding of the physics of transport in paper is far from complete. A first level of description amounts to assimilate paper to an isotropic, undeformable homogeneous porous medium. This simplification is supported by physical studies performed in the recent years. Early studies [63] validated Darcy and Washburn laws in one-dimensional strips. More recent work addressed two-dimensional geometries, relevant to biotechnological applications [64,65]. In Ref [64], the standard microfluidic geometries for hydrodynamic focusing, size-based extraction of molecules, micromixing and dilution have been revisited. As a whole, the data indicate that D'Arcy law and Washburn laws apply, which supports the hypothesis that, despite inherent heterogeneities due to paper fabrication, and the proximity of the paper surface, paper can be considered as a homogeneous porous medium. More detailed experiments are probably needed to assess this hypothesis. Paper-based microfluidics is only at its beginning. Many developments are expected in the future. The understanding of its physical behavior, using simple, complex, multiphase fluids will certainly provide a support for the expansion of this domain (Figure 3).

Conclusion

Because of lack of space, the present review was restricted, somewhat arbitrarily, to three domains in which progress in the physical description has been made recently (droplet-based, inertial and paper-based microfluidics) and for which biotechnological applications are foreseeable. Microfluidics is driven by a number of applications. It presently grows at a larger rate, and it is likely that the increased flux of observations will keep challenging our understanding of the physics of microfluidic flows.

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