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## Microfluidic particle trapping and separation using combined hydrodynamic and electrokinetic effects

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# 1 General introduction and scope of this thesis

## 1.1 Introduction to microfluidics



Microfluidics: this term has appeared ubiquitously in scientific literature for the last three decades, making reference to an immense range of applications in physics, chemistry and biology. But, what is actually microfluidics, and why has it become so important in such a short space of time? In the words of George Whitesides, microfluidics is the "science and technology of systems that process or manipulate small ( $10^{-9}$  to  $10^{-18}$  liters) amounts of fluids, using channels with dimensions of tens to hundreds of micrometers" [1]. This astute combination of fluids and channels dates back to the early 1990's, when Andreas Manz first introduced the concept of Miniaturized Total Analysis Systems ( $\mu$ TAS) as a major revolution in chemical analysis [2]. The main aim of the  $\mu$ TAS concept was therefore to downscale and integrate the conventional steps of the analytical process (sample pretreatment, separation and detection) into miniaturized platforms with minimum footprint [3]. Since then, myriads of new microfabricated devices, designs and strategies have been developed, as the  $\mu$ TAS concept was adopted by researchers in a wide range of fields to become "microfluidics" (the technology underlying small volume solution handling) and "laboratory on a chip" (applied microfluidics). All these examples are based on the essence of microfluidics technology, namely, the superbly-controlled manipulation of small fluid volumes on the microscale. Micro liquid handling enables many significant advantages that make microfluidic systems unique and very attractive to work with [4]. Using small fluid volumes greatly reduces the consumption of sample and reagents, which is ideal for samples obtained in limited quantities and ultimately results in smaller waste output too. Furthermore, small volumes of fluid can be handled with high throughput in dense but yet compact networks of microchannels integrated in a single hand-held device, allowing for multiple processes running in

parallel. From the operative point of view, the small dimensions of these channels result in high surface-to-volume ratios that ensure exceptional mass and heat transfer, making them excellent candidates for the transportation of samples susceptible to thermal degradation [5, 6]. At these dimension scales, the regime of the fluid flow is typically laminar. This results in adjoining fluid streams mixing slowly and gradually by molecular diffusion only, offering great control of the entire fluidic system [1, 7].

Despite finding its origin in the realm of chemical analysis, microfluidics has broadened to address a wide range of applications in many other fields, as evidenced by the emergence of the term “lab on a chip technology” in the mid 1990’s. Clinical diagnostics, for instance, has registered a fair number of novel microfluidic contributions over the last decade based on miniaturized PCR for DNA analysis [8, 9] and immunoassays for the early detection of multiple diseases [10–12]. More recently, the introduction of point-of-care (POC) devices for rapid and *in situ* medical testing has established a milestone in this field. Organic chemistry has also introduced many microfluidic strategies for chemical synthesis. The development of micro- [16, 17] and nanoreactors [18] and new reagent delivery mechanisms such as droplet generation systems [19, 20] has facilitated the high-yield synthesis of organic compounds and biomolecules in miniaturized platforms. Notwithstanding this, among all the microfluidic applications reported so far, cell biology has probably enjoyed the most privileged immersion into lab-on-a-chip technology. Miniaturized cell culture environments have enabled the study and manipulation of cell systems using an ample set of approaches, including continuous-flow cell assays [21, 22], encapsulation and genome amplification [23, 24]. The study of tissues has also been attained in microfluidic platforms, highlighting the development of organ-on-a-chip models as a way to better understand aspects and processes of human physiology *in vivo* [25, 26].

Lastly but not less important, the separation of cells and bioparticles has also been intensively tackled in this field. This thesis covers this specific area of microfluidics, focusing on the use of combined hydrodynamic and electrokinetic phenomena in channels that are less than 300  $\mu\text{m}$  wide and 100  $\mu\text{m}$  deep for the separation of polymer particles. The characterization of this technique, named flow-induced electrokinetic trapping (FIET), has been explored and characterized on the basis of particle size and surface charge, making it promising as a miniaturized multi-parameter particle separation mechanism.

## 1.2 Scaling down fluidic systems

The miniaturization of any physical system necessarily implies the variation of certain physical quantities as a result of the induced change on the system size [27]. Scaling fluid processes is subject to this principle too, seeking not only the downsizing of the currently existing technology, but also the optimal exploitation of the fluid physics occurring at the new scale. This alteration of some physical quantities and its actual impact on the behavior of fluids in the microscale is described by the so called scaling laws, which evaluate the relation between the quantities themselves and the dimensions of the system [2]. The practical effects of scaling laws are key to understanding microfluidic processes and, in our particular case, the flowing fluid model described in this thesis. One of the most remarkable scaling effects observed in microchannels is the high surface-to-volume ratio, directly reflected in the relation between surface and volume forces [28]. Assuming that the channel dimensions scale as  $l$  (keeping constant aspect ratios between the three dimensions), the relation of these two forces can be expressed as:

$$\frac{\text{Surface forces}}{\text{Volume forces}} = \frac{l^2}{l^3} = l^{-1}, \quad \lim_{l \rightarrow 0} l^{-1} = \infty \quad (1.1)$$

This means that surface forces become more relevant than volume forces at smaller dimensions ( $l \rightarrow 0$ ). Two major examples of these forces are inertia and pressure forces ( $\propto l^2$ ), essential in driving liquids through microfluidic channels, as described below in the upcoming subsections.

### 1.2.1 Fluid motion and Navier-Stokes equation

As with analogous systems defined in larger scales, the motion of fluids through microfluidic channels is formally described by the Navier-Stokes equations [29]. In general terms, these equations are obtained from the principles of continuity and conservation of mass, momentum and energy. In the particular case of incompressible Newtonian fluids, the expression of the Navier-Stokes equation is expressed as follows:

$$\rho \left( \frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u} \cdot \nabla) \mathbf{u} \right) = \sum_i f_i = \rho g - \nabla p + \eta \nabla^2 \mathbf{u} \quad (1.2)$$

Where  $\rho$ ,  $\mathbf{u}$ , and  $\eta$  are the density, average velocity and dynamic viscosity of the fluid. The equation comprises the sum of the different forces acting on the fluid: gravity ( $\rho g$ ), pressure ( $-\nabla p$ ) and viscous ( $\eta \nabla^2 \mathbf{u}$ ) forces.

The small dimensions of microfluidic systems lead fluids to flow in the laminar flow regime, moving in well-defined parallel streams that do not mix with one another other than through diffusion, a slow process. One of the most desirable consequences of laminar flow in microfluidic channels is precisely that mixing of adjacent flow streams only happens by molecular diffusion in a relatively predictable way [1, 7]. This attribute has traditionally facilitated the integration of processes especially dependent on mass transport in microfluidic platforms, such as those related to particle sorting, cell analysis and bioassays. The flow regime in microchannels can be characterized by the dimensionless form of the Navier-Stokes equation (Eq. 1.2), given by the ratio of inertial forces and viscous forces. This results in the Reynolds number,  $Re$ , a dimensionless parameter given in Eq. 1.3:

$$Re = \frac{\text{Inertial forces}}{\text{Viscous forces}} \propto \frac{\rho u^2 L^2}{\eta u L} = \frac{\rho u L}{\eta} \quad (1.3)$$

## 1.2.2 Flow profiles and other electrokinetic effects

### 1.2.2.1 Pressure-driven flow

Undoubtedly one of the most common ways of handling fluids in microfluidic systems is by means of so-called pressure-driven flow (PF, also known as Poiseuille flow). PF is established by application of a pressure difference between the inlet and the outlet of a channel to dynamically propel fluid through [28]. This class of flow is described by one of the very few analytical solutions of the Navier-Stokes equation (Eq. 1.2). For this, it is assumed that the longitudinal dimension ( $x$ ) of the channel is invariant, and so the forces acting inside the channel are uniformly dissipated in the other two dimensions ( $y, z$ ). The velocity field of the flow is thus defined along the  $x$  axis, this being the only direction in which the motion of the flow is actually defined. Neglecting the effect of gravitational forces (as we generally deal with incompressible fluids), the velocity field (above) and the governing equation of the flow (below) can be written as:

$$\begin{aligned} \mathbf{u}(\mathbf{r})_x &= \mathbf{u}_x(y, z) \mathbf{e}_x \\ \eta \nabla^2 [\mathbf{u}_x(y, z) \mathbf{e}_x] - \nabla p &= 0 \end{aligned} \quad (1.4)$$

The assumed no-slip boundary conditions at the walls of the channel leads to a zero velocity situation in this region  $(\partial_y^2 + \partial_z^2) u_x = 0$ . For instance, considering the easiest two-dimension example of a microchannel (Figure 1.1) in which the fluid moves between two parallel plates (resembling the channel walls) defined in the  $xz$  plane and separated by a distance  $h$ , the velocity equation of the flow can be written as:

$$(\partial_z^2) u_x(z) = -\frac{\Delta p}{2\eta}, \quad u_x(0) = 0, \quad u_x(h) = 0 \quad (1.5)$$

The solution is a parabolic velocity profile centered at the middle-distance point between the two plates,  $h/2$ :

$$u_x(z) = -\frac{\Delta p}{2\eta L}(h-z)z \quad (1.6)$$

This parabolic shape of the velocity distribution is the distinctive fingerprint of pressure-driven flows (Figure 1.1), and applies also to other similar three-dimensional channel geometries, i.e. square and rectangular cross sections.

### 1.2.2.2 Electro-osmotic flow

Another type of flow profile based on the electrokinetic properties of fluids and microchannels is the electro-osmotic flow (EOF). In microfluidics devices, the EOF is generated by the motion of ions or charged particles through a microchannel with a net separation of charge between the channel walls and the bulk solution [28]. This ion motion is driven by a difference of potential applied between either end of the channel ( $\Delta V$ ), generating an electric field along the channel longitudinal axis. Similarly to the pressure-driven flow, the EOF velocity can be deduced directly from the Navier-Stokes equation:

$$\rho \left( \frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u} \cdot \nabla) \mathbf{u} \right) = -\nabla p + \eta \nabla^2 \mathbf{u} + \rho_{el}^{eq} \mathbf{E}_{ext} \quad (1.7)$$

Being  $\rho_{el}^{eq}$  the local density of charge on the channel walls and  $\mathbf{E}_{ext}$  the external electric field. In this case, it is assumed that the electric potential existing between the surface of the channel and the bulk solution (commonly known as zeta potential,  $\zeta$ , explained in more detail in Chapter 2) and the electric field applied along the channel are homogeneous. Furthermore, the flow is assumed to be in steady state ( $\nabla p = 0$ ), and the Debye length of the channel, much shorter than its half-width ( $\lambda_D \ll h/2$ ). Keeping into consideration these four conditions, the solution to Eq. 1.7 can be written as:

$$u_x(z) = f(z) u_{EOF} \quad (1.8)$$

Being  $u_{EOF}$  the electro-osmotic velocity and  $f(z)$  a function depending on the Debye length ( $\lambda_D$ ) and the channel height,  $h$ . This function can be approximated to 1 when the Debye length is significantly shorter than the channel half width,  $\lambda_D \ll h/2$ , which leaves the velocity expressed as:

$$\mathbf{u}(\mathbf{r}) \approx u_{EOF} \cdot \mathbf{e}_x \quad (1.9)$$

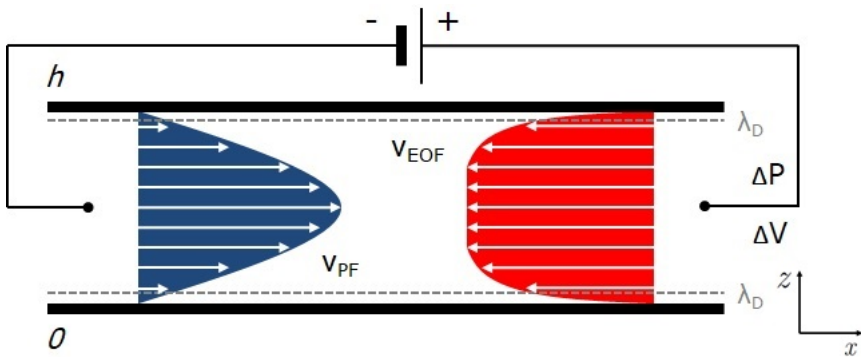
With the external electrical field being applied in the negative  $x$  direction ( $-\mathbf{e}_x$ ),  $\mathbf{E} = -E\mathbf{e}_x$ . The modular electro-osmotic velocity,  $u_{EOF}$ , is then defined as:

$$u_{EOF} = \mu_{EOF} \cdot E \quad (1.10)$$

Where  $\mu_{EOF}$  is the electroosmotic mobility, and is expressed as:

$$\mu_{EOF} = \frac{\epsilon_0 \epsilon \zeta_w}{\eta} \quad (1.11)$$

Being  $\epsilon_0$  and  $\epsilon$  the electric permittivity of vacuum and buffer, respectively and  $\zeta_w$  the zeta potential of the channel wall. Unlike the typical parabolic distribution of the pressure-driven flow velocity, the EOF velocity reaches its maximum near the Debye length of the channel walls,  $\lambda_D$ , which results in a flat profile across the transversal cross section of the channel (Figure 1.1).



**Figure 1.1:** Representation of pressure-driven (blue) and electro-osmotic (red) flow profiles in a two-dimensional model of parallel plates.

### 1.2.2.3 Electrophoresis

One of the common electrokinetic effects in aqueous solutions is electrophoresis, which consists of the movement of an electric charge with respect to the fluid itself as a result of the application of an external electric field [30]. Under these conditions, a charged, spherical particle dispersed in an electrolyte experiences two opposed forces: an electric force (oriented in the direction of the electric field) and a Stokes drag force (opposed to the direction of the electric field), given as:

$$\mathbf{F}_{\text{el}} = q\mathbf{E}, \quad \mathbf{F}_{\text{drag}} = -6\pi a\eta\mathbf{u}_{\text{ep}} \quad (1.12)$$

Being  $q$  and  $a$  the electric charge and radius of the particle and  $\mathbf{u}_{\text{ep}}$  its electrophoretic velocity in the solution. Assuming the cancellation of both forces at the dynamic equilibrium ( $\mathbf{F}_{\text{el}} + \mathbf{F}_{\text{drag}} = 0$ ), the latter can be written as:

$$\mathbf{u}_{\text{ep}} = \mu_{ep}\mathbf{E} = \frac{q}{6\pi a\eta}\mathbf{E} \quad (1.13)$$

Similarly to electro-osmosis,  $\mu_{ep}$  is described as the electrophoretic mobility of the particle. Another way of writing this expression is by integrating the dimensionless ratio between the radius and the thickness of the electrical double layer of the particle (defined by the Debye-Hückel parameter,  $1/\kappa$ ):

$$\mathbf{u}_{\text{ep}} = \frac{2\epsilon_0\epsilon\zeta_p}{3\eta}\mathbf{E} \quad (1.14)$$

Where  $\zeta_p$  is the zeta potential of the particle. For particles whose radius are much greater than the thickness of the electrical double layer, the parameter  $f(\kappa a)$  approaches the value of  $3/2$  (Smoluchowski's equation). The opposite situation (double layer thickness greater than the particle radius) results in values of  $f(\kappa a)$  close to 1 (Hückel's equation).

## 1.3 Introduction to microfabrication techniques employing rigid substrates

Microfabrication techniques play a fundamental role in the design and application of microfluidic devices [31]. The conception of any microfluidic approach always requires



the right microfabrication technique to bring the preliminary design out of the computer screen, making it tangible and providing it with the right geometry and physical properties. This thesis focuses on glass-made microfluidic devices, and so, the two main microfabrication techniques applicable to this material are briefly introduced below.

### **1.3.1 Wet etching**

The technique employs etchant solutions to transfer a pattern by selectively subtracting material from well-defined areas on the surface of the substrate. The depth profile of the etched structures is ultimately determined by the solution employed and the agitation conditions. The use of mineral acids (HF, HNO<sub>3</sub>) or mixtures of these with weak organic acids (HNO<sub>3</sub>, HF and CH<sub>3</sub>CO<sub>2</sub>H) are typically used to achieve isotropic etching conditions. This means that the etching process has no defined orientation, resulting in a uniform removal of the substrate from the surface of the material downwards. Solutions of strong bases such as NaOH or KOH, on the other hand, display faster etching rates on certain crystallographic faces of the substrate, leading to anisotropic structures. This means that the removal of material is directional, and thus, the size and shape of the etched features vary considerably depending on which dimension one is looking at. Lastly, the etching process is strongly affected by eventual agitation of the employed solution. Agitation ensures a constant transport of fresh solution to the areas of the substrate where the material is being removed, enhancing this way the overall etching rate.

### **1.3.2 Dry etching**

Instead of using aqueous solutions, dry etching employs plasma of highly reactive gases, such as O<sub>2</sub>, F<sub>2</sub>, Cl<sub>2</sub>, CH<sub>4</sub>, BCl<sub>3</sub>, SF<sub>6</sub> (typically employed for glass substrates) or NF<sub>3</sub> to remove material from the surface. The etching process takes place at relatively low pressure and temperature conditions by simple impact on the plasma ions (physical dry etching), chemical reactions with the substrate surface (chemical dry etching) or a combination of both. Similarly to wet etching, the continuous bombardment of plasma ions provokes the isotropic removal of material, leading to structures that, although precisely patterned, are equally etched in all directions.

## 1.4 Scope of this thesis

The aim of this thesis was to further develop the technique known as flow-induced electrokinetic trapping (FIET) in order to perform multi-parameter separations of polymer microparticles in a microfluidic platform. The characterization of particle behavior under bidirectional flow conditions based on hydrodynamic size and surface charge was pursued so as to establish the basis of a robust microfluidic methodology for particle sorting.

**Chapter 1** introduces the concept of lab-on-a-chip technology and its most important applications nowadays. A brief induction to the fluid flow models and microfabrication techniques employed in this thesis is also provided to better understand the following chapters.

The most recent separation strategies of particle and cell systems employing external electric fields are extensively reviewed in **Chapter 2**. An in-depth description of the most important electrokinetic phenomena (electrophoresis and dielectrophoresis) is herewith provided along with its applicability for particle separations in microfluidics.

The characterization of particle trapping under bidirectional flow conditions is provided in **Chapter 3**. Here, a Gaussian distribution model based on particle velocity is introduced to describe the motion of particles trapped in non-uniform channel geometries, understood as the driving mechanism for eventual particle separations.

In **Chapter 4**, the separation of binary particle mixtures with different size and surface charge is investigated using the Gaussian distribution model introduced in the previous chapter. The effect of these two intrinsic physical properties on particle velocity acquired inside the channel will be taken into account to predict the optimal separation conditions for different types of beads.

In **Chapter 5**, a time-based variation of the Gaussian velocity distribution model used in the previous chapters is provided to describe the separation of ternary particle mixtures on the basis of particle size and charge simultaneously (orthogonally). The advantages and limitations of this strategy will be discussed and compared to other techniques meant for the same purpose.

**Chapter 6** rounds off this manuscript with a brief discussion, conclusions and future perspectives of the presented methodology.

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