Lab on a Chip

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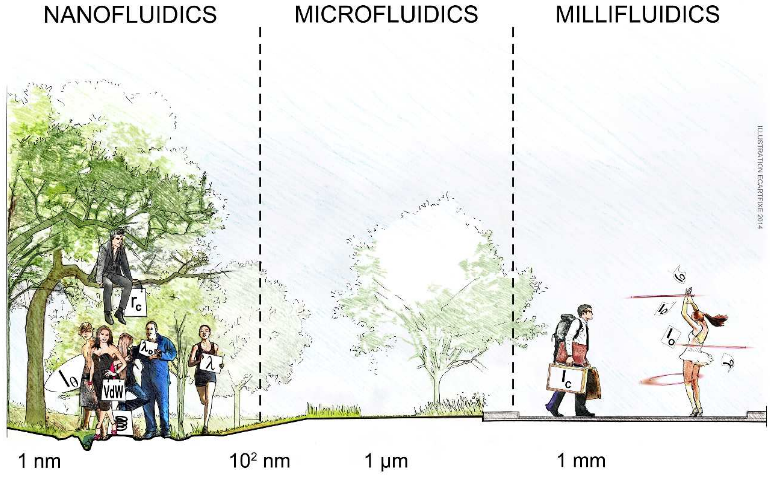
Sentence :

The paper review recent progress made in the field of nanofluidics, from a physical prospective, emphasizing on promising directions.



Caption: Cartoon representing the main mechanisms that operate in the nano, micro and millifluidic realms. The mechanisms are illustrated by characters, whose positions in the spectrum of scales are fixed by the characteristic lengths they are associated to. Fundamental questions of nanofluidics are : How the characterisctic scales pertaining to the 1-100 nm range interfere with the system size ? Can they combine together to produce new physical effects ?

Physics and technological aspects of nanofluidics

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Nanofluidics represents, from a physical prospective, an extremely rich domain. It hosts many mechanisms acting at the nanoscale, that combine together or interact with the confinement to generate new phenomena. Superfast flows in carbon nanotubes, nonlinear electrokinetic transport, slippage over smooth surfaces, nanobubble stability,... are the most striking phenomena that have been unveiled over the last few years and some of them are still awaiting an explanation. One may anticipate that new nanofluidic effects will be discovered in the future but at the moment, the technological barrier is high. Fabrication of nanochannels is most often a tour-de-force, slow and costly. However, with the accumulation of technological skills along with the use of new nanofluidic materials (like nanotubes), nanofluidics is becoming increasingly accessible to experimentalists. Among the technological challenges faced by the field, fabricating devices mimicking natural nanometric systems, such as aquaporins, ionic pumps or kidney osmotic filtering, seems the most demanding in terms of groundbreaking ideas. Nanoflow characterization remains delicate, although considerable progress has been achieved over the last years. Targeted application of nanofluidics are in the field of genomics and membrane science – with disruptive developements to be expected for water purification, desalination, and energy harvesting – but also for oil and gas production from unconventional reservoirs. To-day, in view of the markets that are targeted, nanofluidics may well impact the industry more than microfluidics; this would represent an unexpected paradox. These successes rely on using variety of materials and technologies, using state of the art nanofabrication, or low tech inexpensive approaches. As a whole, nanofluidics is a fascinating field, that is facing considerable challenges to-day. It possesses a formidable potential and offers much space for creative groundbreaking ideas.

1 Introduction: going deeper

Just like microfluidics concerns fluid transport in micron size channels, nanofluidics obviously extends the fluidic domain to the nanoscale realm. Fluid transport at the nanoscales is one of the remaining virgin territory in fluid transport – in spite of hydrodynamics being a very old and established domain – where laws are still to be invented. A new eldorado to conquer for fluid physics, which makes nanofluidics attractive on its own.

Since a few years, the activity around nanofluidics strongly increased with a number of groups developing ever more ingenious tricks to fabricate nanoscale fluidic systems as well as new experimental tools to probe the behavior of fluids in such ultra-confined environments. But the extension to nanoscale remains by no mean an easy task. So, is going down the scales worth the effort ? What does one gain by reaching the nanoscales ?

The hope is of course that nanofluidics is not just an extension of microfluidics and that new specific behavior and properties will emerge at the nanoscales which are unattainable at the micro or larger scales.

The goal of the paper is to address these questions. After a decade of work, a clearer view of the achievements of the domain, of the new avenues, as well as of the challenges to be addressed has emerged and we are now in a more favorable situation than in the past to perform this task. The existing reviews of nanofluidics have described the field in a comprehensive manner, from different prospectives, physical or engineering[1–5]. The focus here is not to update on these works, but rather to attempt to take a step back and discuss critically the aforementioned aspects in order to outline the future of the field along with its applications.

One idea that seeded the development of micro-fluidics was – to some extent – to mimic electronics: decreasing the scales in order to increase the efficiency of the processes at stake. To-day, the comparison with microelectronics is still used to position microfluidics in the landscape of nanosciences. Emphasising on this analogy naturally leads to envision that the future of microfluidics is nano-fluidics, i.e a domain that embraces a range of scales comprised (with some arbitrariness) between 1 and 100nm, thus including the smallest scale at

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which a fluid can conceivably be driven [‡] An underlying aim is accordingly to be able to design individual fluidic channels at the nanoscale, with dedicated geometrical or chemical specificities. In electronics and solid-state physics, nanoscales correspond to the emergence of strong quantum ’couplings’ for electronic transport and new nanoscale materials like carbon nanotubes or graphene have opened vast perspectives for disruptive material properties. In fluids, the situation is quite different: nanoscale quantum effects are not expected to couple easily to flow and fluidic transport – although some perspectives in this direction are worth exploring –. In fact, the specificity of nanofluidics is not to host quantum effects, but rather to host a broad spectrum of nanometric forces that work at controlling the fluid behavior. In the nanofluidic realm, many mechanisms operate efficiently in an exiguous range of scales: Van der Waals forces, electrokinetic effects, rarefied dynamics for gases, nucleation phenomena,... Their description can be found in classical textbooks (*e.g.* the books by Israeladvilli[7], or Hunter[8] ...) and, more specifically for nanofluidics, in the previously quoted reviews or in[9,10]. They are represented in Fig 1, in a cartoon, according to the characteristic scale they are associated to [§]. There is an overcrowding of players acting at the nanofluidic scale. In fact, most of these actors play a role in the microfluidic range of scales as well, but indirectly. In microfluidics, the only scale that matters is the system size, so that flow phenomena are fully controlled by the geometry. In nanofluidics, the spatial structure of the forces acting at the nanoscale must be fully taken into account to understand how fluids behave. This induces a level of complexity that constrasts with microfluidics, but, on the other hand, by combining different contributions, may give birth to new outstanding physical effects. To-day, the search for new couplings between them, or between them and the interfaces, that could allow to drive and manipulate fluids in a unprecedented manner is just at its beginning. Discovering and harvesting such new mechanisms is the main goal of nanofluidics.

Are there great expectations for fluidic transport at the nanoscales ? Our answer is definitely positive.

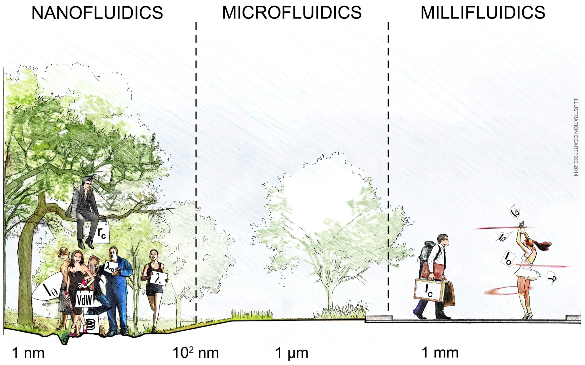

Fig. 1 Cartoon representing the main mechanisms that operate in the nano, micro and millifluidic realms. The mechanisms are illustrated by characters, whose positions in the spectrum of scales are fixed by the characteristic lengths they are associated to: the electrician for the Debye length[9], the dreamer on the tree branch for the nucleation critical radius, the runner for the mean free path in the gases[9], the surfer for the thermal capillary length, the heavy man for the capillary length, the dancer for the Oseen length, etc... Fundamental questions of nanofluidics are : How the characterisctic scales pertaining to the 1-100 nm range interfere with the system size ? Can they combine together to produce new physical effects ? For example, what happens when the Debye length becomes comparable to the channel height, how nucleation is inhibited by the confinement, how gas rarefaction is induced by the same, how nanoscale forces combine to control the movement of nanoparticles close to a wall, etc.. In the microfluidic realm, no such interactions exist, and the only scale that matters is the system size. As we move to millifluidics, one must address again the question of the interactions of a number of dynamical scales with the system size (capillary length, Oseen length). Picture made by Ecartfixe

First it is not by chance that many – no to say most – of the biological process involving fluids do operate within pores of nanoscopic dimensions and less (ionic channels, transmembrane proteins, *e.g.* aquaporins (AQP), to quote a few examples (Fig.2). Nature has optimized its process by scaling down the fluidic process. This has actually motivated a huge amount of studies in the physiology domain, in particular to explore the corresponding electric functionalities. Understanding how these systems work would provide out-of-the-box ideas to propose new solutions for important technological questions. This is the case for example of desalination and separation. Natural systems have developed uncommon strategies to separate species. An interesting example is kidney filtration which follows by no means the simple membrane separation technologies which we are used to. Basically filtration of urea is achieved by an active re-adsorption of water and ions in the so-called Henle loop[11]. Using aquaporins and active ion pumps, this osmotic exchanger achieve the readsorption of huge amounts of water (∼ 200 liters per day) and salt (∼1.5kg per day) to separate urea waste at a very economical cost of order 100kJ per day. This value could be compared *to some extent* with the energy required to desalinate 200l of sea water, which, using state-of-the-art reverse osmosis mem-

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[‡] Funding agencies and the community consider that the typical scales of nanofluidics lie between 1 and 100 nm, an arbitrary definition that can nonetheless be justified physically, as shown herein.The range of scales between 100 nm and 1μm is sometimes called ”extended nanofluidics”[6].

[§] We may recall here that the Oseen length, rarely used in fluid dynamics, is defined as ν/U, in which ν is the kinematic viscosity of the working fluid and U a characteristic flow speed. Oseen lengths smaller than the system size imply Reynolds numbers larger than one. Another rarely mentioned scale is the thermal capillary length, defined as the square root of the ratio between thermal and interface energies, which characterizes the (nano)waves excited at a fluid interface by the brownian fluctuations

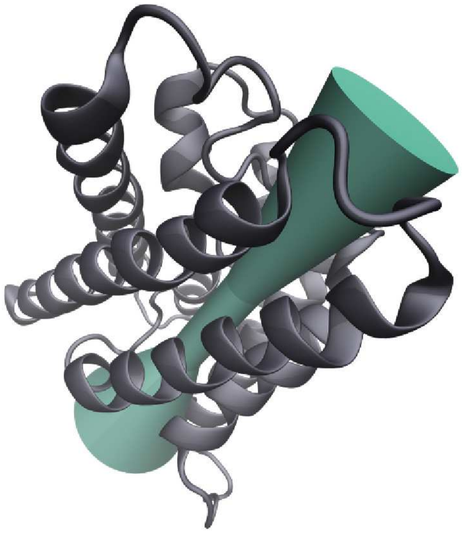

Fig. 2 Aquaporins are nanometric water channels which selectively conduct water molecules in and out of the cell, while preventing the passage of ions and other solutes. Water molecules traverse through the pore of the channel in single file. The water channel has typically an hour-glass shape, as sketched on the figure. Courtesy of S. Gravelle.

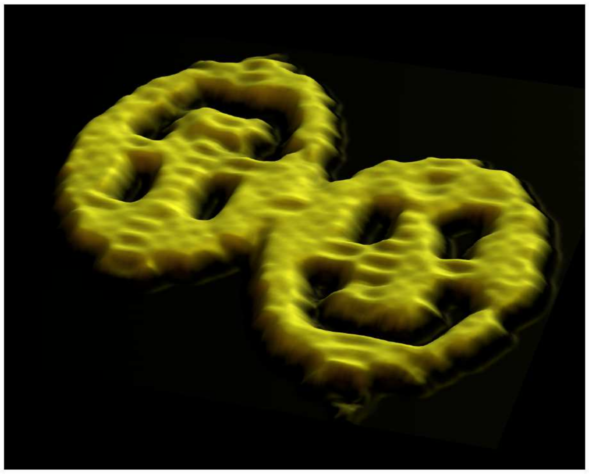

Fig. 3 DNA nanotechnology: Self assembly based on the affinity between complementary DNA strands. Image from Rothemund lab [12].

branes, is merely in the order of 3MJ, *i.e.* 30 times larger. Note however that the energy cost of desalination cannot be lower than the thermodynamic limit – typically the free energy of mixing – and actual desalination processes already work close to that theoretical limit. What is interesting with the multi-step separation of urea is that the process involves salt separation at some intermediate point, but, due to its design, avoids paying the full price of it. From a broad perspective, this suggests that the possibility indeed exists to go beyond actual technologies by taking benefit of nanoscale behavior and using new smart separation process.

Such types of performance constitute a strong motivation to explore the fluid transport across nanoscales objects, with the aim of proposing new solutions to big challenges.

An immediate difficulty is that in contrast to biological systems, nanotechnology still do not handle genetic engineering to build systems with nanoscale features. A notable exception is the marvelous DNA origami systems which allow to design *on-demand* nanoscale pores with specific geometries and properties [12,13,15,16], Fig.(3). Building an artificial nanosystem structure as complex as an aquaporin is still out of reach within the present state of the art, but could well become feasible in a near future [14]. This is one important requirement for the nanofluidic domain, as well as its specificity. Indeed advancing our fundamental understanding of fluid transport on the smallest scales requires mass and ion dynamics to be ultimately characterized across an individual channel to avoid averaging over many pores. A major challenge for nanofluidics thus lies in building distinct and well-controlled nanochannels, amenable to the systematic exploration of their properties. While there has been much technological progress over the recent years to develop nanoscale fluidic devices, the question of designing and fabricating well controled nanodevices still remains a bottleneck which could impede the development of nanofluidics beyond the frontier of the lab.

Though, it is interesting to note that the development of nanofluidics was recently boosted by the use of nanomaterials, out of their common solid-state purpose. Materials like carbon nanotubes, boron-nitride nanotubes, graphene, have all raised great hopes in terms of nanofluidic transport because they were shown to exhibit groundbreaking behavior: superfast flows through carbon nanotubes [17–19], large osmotic power conversion in boron-nitride nanotubes [20], or the predicted optimal desalination capability of nanoporous graphene and graphene oxides [22], motivating experimental exploration [23,24]. This has raised considerable hopes for societal questions like desalination and energy harvesting.

Finally, it should not be forgotten that nanoscales are ubiquitous in microfluidics, implying that a better control of these scales would be highly beneficial to microfluidic technology: Debye layers, molecular layers controlling the surface chemistry, surfactants monolayers controlling interfacial surface tension, ... play instrumental roles in microfluidics. All represent nanofluidic subsystems embedded in microfluidic environments. At the moment, owing to instrumental limitations, these subsytems are not investigated at the appropriate scale *in situ*. They are black boxes, difficult to control, that jeopardize handling microfluidic flows at an exquisite level. In the future, progress in nanofluidics will certainly help improving the control of the behavior of microfluidic devices. This remark also concerns other domains, such as colloidal science, which bears on nanofluidic processes. These various aspects of nanofluidics point to another key question: for nanofluidic to develop we need not only to be able to fabricate nanosystems, but also to develop new measurements techniques to probe the transport properties at such nanoscales. The majority of existing techniques are based on the measurement of electric currents, such as the patch-clamp or the Coulter counter techniques, which have been greatly developed since the early days of physiology. Beyond, there is a lack of techniques to probe flow and/or solute transport at the nanoscale. Why is it difficult ? Because global measurements have to strive with the tiny volumes transiting across the system. Measuring a flow-rate of 1 zeptolitter (10^{-21} l) per second, typical for a flow of water through a carbon nanotube (CNT), is a formidable challenge. If collected in a reservoir of one nanoliter (a typical microfluidic droplet), it would take one month to increase the droplet size by one Angstrom. Likewise, local speed measurements based on nanometric probes seeding the fluid are challenging. As shown below, brownian motion limits the spatial resolution. Furthermore, charge and wall effects, impossible to characterize in situ, complicates the interpretation of the trajectories. Progress in this area would need extremely sentitive cameras, with frame transfers in the range of the nanosecond to reach a one nanometer resolution. This equipment does not exist yet.

Altogether the potential of nanofluidics is huge, although there are still high barriers to bypass. But this makes of nanofluidics an exciting, frontier domain, where a lot remains to be invented. In this review, we will both hightlight a number of exciting potentialities of the field, and discuss the challenges to be solved for the nanofluidic field to expand. We will also attempt to suggest a number of scenarios that nanofluidics may undergo in the future, being aware that gazing into a crystal ball is always adventurous.

2 The challenges

Let's start with the 'bad' news: the field of nanofluidics faces a number of important challenges which impede its development. These are mainly twofold: the fabrication step of nanochannels, and the development of new instruments to probe the transport properties.

2.1 Technologies for nanofluidics

The introduction of soft lithography by Whitesides *et al.*[25] had a considerable impact in the development of *micro-fluidics* to make it the well developed field which it is nowadays. This simple technological tool gave nearly everyone the possibility to create microfluidics systems in a simple and cheap way, say 'in the kitchen', without the absolute necessity of expensive clean room equipements. This has created a surge of activity in any lab, from the larger to the smaller, boosting the creativity which has caracterized the field over the last 15 years.

Nanofluidics still lacks of such a disruptive step. Fabricating individual channels with dimensions in the nanometric range, together with well-controled surface properties, remains a challenge. There is no simple toolbox which one may use to fabricate on-demand a nanopipe. Let us review quickly some of the main approaches up to date and some alternative approach to be developed.

The top-down approach – By exploiting the capabilities of well equipped clean rooms to fabricate nanochannels, this is in some sense the most natural approach. Indeed lithography process, such as electron-beam lithography or deep-UV projection lithography are efficient, but costly, tools which are able to fabricate nanochannels with heigths in the nanoscale range. This leads usually to nano-slit geometry, where one dimension is in the tens and even lower nanometer range, while the other dimensions are typically in the tens of microns and/or millimeter range. Silicon chips can be processed with such tools to obtain nanochannels amenable to fluidic transport.

A method which is close in spirit to the soft lithography developped for microfluidics is the nano-imprint lithography[26], whereby a hard mold with a designed nanostructure is processed once and then allows to imprint a soft polymer matrix to transfer the nanostructure. The method is less expansive and allows to pattern polymer nanostructures with features in the ∼20nm range.

In a different context, there are a number of techniques which allow to drill nanopores in membranes. Focus Ion Beam (FIB) has been extensively used in the field of solid-state nanopores[27,28], reaching nanopores a few nanometers in diameter. The nanopore have usually a conical or hour-glass shape due to the drilling process[4]. This method has a certain flexibility and for example networks of nano pores of various topology can be obtained[29]. This method has now been extended with great success to the drilling of graphene atomic sheets[23,30].

Once the channels have been fabricated it is possible to tune the surface properties through adequate coatings of the surfaces, or by deposition/etching techniques. For example asymmetric nanochannels were obtained by asymmetric chemical deposition[31]. However one must admit that we are still far from being able to realize nanometric lab-on-a-chips devices with a complexity comparable to the microfluidic state-of-the-art (see for instance[32]). Instrumenting the nanochannels is not an easy task. One bottleneck that must be unlocked here is the fabrication of valves that can be scaled down to nanometric dimensions. PDMS valves have already shown their limit (roughly 7 μm[33]). Hydrogels, initiated by J.Frechet[34], have some potential, but their application to nanofluidics remains to be done.

Altogether for the techniques described in this paragraph, a good relationship with either a clean room facility and/or an equiped microscopy center is highly recommended.

New nanomaterials – Nanomaterials, nanotubes and graphene constitute ideal materials as nanofluidics devices. As we recall in the next section, these systems have raised great hopes to obtain new fluid transport properties. Fluidic transport across carbon nanotubes (CNT) with diameters in the range of 1-2 nm was first investigated on the basis of large scale membranes fabricated using chemical vapor deposition process (CVD). These membranes constitute a great material to probe transport, but transport is intrinsically averaged over billions of nanopores. This makes it difficult to study fundamentally the origin of the unexpected transport properties of these systems in all its glory.

A number of groups therefore tackled the challenging objective to study transport inside single nanotubes. The great difficulty is to embed the nanomaterial into a larger micro/macro fluidic device allowing to impose various forcings. Various approaches were followed to fabricate the corresponding devices. A first approach is to deposit nanotubes on a surface and then fabricate a microfluidic device around the chosen CNT. This is the approach followed by the groups of Strano[35], Lindsay[36], who then studied ion and macromolecule transport inside single wall and double wall CNT. In a different perspective, Gogotsi *et al.* have developed a carbon nanotube 'endoscope', with a nanotube place at the end of a micropipette in order to interrogate the internal environment of cells[37]. An alternative approach is to make use of nanomanipulation tools to insert a single nanotube into a pierced membrane, leading to a transmembrane geometry. This is the route followed by Siria *et al.*[20]. One key advantage of this geometry is that it allows to probe the transport inside the single nanotube under various forcings: beyond voltage drop, pressure drops or salinity gradients can be applied, as was explored by Siria *et al.* in boron-nitride nanotubes. Nano-manipulation is quite versatile[21] and can be developed to create nanofluidic systems with various geometries, which are suitable for experimental investigation of both linear and non-linear transport.

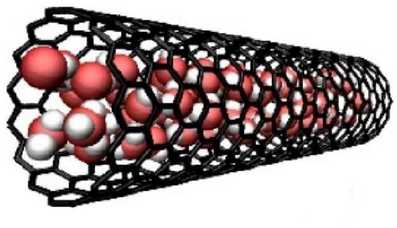

Fig. 4 The existence of superfast flows through carbon nanotubes (CNT) – orders of magnitude faster than standard hydrodynamic estimates – has challenged the physicists for several years. Now, a number of ideas have been proposed to explain this behavior. Image courtesy of K. Falk.

A third approach was also proposed by the group of Wu[38] who followed a completely different route to insert short (5-10nm) Single Wall CNT (SWCNT) into a lipid bilayer using a micro-injection probe. This allowed them to explore the translocation of DNA through these ultrasmall CNTs. This smart fabrication method has the great advantage of being both versatile and low-cost. It can be easily developed using generic lab tools.

We conclude this paragraph by mentioning graphene as another nanomaterial of great interest for nanofluidics. Graphene now becomes popularized and many large-scale fabrication techniques are now available, not to speak of commercially available graphene materials. As quoted above, the limiting step is however to drill nanoholes in graphene, which still requires FIB type of apparatus. But graphene oxide membranes are definitly interesting tools to play with[24].

Alternative methods – Beyond the methods discussed above, there are a number of alternative routes which were followed by various groups to create nanofluidic plateforms. One very simple route is to use standard methods based on pipette pullers. With some optimization, nanopipettes with a mouth diameter down to 10-20 nanometers can be prepared[39]. This represents an easy way to fabricate nanopipes at a very low cost.

Along the same idea of simplicity, soap bubbles provide an interesting example of nanofluidic channels which can be blown in the kitchen[40]. Due to a balance between electrostatic repulsion/osmotic pressure and van der Waals attraction, the thickness of the soap film is typically in the nanometric range, down to a few Angström for the Newton black films. This soft nanofluidic system provide a very versatile and cheap system which allow to explore fluid transport in nanoscale confinement under various (electrostatic or osmotic) forcings.

A more involved route which has been followed lately is based on the DNA origami technology[12]. This process makes use of the specificity of the base-pair interaction of DNA and the molecule is folded in programmed complex shape using staple strands. This amazing technology was applied to create hybrid origami nanopores with nanometer-size pore[13–15], which is then associated with a solid-state nanopore or inserted in a lipid layer. As such origami techniques should become popularized in the future, they would constitute an interesting tool to explore a number of questions for nanofluidic transport.

Finally we end this paragraph by quoting that 'standard' nanoporous membranes should not be forgotten from the toolbox of nanofluidics. Membranes like Anodic Aluminium Oxides (AAO) membranes or equivalent, which are commercially available, exhibit a well ordered structure of pores with diameter from hundreds to a few tens of nanometers. Therefore, the difficulty associated the averaging of transport over many pores can be compensated by the perfectly organized structure at large scale. Such membranes were used recently to explore diode like effects[41], or the exploration of nanobubbles as soft osmotic membranes[42].

Nanorheology and force apparatus – Last but not least, it is worth mentionning that while the above approaches focused on the fabrication of nanochannels, nanopipes or nanopores, the nanofluidic domain has greatly benefited from the development of surface force tools. Here the geometry is typically more open with a fluid squeezed between two confining plates (Surface Force Appartus), or between a surface and the head of a tip (Atomic Force Microscopy)[3]. Surface Force Apparatus have allowed to probe the fluid rheology at the nanoscale with a number of great successes, in particular in the context of fluid slippage on surfaces[44]. Such tools are usually technically involved and represent a considerable investment to develop them. AFM are more spread, although beyond imaging, quantitative AFM measurements to probe the nanoscale rheology still remain difficult[45,46].

2.2 Instrumentation for nanofluidics

A second big challenge for nanofluidics is the question of transport characterization. As we discuss now, there is a real need to develop new experimental techniques to probe flow (flux and/or profile), chemical composition, solute concentration, etc. at the nanoscale.

It is not by chance that most of the current techniques to caracterize transport are based on electric current measurements. Transporting one ion from one reservoir to the other represents a considerable change in the system (*e.g.* in free energy), which can be easily tracked. This is not the case of transporting a single water molecule. Methods to measure currents in the pico-Ampere, even down to femto-Ampere, are now available (depending of course on the targeted frequency window). Such sensivity allowed for the development of the so-called patch-clamp technique by Neher and Sackmann in 1976, which revolutionarized physiology by allowing to measure ion transport across single ion channels. These methods are now widely used in any lab with commercial patch clamp amplifier available. The response to voltage drops (current-voltage characteristics) is the 'easiest' measurement which can be achieved in individual nanochannels.

Extending on this know-how, a number of alternative techniques use ion transport as a probe. One may quote the Coulter-counter technique, which makes use of statistics of current blockade as a probe of the translocation of macromolecule in nanopores. This method is widely used in combination with solid-state nanopores to probe the structure of DNA or proteins[27].

Now, flow measurement are far more challenging. Just to fix orders of magnitude, consider the flow rate of water across a tube with radius 1nm, length 1μm, under a pressure drop of 1atm (assuming no-slip at its surface): this corresponds to 10^6 water molecules crossing the tube per second, or $\sim 10^{-20}$ liter per second. As pointed above, creating a flow meter capable to measure such minute flow rates is a real challenge.

But some progress is on its way, as there is a growing number of creative attempts over the recent years. As expected some methods extends on current-based measurements. For example methods based on Coulter-counter techniques is a lead, althougth chemical fouling of the nanopipes by the macromolecules is a difficult issue. Lemay *et al.* developed recently an electric cross correlation spectroscopy technique which is based on measuring the time-of-flight fluctuations of charge carrier between two electrodes. This method allows to reach 10pL/min[47]. An alternative method is based on the characterization of ion distribution out of a pore using micro-electrodes, as developed by Pohl and collaborators[48].

Alternative to electric measurements are optical techniques, usually based on fluorescence. Fluorescence recovery after photobleaching (FRAP) has been used by Bodiguel *et al.* to characterize flow of polymers in nanoslits[49]. Methods like Fluorescence Correlation Spectroscopy pushed towards single molecules sensitivity could be used as well to investigate flow and diffusion in nanochannels. There is definitly an effort to develop such optical methods for nanofluidic transport.

A completely different method has been proposed more recently by Keyser *et al.* to measure fluxes of water emerging out of a nanopipette. The method uses a troncated colloid particule trapped *outside* the nanopipette using a classical optical tweezer[39]. Under an induced hydrodynamic flow emerging from the nanopipette, the asymmetric colloid undergo a

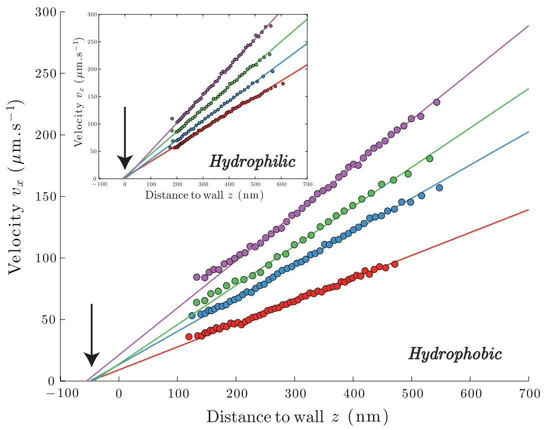

Fig. 5 Series of velocity profiles obtained with a sucrose solution driven by a pressure gradient, in a microchannel with hydrophobic (main figure) and hydrophilic (insert) walls.The profiles are well resolved in space, thanks to a superresolution technique that provides a sub-decananometric accuracy on the particle location. With the particles at hand (100 nm in diameter) the very near wall region cannot be explored. By extrapolating the profiles down to the horizontal axis, one obtains slip lengths on the order of 32 ±5 nm for the hydrophobic case, and 1 ±5 nm in the hydrophilic case (based on 95% confidence intervals)[52]. Image courtesy by Z.Li and L.D'Eramo

rotation which identifies basically with the local shear rate, thereby allowing to map out the vorticity and velocity fields. This method was shown to be able to measure a flux of a few pL per second. Most important is the fact that this technique is purely passive, meaning that it avoids the use of particles to cross the nanochannel in order to probe the inner flow. This is a great advantage.

SFA and AFM techniques have been already mentioned in this review. As quoted above, Surface Force Apparatus has allowed to probe the fluid rheology at the nanoscale[44]. AFM has played a key role in the exploration of various surface phenomena measurements. For example, it has allowed to discover the unexpected stability of nanobubbles[50,51], prompting the emergence a new field in the landscape of nanosciences. It also played a key role in the context of slippage at nanoscales[3]. A challenge is to extract quantitative information for dissipation, especially for measurements involving liquids where the surface contribution should be disentangled from other contributions[45,46].

The techniques we discussed precedently are global. In all cases, a global flux of matter or ions is measured and some averaged observable is obtained. What about local measurements ? Classical μPIV (MicroParticle Image Velocimetry) technique, developed in 1999[53] is subjected to diffraction limit and therefore is not suitable for carrying out local measurements with a nanometric resolution. One way to improve the situation is to work close to a wall, in an evanescent field, and use intensities measurements to infer particle positions. The idea was proposed and developed by Yoda[54], and Breuer[55] and further expanded by a number of investigators[56,57]. In fact, the presence of brownian motion, coupled to the finite speed of acquisition of the camera, limits the spatial resolution of the technique. For a given laps of time, the smaller the probes, the larger volume they explore. This leads to define an optimal probe size below which resolution worsens. With the best camera available on the market, the optimal diameter of the seeding particles is 100 nm - quite a large size -, and the best accuracy that has been achieved today on the measurement of their positions is on the order of 50 nm[54]. Improving the situation thus bears on the development of high speed sensitive cameras. Another issue is the interpretation of the trajectories of the seeding particles. Owing to various effects (electrokinetic, wall proximity, statistical biaises associated to brownian fluctuations, ...) the particles deviate from streamlines. Due to an overcrowding to effects that come into play, the situation is complicated and Langevin or Fokker-Planck simulations are needed to disentangle the contributions, understand the trajectories and relate them to the flow[58,60]. Fig 5 shows a very recent example where such an analysis was performed, together with an improvement of the method of observation of the particles, yielding in the end an accurate (±5 nm) slip length measurement. Still, on awaiting the next generations of cameras, there is much room to improve the technique, both on the analysis of the phenomena that control the movement of the colloids and the optimization of the measurement conditions. Smart ideas may very well give rise to spectacular advances in this area.

To complete the presentation, one must mention, beyond SFA and AFM, the important catalog of techniques of surface characterization, that often provide key information on the nature of the fluid/solid interface in situ and their roles on the structure of nanofluidic flows. Historically, X-ray diffraction at grazing angles and neutron scattering[7], have enligthened the problem of slippage over hydrophobic surfaces by bringing critical information on the hydrophobic gap. This points to the idea that strong overlaps exist between surface nanoscience and nanofluidics, generating numerous interactions between the corresponding communities.

To conclude on this part, characterizing flows at the nanoscale thus raises interesting intellectual challenges, where there is a strong need for clever ideas. The recent progresses show that there are possible groundbreaking solutions to this very difficult question. Much work is required in this direction.

2.3 The numerical simulations

A point which we barely mentionned up to now in this review is the key role played by molecular simulation for the development nanofluidics. We will not make a thorough discussion which would require a full review. Some aspects have been reviewed elsewhere[61,62]. The configuration of nanofluidics is indeed ideal for simulations: strong confinement corresponds to little amount of molecules and much progress has been achieved in computational techniques, with state-of-the-art molecular dynamics tools now allowing to explore the dynamics of large scale materials. Molecular simulation have played a key role in the development of nanofluidics, playing sometimes the role of a guide pointing to new directions. For example the work of Hummer *et al.* on fast water transport in carbon nanotubes[63] has seeded the idea of testing these materials experimentally for nanofluidic applications. Also works on hydrodynamic slippage have accompanied experimental aspects since the beginning of this domain[3].

There is no doubt that numerical simulations will remain a tool of choice to generate new ideas in the field of nanofluidics.

3 Highlighting some recent developments

After so much efforts, now comes the good news: nanoscales are considerably rich and host many new phenomena. A number of them (such as DNA entropic trapping or separation in nanochannel, DNA translocation through nanopores, Washburn law, ...) have already been reviewed[1,3,27,64]. Here we focus on recent progress that, combined to previous work, help to envision the future of nanofluidics.

3.1 Emerging behaviors

Towards the limits of continuum approaches – In water hydrodynamic breakdown is expected around 1nm[3]. This nanometric limit can be interpreted in terms of a lack of separation of time scales, as suggested in[3]. This is both good and bad news: good news because one may use standard continuum approaches to account for the dynamics of fluids in pore larger than 1nm in size (of course, provided boundary conditions are well accounted for); bad news because it suggests that subnanometric pores are required in order to observe 'exotic' transport, beyond the hydrodynamic dogma. This is actually the case of most biological pores, which usually involve a molecular region. This question can be furthermore extended to other types of transport: solute transport and Fick law, heat transport and Fourier law, etc.

Now, it would be worthwhile to explore more systematically this transition between continuum and discrete transport, especially on the experimental side, in proper conditions. Furthermore how this continuum-discrete threshold extends to other fluids, *e.g.* alcanes or oils with variable length, and/or thermodynamic conditions remains largely unknown.

Fluctuations – As size decreases, it is a statistical law that fluctuations becomes increasingly important. Transport in nanoscales channels follows this rule and fluctuations should be taken into account when describing transport in the smallest pores. In a reverse point of view, fluctuations contains a wealth of information. For example Golovchenko et al.[28] have shown how electrical noise in solid-state nanopores can provide much information on the surface properties and/or chemistry of surfaces. Similarly Lemay and collaborators have demonstrated how the analysis of noise associated with electro-chemical reactions in nanochannels provide much information both the electrochemical process but also on the fluid transport[47]. An open question concern the origin of low frequency components of the noise which are systematically measured in nanochannels and nanopores, see *e.g.*[65], leading to algrebraic frequency dependence as $f^{-\alpha}$, with an exponent of order unity. The existence of long time scales in the dynamics of the confined fluid remains to be understood.

There is therefore a lot to be developed on this noise question, both on the theoretical and experimental side.

Translocation of molecules in nanopores – It is difficult to summarize in a few lines the advances realized lately in the domain of molecule translocation through nanosized pores inserted in membranes. This very active domain represents a field on its own, furthermore with large potential economic outcomes at stake. We refer to existing reviews for detailed descriptions, *e.g.*[27,64]. This domain started with the seminal works of Bezrukov and Kasianowicz who demonstrated how the passage of a DNA molecule through α-haemolysin could be recorded via an electric signal[66]. It raised hopes to be able to "read" the sequence of DNA with an unprecedented efficiency thanks to the nanoscales involved. Beyond the use of biological nanopores as sensors, solid-state nanopores based on silicon membranes have become a system of choice to explore these questions. Solid state nanopores are more stable in a broad range of conditions than their biological counterparts and their properties and characteristics can be tuned on demand. This domain has developed considerably, with key progress in the understanding of transport phenomena in nanopores, translocation dynamics of individual molecules, as well as protein dynamics at the single molecule level, to cite a few[27,67–70]. Recent advances allowed to highlight the – sometimes subtle – interplay of the electro-phoretic/-osmotic transport with polymer dynamics[67–69]. Furthermore the role of unexpected actors, like salinity gradients across the membrane, was highlighted and shown improve considerably the detection of DNA[70]. This points to the subtle role of osmotic and diffusio-osmotic process in nano-confinement.

Furthermore, beyond silicon based materials, graphene has been explored as a membrane and the translocation of DNA through graphene nanopores has been demonstrated[30,71,72]. The conductive nature of graphene, as well as its molecular thickness, offers new perspectives to considerably improve the efficiency of DNA sensing.

Obviously, although the focus is slightly different, this domain shares many scientific questions with nanofluidics. In order to understand and control the translocation dynamics for optimal sensing efficiency, a good knowledge of the transport inside the nanopores is required: this involves electrokinetic and osmotic transport, in relation to electrostatic couplings, as well as the behavior of macromolecules in confinement, the nature of the confining environment, fluctuations, etc. Many open fundamental questions are remaing, which are common to the other topics discussed in this review.

Hydrodynamic slippage – Slippage of newtonian fluids has attracted the interest of most of the nanofluidic community over the last decade and much progress has been realized. It is now accepted that slippage of water at solid surfaces increases with the hydrophobicity of the walls, with a slip length typically in the tens of nanometer range, typically between 20 and 70 nm. This interdependance is accounted for by molecular simulations, see *e.g.*[73], and rationalized by a theoretical description of the liquid-solid friction[3]. Still some fundamental questions remain. In particular, numerical simulations have calculated slip lengths on the order of a few nanometers for repulsive surfaces, one order of magnitude smaller than the experiment exhibiting similar contact angles. There is an important gap to be understood, from which a lot could probably be learned, both on the numerical modelisation and on the nature of interfaces.

For example, how well do the simulations represent the fluids considered, along with the *in situ* physical-chemistry of the walls ? The molecular models represent well the statics but how about the dynamics of fluids at the interfaces ? The description of interfacial dielectric effects at the molecular scale, as well as their coupling to electrokinetic effects is also a topics of great interest[74]. Another question concerns the presence of nanobubbles, whose stability is now established on hydrophobic surface (see below). These are examples, among others, of relevant questions. A lot remains therefore to be explored on dynamical behavior of solid/water interfaces at the nanoscale, which is so ubiquitous in nature.

Slippage phenomena are not restricted to newtonian fluids. The slippage of complex fluids over smooth surfaces, such as polymers, living micelles, concentrated emulsions or microgels, often control flow behaviors[49]. How thick is a film separating a concentrated emulsion from the walls ? How do polymer blobs behave at the surface ? How do functionalized surface react to the presence of a shear ? These systems have not benefited yet from the most recent nanofluidic instrumental developments. There is a space to learn a lot on these systems, and perhaps revisit dogmas. It should also be noted that these fluids are extremely important industrially.

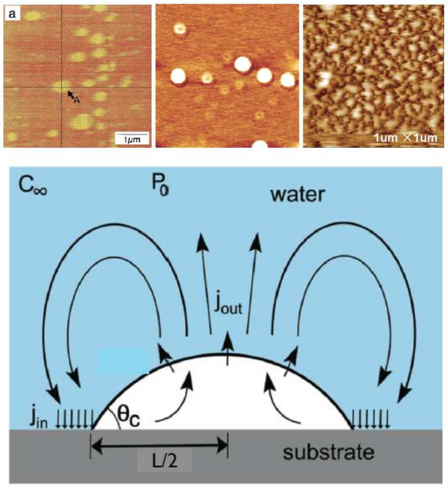

Fig. 6 Top: Nanobubbles visualized by AFM[75]. Bottom: Sketch showing the mechanism proposed in Ref[50] for explaining the stability of nanobubbles. Note that, at the time the review is written, the idea is no longer pushed by the authors

Nanobubbles –
Nanobubbles represents a fascinating subject, that has generated controversies for years and now tends to a clarification[75]. The existence of these nanobubbles was suggested twenty years ago[76] but the first images were obtained with AFM by the turn of the century[51,77]. These nanobubbles are approximately 20 nm high, 100 nm wide, with a contact angle departing from its equilibrium value, and they survive for days. The puzzle was that estimates based on the Laplace pressure inside the nanobubble indicate that they should collapse in μs. Was it an artefact caused by the AFM ? Since 2003, the community has developed effort to develop new techniques of observations for these nanoobjects, and now, we have series of experiments using ATR-IR, quartz crystal microbalance, neutron reflectrometry, x-ray reflectivity and, recently, interferometry, which confirmed their existence, geometrical charateristics, and (meta-) stability. In the meantime, several explanations have been provided for explaining the surprising long lifetimes of these objects[78,79], the most recent being based on kinetics[50] (see Fig 6). Still, the subject is open and may very well give rise to new developments in the future, both theoretical and instrumental[75].

Transport in nanoslits: from linear to non-linear transport – Many results in nanofluidics have been obtained in the nanoslit geometry, where one dimension is typically in the tens of nanometre (down to a few nanometer in some cases), while the other dimensions are more standard to microfluidics. This is not our purpose here to review all of them. Transport of fluid confined in these nanoslits have been explored under various forcings, voltage drops, solute gradients, pressure drop, etc. which allowed to obtain a thorough picture of transport. These works have explored permselectivity effects[80], surface conductance and 'Dukhin' type of effects[3,81], streaming currents, electro-/diffusio-osmosis, capillary invasion[82], etc. Slippage during flow of polymers has also been investigated in nanoslits[49]. The overall picture is that linear transport is usually quite well described by the macroscopic concepts, except in the smallest nanochannels of a few nanometer in depth where anomalous ion transport was reported[83].

But beyond, the most exciting results certainly concern the non-linear response in these nanochannels, which proves to be extremely rich. A number of work have first demonstrated diode-like effects of ion transport under voltage drop in asymmetric channels, where either the surface is coated asymmetrically by different chemistry, or the geometry of channel is itself asymetric (like in conical nanopores), see Refs[3] and[4] for a thorough bibliography on this topics. At the level of the so-called Poisson-Nernst-Planck (PNP) framework, this behavior can be interpreted in simple terms with an analogy with PN junctions in solid-state materials, where the role of doping is played by the surface charges. In the end, such phenomena take their root in the couplings between ion transport and electrostatics inside the nanochannels, which is maximized when the height of the channels is small enough that an overlap of Debye layers occurs. It was shown recently that such ideas – which were demonstrated for ion transport – could be extended to osmotically induced flow, leading to the notion of *osmotic diodes*, where the osmotic pressure is an asymmetric function of the salt gradients along the nanochannels[84]. This points that many new functionalities could be invented on the basis of non-linear transport in nanochannels, with application in desalination, separation, ... Furthermore, it would be interesting to explore the couplings between chemistry and transport at the nanoscales, as commonly used in biological systems. In this line, a great challenge would be to build nanoscale device mimicking the functionality of ion pumps.

Another important non-linear effect is concentration polarization, which occurs when a nanopore transport selectively one ionic specie, while the other is left at the entrance, *e.g.* due to electrostatic repulsion. This non-linear behavior is usually thought as a nuisance, as it counterbalances the imposed gradients, like in ion-selective membranes. Such effects are subtle as they originate from the feedback coupling between electrostatics and ion transport[85]. But on the positive side, it was shown recently that they could be harnessed for filtration and desalination purpose by creating a so called 'shock electrodialysis'[86].

Entering the corridor: entrance effects – The discussion on concentration polarization points to entrance effects: nanopores are in one way or another connected to the oustide, macroscopic, world. This transition zone is at the root of an unexpected wealth of behaviors. Concentration polarization is one of entrance effects. But many others may occur. The effect of entrance resistance on ionic transport is known in the physiology literature since the works of Hille[87] and Hall[88], which show that the contribution of the entrance resistance can be dominating for nanopore with low aspect ratio (say, with a length smaller than their diameter). But this is not the end of the story and several recent results showed that the transport at the entrance couples in a subtle way to the inner transport. For example, the surface conductance inside the pore was shown recently to modify transport deep inside the bulk of the reservoir, thereby modifying deeply the conductance of a nanopore and possibly the translocation of macromolecules[89]. Another effect in the same line is the collective sub-additive nature of ionic transport across arrays of multi-pores[29]. In a different context, the hydrodynamic entrance effect could limitate the fast transport across nanotube[90]. But, as shown recently, the hour-glass shape of aquaporins was recently shown to considerably reduce this limiting effect and strongly increase the hydrodynamic permeability of a nanopore[91]. This points to the possibility of strongly increasing the permeability of membranes by a fine tuning of the (entrance) geometry of the pores.

These are just a few illustrations of unexpected entrance effects and this question would desserve a more systematic exploration, with potential interesting outcomes for applications.

Transport in nanomaterials: Fundamentals – In a seminal paper in Nature in 2001[63], Hummer *et al.* demonstrated the potential offered by carbon nanotubes as water conducting pores. This paper was followed a few years later by several experimental works which investigated the permeability of (large scale) carbon nanotube membranes, in particular in the groups of Hinds[18], Bakajin[17] and then by Whitby *et al.*[19]. These works demonstrated an unexpected ultra-high permeability of the CNT membranes, which is up to 4 orders of magnitude larger than expected with standard continuum predictions with no-slip bounary conditions. This groundbreaking result was even more unexpected as the tube diameter in these studies was sufficiently large so that continuum approaches are expected to work. Interpreted in terms of boundary slippage, it would correspond to a slip length in the range of a few hundreds of nanometers, up to microns ! This is at least one order of magnitude larger than the typical slip lengths measured on hydrophobic surfaces, as we discussed above. These results have generated some debate and a surge of activity to understand the origin of fast flows in carbon nanotube. We will not review them here, we refer to several reviews where some extensive discussions are given[3,61,62]. We will just quote here the results by Falk *et al.*[92], as they provide a basic theoretical understanding of this behavior, pointing the specificity of nanoscales for boundary effects. Analyzing in details the liquid-solid friction, Falk *et al.* showed that the water-carbon friction is strongly dependent on the curvature of the carbon interface: while the wall-fluid friction coefficient – inversely proportional to the slip length – does not depend on confinement for a flat graphene-like surfaces, the friction coefficient increases with the decreasing CNT radius for water *outside* the CNT, but – in a very unexpected way – it does strongly *decrease* for water *inside* the CNT as the radius decreases. The friction even becomes unmeasureable for tube radii below ~ 8 Å. This counter-intuitive effect was interpreted in terms of the coupled effects of an increased incommensurability between the water structure and graphitic surface for small CNT radii, together with a smoothening of the potential landscape. This is a truely nanoscale boundary effects, whose effects are expressed for CNT diameters below $\sim 10-20$nm.

In this context CNT are truely specific w.r.t. water conduction mainly because they exhibit a 'perfect' crystalline structure along their length, which is not the case of most nanoporous materials. This explains why these systems are so interesting in the context of nanofluidics, with specific properties which are not encountered with other nanomaterials. Beyond the theoretical and computational developments, these materials desserve therefore a systematic experimental investigation at the fundamental level, which is just starting.

One direction which is followed by several groups – as we already indicated in the previous section – is to explore more fundamentally the transport across individual nanotubes, as explored by various groups both on individual carbon nanotubes[35,36,38], and individual boron-nitride nanotubes (BNNT)[20].

Results on CNT reveal a number of unexpected behaviors, which desserve deeper investigations both experimentally and theoretically. These works focused merely on electric transport. Interestingly the conductance is found to increase typically as a power law of the salt concentration, like $G \sim c_{\text{salt}}^{\alpha}$ with $\alpha \sim 0.3$, which cannot be understood on the basis of standard framework, including *e.g.* usual surface conduction effects. In a recent contribution, Strano *et al.* also reported 'ion blocking' effects with current bursts: again, such effects cannot be rationalized within standard approaches.

BNNTs also revealed a number of surprises. In contrast to CNT, they were shown to exhibit very large, pH-dependent, surface charge, which suggests that the BN surface reacts to water in line with first ab initio studies[20]. Under salinity gradients along the nanotube, a giant electric current was measured. This effect can be rationalized in terms of difffusio-osmotic transport along the highly charged BNNT surface. This result could have a disruptive impact on the energy harvesting from salinity gradients, as we discuss below.

Altogether only a few groups have developed tools to explore the individual fluidic properties of these materials, in particular at the scale of the indivual object. But much work is still need on these materials, as still little is known *e.g.* on their permeability versus their geometric characteristics, or the nature of the confining material nanotube (carbon vs boron-nitride), etc. Many predictions have been put forward on the modelisation side, which still require further confirmation and/or understanding.

Another line of research has focused on the exploration of graphene-like materials for separation and desalination purpose[22,23]. A major challenge in membrane separation is to combine a high rejection – which requires small apertures for ion or molecule sieving – with a high permeability: reconciling these two properties is like squaring the circle. Graphene like materials offers a new opportunity to resolve this challenge. Graphene is a molecularly thin membrane in which subnanometric holes can be drilled[23]. In doing so, it can combine a high ion rejection and a high permeability due to the ultra-high gradients which are created across its molecular thickness, as confirmed by molecular simulation performed by Cohen-Tanugi and Grossmann[22]. Now first works started to adress experimentaly the behavior of graphene and graphene oxides surface[23,24]. While there are of course experimental difficulties to be solved, this is an emerging field with very high expectations.

Following these advances, a longer term research should focus on the coupling of fluid transport with the solid state properties of the confining materials. Such meso-scale properties may be expected to show up for nanometric nanotubes with the smallest dimensions. This line of research remains essentially a blank page.

4 The growing number of nanofluidic applications

In this section, we put in perspective a number of potential applications of nanofluidic phenomena, beyond the fundamental aspects discussed previously.

4.1 Nanofluidics and Membranes for separation, desalination and water purification

Membranes are at the heart of many separation processes[93]. For example, desalination of sea water is commonly performed on the basis of reverse osmosis, which consists in forcing the passage of salty water through a semi-permeable membrane: it rejects ions while letting water pass through it. As we discussed in the introduction, in these kind of games biological membranes in living systems – which make use of trans-membrane proteins as nanopores – have reached an efficiency in terms of selectivity and/or permeability, which artificial membranes hardly reach. Reverse osmosis processes typically use polymeric membranes, which are excellent in terms of salt rejection, but the (sub)nanometre pores required for ion separation considerably limitate the water flows. There is a gap to fill in order to reach the efficiency of bio-systems, with considerable impact on key questions for our society.

It is our belief that nanofluidics could propose out-of-the-box ideas to bypass the inherent bottlenecks associated with the usual approaches. For separation and desalination the key challenge is to develop technologies which combine high water flow and high ion rejection rate. First works along these ideas were performed using carbon nanotube membranes in the group of Bakajin *et al.*[94]. One difficulty is to fabricate large scale membranes of CNNT with adequate diameters for separation purposes, and at low cost. This has impeded up to now the development of this technology, although work is still ongoing in this direction. As we mentioned previously graphene-like materials could strongly impact this question. After the first simulation developed by Cohen-Tanugi and Grossman[22], this field is evolving rapidly with a number of experimental results which appeared recently, *cf.* works in the group of Karnik[23], or by Nair, Geim *et al.* on graphene oxide membranes[24].

In a different perspective, Karnik *et al.* recently developed membranes with nanobubbles acting as ion barriers[42,43]. They created a composite membrane with pores coated by a hydrophobic zone which is able to trap a gas bubble when immersed in water. Only volatile liquids like water may cross the gas barrier, while the membrane is impermeable to the non-volatile ionic solutes. An interesting point is that this type of configuration does not require the pores to be subnanometric for sieving. Then, while mass transport in low density gas phase is expected to be less efficient than in the high density liquid phase, the larger pore size yields *in fine* a very good permeability, while achieving ion rejection of 99.9%.

Another promising line of research consists in making use of *non-linear* (electrokinetic) transport properties in order to achieve separation. One example is the so-called shock electrodialysis by Bazant *et al.*, which takes benefit of non-linear structures induced by concentration polarization in order to purify water[86]. Another example is the idea of creating an osmotic diodes which can be obtained in asymmetric membranes, suggesting the possibility of voltage-induced reverse osmosis[84]. This remains to be explored experimentally.

Altogether these examples show how new nanomaterials and clever configurations may provide new views for aplication in desalination and separation purposes. It would certainly help to go beyond the basic views involving steric (and/or electrostatic) hindrance for sieving. Biomimetic approaches involving active transport process would be interesting to explore in this matter.

4.2 Nanofluidics and Membranes for energy harvesting

Another interesting application for nanofluidic concepts is in the field of sustainable energy harvesting. As discussed in detail in the review by Logan and Elimelech[95], membrane-based technologies are currently explored to extract electric power from the mixing of salty (sea) water with fresh (river) water. Two main processes are currently explored to this end: the so-called pressure-retarded osmosis (PRO) and reverse electrodialysis (RED). In the PRO approach one harnesses mechanically the ~ 30 bars of osmotic pressure which builds up across a semi-permeable membranes between the salty and fresh reservoirs. In the RED approach, the salinity gradient is made use to separate cations from anions across stacks of cation-selective and anion-selective membranes, thus creating directly an electric current.

In both cases membranes with sub-nanometric pores are required which – as for desalination purposes – considerably hinders the efficiency of the processes, which is at most of a few Watts of electric power per meter square. In this context it was shown that the efficiency of the process is considerably enhanced by using BNNT nanotubes as a membrane[20]. This increase takes its origin in the high charge measured on the surface of the confining BN surface, together with the relatively small length of BNNT. Furthermore, it was shown that the physical mechanism at play in this energy conversion does not require ion-rejection, as for PRO and RED, as it relies on the so-called diffusio-osmosis, which takes its origin at the interface of the tube. This is a key advantage for upscaling towards large-scale. The transfer towards large scale membrane of BNNTs remain to be developed to fully assess the viablility of these nanomaterials for osmotic power. But it demonstrates *de facto* how the coupling of nanofluidic transport with new materials may help inventing new avenues to bypass existing bottlenecks. The domain definitly needs new fundamental views, which the nanofluidic perspective can indeed provide.

4.3 Genomics and sequencing –

Sequencing is a fascinating application of single molecule technologies[4]. The subject pertains to nanofluidics in the sense that here, the goal is to control a nanoobject in a small cavity in a liquid. The gene sequencing market, whose size is several B$ is one of the largest markets that micro/nanofluidic technology has the capacity to impact on the short term. The critical issue being the speed of sequencing, operating at the molecular scale, where processes potentially much faster, makes sense. As we discussed above, a very fruitful line of research in this context has been the exploration of translocation of biological macromolecules, like DNA and proteins, through nanopores[4,64,72]. Beyond the biological nanopores like alpha-haemolysin, there has been a strong developement using solid-state nanopores and more recently using pierced graphene. This has become a domain on its own, although sharing a number of questions with nanofluidic transport. Confining such molecules in nanopores allows for a considerable increase in sensitivity with great hopes towards an effective DNA and protein sequencing. This is route followed by a number of companies, like Oxford Nanopore Technologies Ltd *. However, at the moment, the breakthrough taking place in the field of DNA sequencing follows alternative routes. For example, the idea developed by Pacific Biosystems † consists in detecting each step of hybridation performed by a single polymerase, covalently bonded to the bottom of a zeromode cavity, duplicating the unknown DNA strands. This performance can be achieved thanks to the development of new techniques, allowing to label individual nucleotides with a specific wavelength. The speeds that are obtained with this approach allow to sequence the human genome in a few hours, at a cost of several hundreds of dollars. Nonetheless, since other disruptive technologies are developing in the meantime, it is difficult to say which sequencing platform will be used in the future. It remains that, at the moment, the evolution of the technology is so rapid that the development of genomic-based personalized medecine can be seriously envisaged in the mid-term.

4.4 Nanobubbles

While the scientific community was striving to explain the stability of nanobubbles *at surfaces*, in the meantime, a number of groups reported lifetimes of several days for nanobubbles *in the bulk*[96] (- see a short discussion by[97] -). The arguments developed for surface nanobubbles do not apply for bulk and therefore, at the moment, such observations, if confirmed, raise a new puzzle. In the meantime, a number of companies attempt to support the idea that bulk nanobubbles interact advantageously with living systems, speculating on mechanisms based on oxygen transport or engulfing. The situation seems quite intriguing at the moment.

4.5 Nanostructured superhydrophobic surfaces

The field of superhydrophobic surfaces, which has exploded recently[98,99], shares a number of common interest with nanofluidics: both in terms of nanofabrication and investigation techniques.

It is also a more mature domain, which illustrates well the idea that submicron behavior, here associated with multiscale surface textures, may give rise to groundbreaking applications.

Superhydrophobicity has been studied for a long time, the traditional example illustrating the phenomenon being the Lotus leaf. Lotus leaves have doubly structured surfaces, including multiscale micrometric and nanometric repellent structures that force the liquid sitting on the surface to develop a solid/air/liquid sandwich stabilized by the roughness. It is well known that this structure, which has been mimicked on artificial systems in many different manners, gives rise to frictionless and antiadhesive properties (see for instance[98,99]). Droplets roll and bounce over superhydrophobic surfaces almost without friction nor adhesion, while liquids develop large slippage phenomena on them, with slip lengths ranging between 1 and several hundreds of micrometers[100]. Preparing such surfaces for industrial applications has long been thought as a formidable challenge, but recently, several companies have found ways to unlock the bottleneck. Recently, Liquiglide Inc. ‡ was able to demonstrate that spraying surfaces with hydrophobic particles, a binder and, in most cases, and a liquid trapped by the structure, confers superrepellant properties suitable for developing groundbreaking applications in oil, food, aeronautic, and automotive industries. According to the company, the technique has the potential to avoid the formation of one hundred million of tons of food waste on the planet.

4.6 Transport in unconventional oil and gas reservoirs

An interesting, though fully unexplored, domain of application of nanofluidics concerns the field of oil and gas production from unconventional reservoirs. Over the last 5 years, there has been a huge surge of industrial activity on the extraction of oil and gas from deep shale formations. This is not an overstatement to say that this new source of hydrocarbon is revolutionizing the world energy balance[102], with deep geopolitical and societal implications – not to speak about the tense debate that it has generated in many countries –.

From the scientific side, still very little is known on the transport processes at play during the extraction. But a specificity of these so-called 'unconventional' reservoirs is that they exhibit extremely low permeability[101]. Hydraulic fracturing is accordingy used to open and maintain transport channels. One key question is the predictability of oil recovery in terms of flux or composition in order to forecast the production. The use of water as a fracking liquid may also be questioned, not only for the efficiency of the process, but also in the context of the environmental issues that it raises.

The permeability quantifies the relationship giving the velocity of the fluid – here a gas or oil – driven under a given

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* `http://www.nanoporetech.com/`

† `http://www.pacificbiosciences.com/`

‡ `http://www.liquiglide.com/`

pressure gradient:

$$v_f = \frac{k}{\eta} \times (-\nabla P) \tag{1}$$

which is usually known as the Darcy equation. Here k is the permeability and η is the viscosity of the fluid under consideration. The permeability is a key input quantity to predict extraction. It has the dimension of a length squared and is measured in Darcy units, 1 Darcy being $10^{-12}\mathrm{m}^2$. In a linear pipe, the permeability would be roughly given by the square of the tube diameter according to Poiseuille law. In disordered – percolating – porous media, an estimate for k has to account for the main flow path and its 'degeneracy' [103]. But while conventional reservoirs exhibit permeabilities in the milli-Darcy range, unconventional reservoirs rather stand in the *tens of nano-Darcy*. This is associated with pore sizes of the gas reservoirs (the so-called 'kerogen') which lies in the nanometer range, from 50nm down to subnanoscales, as confirmed by various experimental characterizations of the pore structure [104].

Transport models of alcanes in such confinements have to be fully revisited in order to be able to forecast the gas and oil production from shale [102]. This is a challenge that the oil industry is now facing and this crucially requires scientific inputs. Furthermore, the domain completely lacks of relevant 'model' experiments of alcane transport at the nanoscales in order to benchmark the corresponding transport models, in the same spirit as microfluidic devices were used to benchmark enhanced oil recovery from conventional reservoirs. This is a blank page with huge impact.

5 Conclusion: (R)evolution is down the road ?

We may summarize the review in the following way:

- *From a physical prospective, nanofluidics is an extremely rich domain*
  Nanofluidics hosts many mechanisms acting at the nanoscale, that combine together or interact with the confinement to produce new phenomena. Over the last few years, new surprising effects have been discovered while, in the meantime, others were confirmed : superfast flows in CNT, osmotic energy conversion in BNNT, nonlinear transport, slippage over smooth surfaces, nanobubble stability,... Some of them are still awaiting an explanation. In the future, we may speculate that novel combinations of nanoscale mechanisms will be explored, or new geometries and physico-chemistry environnements will be considered, giving rise to the emergence of novel physical phenomena.

- *In the nanofluidic realm, technological barriers are high but the field becomes increasingly accessible*
  The evolution of nanofluidics is slow because the fabrication of nanochannels is most often a tour-de-force, slow and costly and the control and characterisation of the nanoflows is difficult. Will there be a breakthrough in this field, that would faciliate the fabrication of nanofluidic systems, in a way comparable to PDMS revolution in microfluidics [25], that allowed, in some sense, to do microfluidics in the kitchen ? This is uncertain, but the accumulation of technological skills along with the use of new nanofluidic materials (like nanotubes or graphene) will undoubtedly make nanofludics increasingly accessible.

- *Instrumentation is delicate, new ideas are coming and novel views are welcome*
  Characterisation of nanofluidic systems is delicate because they operate below the diffraction limit, which precludes the possibility to study them with standard optical instruments. Nonetheless, near field microscopy and interferometric measurement allow to circumvent the difficulty, without requiring sophisticated equipment. Other techniques (SFA, AFM,..) remain delicate but new methods are being invented, facilitating the access to observation. Still, new ideas are needed to produce a leap in this domain.

- *We are witnessing tremendous success of nanofluidic applications.*
  Despite the existence of high technological barriers, nanofluidic researchers have found pathways to develop tremendously succesful applications. To-day, in view of the markets that are targeted, nanofluidics may very well impact the industry more than microfluidics. This would represent an unexpected paradox. These successes rely on using variety of materials and technologies, using state of the art nanofabrication (for example, for DNA sequencing), or low tech inexpensive approaches (for example, for elaborating superhydrophobic surfaces). Here we learn that, even though technology may, at first sight, look delicate and expensive, it still can find a market of important size in which it is competitive. Also, the performances of a nanofluidic technology can be degraded without loss of disruptive potential. In the future, with the realisation of new membranes, single molecule separation device or complex nanochips, there will be opportunities for nanofluidics to produce new groundbreaking innovations.

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