REVIEW

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Nanofluidics: what is it and what can we expect from it?

Abstract Starting from the background of nanofluidics in other disciplines, this paper describes the present state of research in this field and discusses possible directions of development. Emphasis is put on the very diverse background of nanofluidics in biology, chemistry, physics and engineering and the valuable knowledge available in these disciplines. First, the forces that play a role on the nanoscale are discussed and then a summary is given of some different theoretical treatments. Subsequently, an overview is given of the different phenomena occurring on the nanoscale and their present applications. Finally, some possible future applications are discussed.

1 Introduction

Nanofluidics is often defined as the study and application of fluid flow in and around nanosized objects. Actually, nanofluidics is not new, but has been around—without a name of its own—for quite a number of years, being implicit in many disciplines. The fact that this previously implicit science of nanoscale fluid flow recently received a name of its own is, however, due to the rise of microfluidics in the 1990s and the recent advent of nanoscience and nanotechnology. The invention and wide availability of many new technological tools like atomic force microscope (AFM) and scanning tunnelling microscope (STM) (both for inspection and creation of nanostructures), the electron, x-beam and

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ion-beam lithographs, and the development of new micromachining techniques like soft lithography and bottom-up assembly methods has made the study and application of nanofluidics much more accessible, and allows a previously unknown measure of control on the nanoscale. Expectations of what we can expect from this new field are, therefore, high.

While looking forward to future fruits, it is important not to forget the roots of nanofluidics, which it has in many other disciplines. How this may easily happen is illustrated by the recent rediscovery of two classical colloid chemistry phenomena, co-ion (Donnan) exclusion (Pu et al. 2004) and semipermeability (Daiguji et al. 2004), in experiments with and simulations for nanochannels. The authors, clearly, were not aware of the classical literature on these subjects, which shows how easily it can be overlooked by nanofluidic investigators exploring their new field. However, it is of great help to depart from the knowledge already gathered. Another reason to start with the roots is to better be able to identify the places where there is growing potential for "modern" nanofluidics. This could, for example, be the case if there is a new and still unexplored area of science or a new area of applications that can only now be opened up by using the newly available nanotechnological tools. The impressive array of nanofluidic applications that already exists, and which are described at the end of this paper, certainly, has resulted from the application of these new tools, and it is quite reasonable to expect that there is a lot more to follow.

Figure 1 shows a schematic diagram indicating a great number of classical disciplines (and one recent one) where knowledge on nanofluidics can be found. For each discipline, some phenomena studied relevant for nanofluidics are mentioned. The disciplines represent an enormously diverse array, demonstrating the multidisciplinary approach that is needed for nanofluidics research. The diversity of the fields also presented the authors with a big problem in writing this paper, since the field is just too broad to represent in a single paper—even a whole book would not be enough. We

250

Fig. 1 Classical disciplines related to nanofluidics and some of the relevant subjects studied
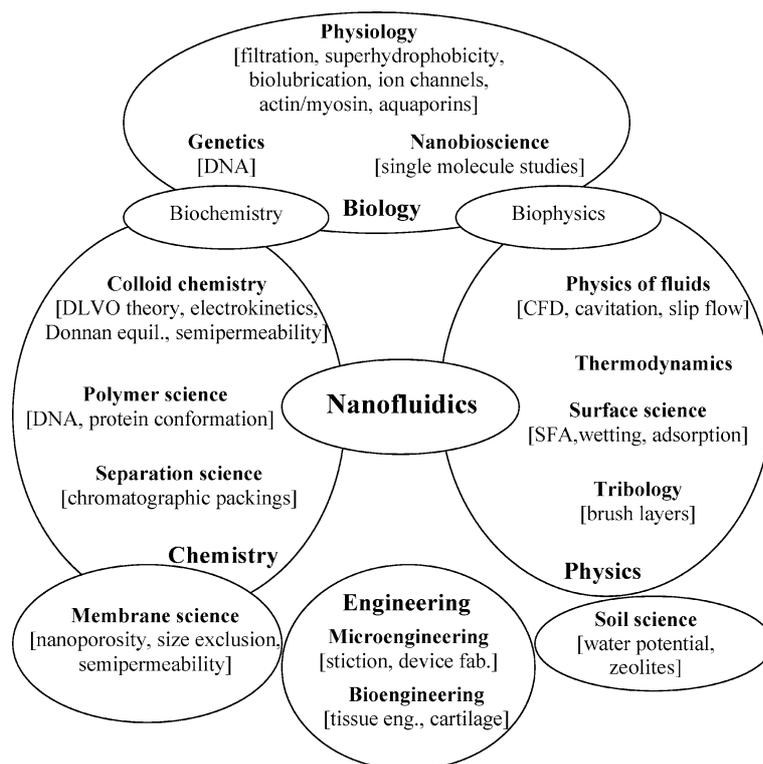
therefore chose a broad brush, i.e. tried to show the main lines, which was also necessary since we are specialists in none of the indicated disciplines, except, perhaps, micromachining. Furthermore, we tried to illustrate the text with as many examples as possible, and to refer to good reference papers where possible.

We want to specifically mention biology as a discipline important for nanofluidics. Biological organisms on their primary cellular level function in a nanofluidic environment, and the solutions that have been found after billions of years of evolution deserve a thorough inspection. For example, nature found a way to harness Brownian motion, which creates a very noisy environment at the molecular scale for active transport (Magnasco 1993). But nature's inventions are not limited to the molecular scale. We will also mention amazing biological examples in this paper that happen at a larger scale (e.g. snapping shrimps and superhydrophobic beetle wings), but which still have nanofluidic implications. All of this truly demonstrates "natura artis magistra," actually much more so in nanofluidics than in nanoelectronics.

Using literature from the classical disciplines mentioned above and shown in Fig. 1, this paper will first summarise the main forces that play a role at the length scales of importance to nanofluidics. Subsequently, it will take an inventory of some theoretical descriptions that are around, and then of the phenomena that these forces give rise to. In the next section, nanofluidics applications of these phenomena will be reviewed and discussed. Finally, at the end of the paper, we will venture into a bit of extrapolation and crystal ball gazing to identify possible new applications of nanofluidics.

2 Nanoscale forces

Many forces are generally distinguished that play a role on the nanoscale (Israelachvili 1992a, 1992b). They can be exerted by walls on particles or solvent molecules or nearby walls, or by the particles and molecules on each other. These forces will govern the behaviour of the molecules or particles in nanostructures, and nanofluidic theory has, therefore, to start with a discussion of these forces. They can give rise both to equilibrium phenomena, like differences in ionic distribution, or kinetic phenomena, like (macroscopic) viscosity. In his excellent book on intermolecular and surface forces, Israelachvili remarks that, although our distinction of these forces in the end is somewhat artificial, since all of them are electrical in nature, such distinction still makes a lot of practical sense because of the many different ways in which the electrical force presents itself (Israelachvili 1992b). Figure 2 gives a schematic representation of a number of forces acting on the nanoscale, expressed for the case of interaction between a spherical particle representing an AFM tip and a flat surface, which is taken from an introductory paper on AFM (Heinz and Hoh 1999). The approximate spatial extension of the forces, generally, is as indicated in the force–distance curves, i.e. reaching furthest for the brush and electrostatic forces, and the least far for the van der Waals forces.

The complete picture of nanoscale forces has been built up slowly in the past century. In the 1940s, Derjaguin, Verwey, Landau and Overbeek developed the DLVO theory, which accounts for the two major forces acting in the nanometre range between surfaces, namely, electrostatic forces and van der Waals forces (Derjaguin and Landau 1941; Verwey and Overbeek 1948). Electrostatic forces act as far as the electrical double layer extends, which is typically from 1 nm to 100 nm, depending on the electrolyte concentration, and are either repulsive or attractive. van der Waals forces predominantly act at distances smaller than 2 nm and are always attractive. The DLVO theory has been, and today, still is, very successful in providing the theoretical framework for observed behaviour of colloid interaction and stability. A dynamic reinterpretation of this essentially static theory has recently been presented, connecting it with electrokinetic phenomena (Lyklema et al. 1999).

Very important contributions to our knowledge of nanoscale forces have come from the use of the surface forces apparatus. In 1954, Derjaguin devised a surface forces apparatus (SFA) consisting of a hemisphere and a surface of polished quartz that could be brought into close proximity (100 nm), the distance being measured by interferometry and the force by an elaborate feedback mechanism (Derjaguin et al. 1954, 1956). This device allowed the direct measurement of electrostatic and van der Waals forces. In the following decades, it was improved by different groups with qualitative jumps in design being made by Tabor and Winterton in 1969 and Israelachvili and Tabor in 1972, who used two crossed cylinders of atomically flat mica (Israelachvili 1992b; Israelachvili and Tabor 1972; Tabor and Winterton 1969). The cylinders could be brought into close proximity (with an accuracy of 0.1 nm measured by interference), which allowed precise measurement of both the shear forces and the normal forces between the surfaces.
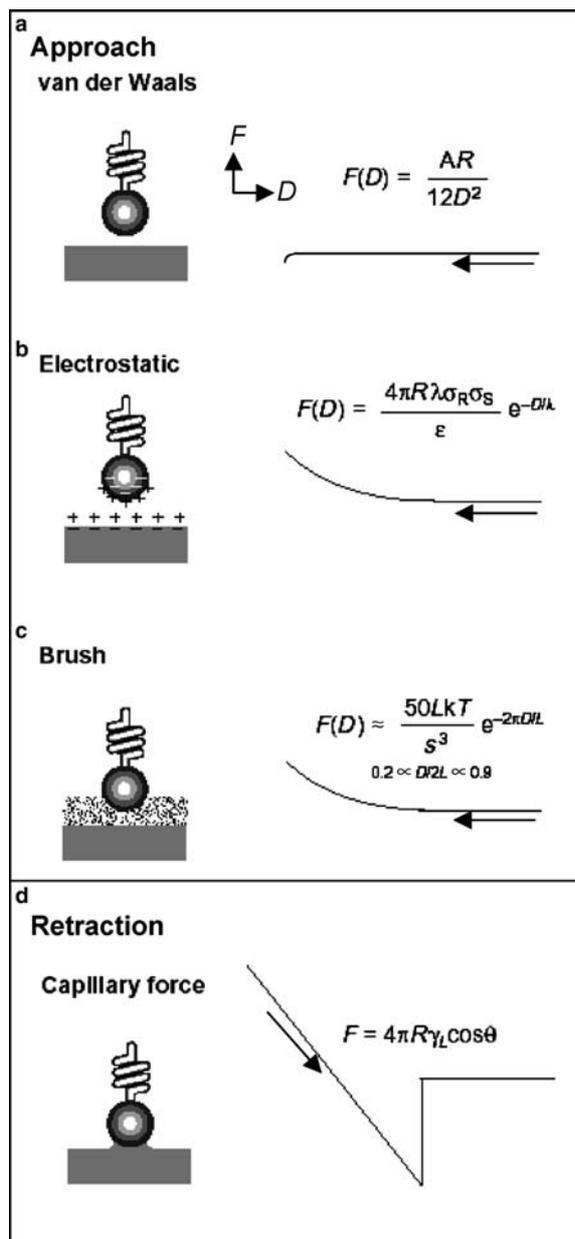
Using the SFA, a new range of forces could now be directly observed and quantified. Thus, solvation forces were observed, representing the attachment of layers of solvent molecules to the surface, which extends several layers into the solution. Such layering gives rise to a certain "quantization" of both the static and the dynamic behaviour, corresponding to the resistance of subsequent liquid layers against being pushed away, or to the sliding of ordered liquid layers past each other (Israelachvili 1992a; Israelachvili et al. 1988). Hydration forces were observed as well, occurring when ionic surface sites or ions in the liquid resist dehydration, but still allow the exchange of one bound water molecule for another, thus, acting more or less like "molecular ball bearings" (Raviv and Klein 2002). Also observed were steric repulsive forces due to entropic stabilization, exerted by freely fluctuating polymer brushes attached to the surface (explained by the Alexander–de Gennes theory) (de Gennes 1980, 1987; Alexander 1977; Taunton et al. 1990). Hydration energy can contribute to the repulsion when the polymer brushes are well hydrated,

as is the case with polyethyleneglycol (Morra 2000). If the brushes carry charged groups, an osmotic pressure is built up, also pushing other surfaces away (Miklavic and Marcelja 1988; Pincus 1991).

The measurements with the SFA, thus, added much to our knowledge about surface forces in the nanodomain, and the resulting picture has a large practical relevance. Brush surfaces can, for example, be of great importance in tribology to decrease friction. In biology and medicine, joint lubrication is an important area of investigation and it is thought that hydration forces of the charged surfaces aid in this (Raviv et al. 2003).

A very strong force that has not yet been mentioned is the capillary force, which originates in the adhesion between the liquid and the solid surface molecules, and the cohesion between the liquid molecules. When both surfaces of an SFA are connected by a liquid bridge, it is energetically favourable for the liquid to minimise its surface area exposed to the air, resulting in an attractive force strong enough to overcome all but the last few solvation layers (Wanless and Christenson 1994) (see Fig. 2d).

Above, we mainly considered forces that are normal to the surface of the SFA, which are important in static conditions. However, shear forces on the nanoscale have also been proven to be different from the macroscopic domain. These forces can be measured when the surfaces of the SFA are moved with respect to each other. Above, we already mentioned a certain quantisation of the dynamic behaviour that was observed when molecular layers slide along each other, and we also mentioned the lubricating effect of polyelectrolytes and hydrated ions. More in general, for simple Newtonian liquids, friction is seen to increase from the macroscopic value when the separation between two surfaces becomes less than, roughly, ten molecular layers. A change in film properties from liquid to solid-like behaviour is often but not always seen, occurring e.g. for alkanes but not for alcohols (Klein and Kumacheva 1995; Mugele and Salmeron 2001). The shape of the molecules seems to determine this, with symmetrically shaped molecules ordering themselves in neat layers and turning into a quasi-solid, but asymmetrical ones remaining in a disordered liquid state (Israelachvili et al. 1990). It should be remarked that, for the experiments mentioned, atomically smooth surfaces are used, in contrast to most practical experiments where surfaces will be rough. Surface roughness is one of the reasons for the hysteresis that is often observed in approach/separation processes like wetting/dewetting, adhesion/decohesion and advancing/receding of the contact angle (Israelachvili 1992b; Israelachvili et al. 1988). Another important issue in nanofluidics is that, sometimes, the liquid is observed to slip past the surface, decreasing the fluid resistance (Schnell 1956; Churaev et al. 1984). A good review of this phenomenon is presented by Vinogradova (1999). In this case, the commonly used boundary condition of zero wall velocity is no longer valid and, in the theoretical description, a so-called slip length has to be

a Approach
van der Waals

$$F(D) = \frac{AR}{12D^2}$$

b Electrostatic

$$F(D) = \frac{4\pi R \lambda \sigma_R \sigma_S}{\varepsilon} e^{-D/\lambda}$$

c Brush

$$F(D) \approx \frac{50 L k T}{s^3} e^{-2\pi D/L}$$

$$0.2 \propto D/2L \propto 0.9$$

d Retraction

Capillary force

$$F = 4\pi R \gamma_L \cos\theta$$

◄

Fig. 2a–d Examples of AFM force curves and the force laws used to interpret them. Notice that the curves are shown as force versus sample position curves, which is the most common way in which they are displayed in literature. However, the force laws are all functions of the separation distance, D. **a–c** Approach curves. **d** Retraction curve. **a** An ideal, attractive, van der Waals force in the absence of other forces (Israelachvili 1992b). **b** Repulsive electrostatic double-layer force in solution (Israelachvili 1992b). **c** Polymer-brushing forces that result from the thermally driven motion of polymers grafted onto a solid surface in solution (Israelachvili 1992b). Capillary adhesion (very common under ambient conditions, under which many surfaces have thin layers of water) results from the formation of a water bridge between the tip and sample (Israelachvili 1992b). Symbols used: A Hamaker constant, D probe–sample separation distance, R probe sphere radius, L brush thickness in a good solvent, k Boltzmann's constant, T absolute temperature, s mean distance between polymers, ε dielectric of the medium, λ Debye length of the medium, σ_R surface charge density of sphere, σ_S surface-charge density of surface, γ surface energy between sphere and surface. Picture and legend adapted with permission from Heinz and Hoh (1999)

circumstances to study molecular properties or to obtain devices with a special function. In the field of biophysics, many studies are performed on the mechanical properties of single molecules, and especially DNA, using optical and magnetic tweezers and microfibres, apart from the AFM. The typical forces and temporal and spatial resolution that can be reached by these different methods, as well as some experimental results obtained, can be found in an excellent review by Strick et al. (2000). Dielectrophoretic forces, generated in rapidly changing high electrical field gradients and resulting from differences in dielectric properties between particles or molecules and medium, can also be of considerable strength (Pohl 1978).

Forces of lesser importance on the nanoscale are the gravitational and inertial forces. Table 1 presents a few dimensionless numbers that are useful at the length scale above approximately 2 nm, where continuum theory can be applied (Oosterbroek 1999; Mela et al. 2004). The length order of 2 for the Bond number and 3 for the Grashof number indicate that gravitational forces are generally negligible in nanofluidic systems. To a lesser extent, the same holds for inertial forces, as indicated by the length order of 1 for the Reynolds number and the Weber number. The ratio of viscous and surface tension forces does not scale with length, as indicated by the capillary number, and, hence, is not affected by down-scaling.

introduced (Vinogradova 1999; Spikes and Granick 2003).

Atomic force microscopy (AFM) has recently become the most outstanding method for measuring surface forces because it enables measurements in a short time span and with a high spatial resolution, and also allows for non-transparent materials to be investigated (Heinz and Hoh 1999). A disadvantage of AFM compared with SFA is its lower sensitivity, which is the necessary trade-off for the high spatial resolution (Heinz and Hoh 1999). AFM, SFA and other experimental techniques for measuring surface properties have recently been compared in a review by Fröberg et al. (1999).

Apart from the forces mentioned above that occur in practically every nanofluidic system, a number of other forces can be specifically employed in experimental

3 Theoretical descriptions

The forces that determine the behaviour of any system are, ultimately, always the forces between the individual atoms. Ultimately, every system will, therefore, be best described by a model that accounts for all the individual atomic interactions. In practice, this is, however, still out of reach due to the available computational power limiting system size to, say, 10 nm. Luckily, above this

Table 1 Overview of dimensionless numbers and their relation to the dimension length (at constant velocity); β thermal expansion coefficient $(1/K)$, γ surface tension (N/m), η dynamic viscosity (Pa s), ρ mass density (kg/m^3), T temperature (K), g constant of gravity (m/s^2), l (characteristic) length (m), v velocity (m/s). Adapted from the more comprehensive list in (Oosterbroek 1999)

Group	Abbreviation	Definition	Interpretation	Order length
Bond number	Bo	$\frac{g(\rho_l-\rho_v)l^2}{\gamma}$	Ratio of gravitational and surface tension forces	2
Grashof number	Gr_L	$\frac{g\beta\rho^2(T_s-T_\infty)l^3}{\eta^2}$	Ratio of buoyancy to viscous forces	3
Reynolds number	Re_L	$\frac{\rho v l}{\eta}$	Ratio of the inertia and viscous forces	1
Weber number	We	$\frac{\rho v^2 l}{\gamma}$	Ratio of inertia to surface tension forces	1
Capillary number	Ca	$\frac{v\eta}{\gamma}$	Ratio of viscous and surface tension forces	0

scale, systems can very often be described with continuum theory, which statistically averages the single interactions. As mentioned in the preceding section, deviations from the predictions of classical continuum theory have been observed for both the static and dynamic behaviour of a liquid confined in a space smaller than 10 molecular diameters, where molecular layers start being quantised. Molecular dynamics (MD) simulations are, therefore, appropriate for such systems and can successfully be applied to explain such deviations (Israelachvili 1992b; Schoen et al. 1989). Recently, MD simulations were, for example, used to model both electro-osmotic and Poiseuille flow in small diameter (2-nm radius down to 0.95-nm radius) nanochannels (Lyklema et al. 1998; Thompson 2003; Qiao and Aluru 2003). One interesting outcome predicted a reversal of the direction of the electro-osmotic flow for 3.5-nm wide slit channels (Qiao and Aluru 2004). MD simulations have also been employed for the description of liquid flow in even smaller 0.24 nm inner diameter (6, 6) carbon nanotubes (Kalra et al. 2003) and in the aquaporins that conduct water through cell walls (Tajkhorshid et al. 2002). Figure 3, for example, shows a molecular dynamics simulation of water molecule transport in aquaporins, illustrating the reversal of the orientation of the water molecules halfway down the single file they form inside the channel. This reversal in orientation is thought to prevent proton conduction by the Grotthus mechanism (Tajkhorshid et al. 2002). Single-file motion of water is predicted by MD simulations of carbon nanotubes, aquaporins and also for nanochannels naturally occurring in zeolites (Demontis et al. 2004).

In general, the molecular-scale visualisations that we have of nanoscale systems, and that we also employ in some figures in this paper, arise from MD simulations. MD calculations can also be used for larger systems, however. In particular, recent MD calculations (with modern computing power, up to 100 million atoms can be considered) have been shown to be capable of describing phenomena induced by thermal fluctuations related to Raleigh–Taylor instabilities that may provide insight in turbulent behaviour as well as nanoscale heat transfer (Kadau et al. 2004).

One length scale larger, we have systems between 10 nm and 100 nm. Smooth-walled liquid-filled channels of simple geometry and greater than 2 nm in diameter can conveniently be described using classical Navier–Stokes theory, while accounting for electrostatic effects by the Poisson–Boltzmann equation. However, almost all real systems will be more complicated than this, either in geometry or composition. To tackle such problems, a large number of computational methods is available. Especially, the lattice Boltzmann equation has been proven useful for the description of mesoscale systems with complicated geometry and composition (Succi 2001).

The description of liquid behaviour in the above-mentioned ''simple'' nanochannels can, in the absence of electrical double-layer overlap, be found in physical chemical literature, e.g. in the classical textbook of Kruyt (1952), the more recent book of Hunter (1993) and in works on physicochemical hydrodynamics (Le-
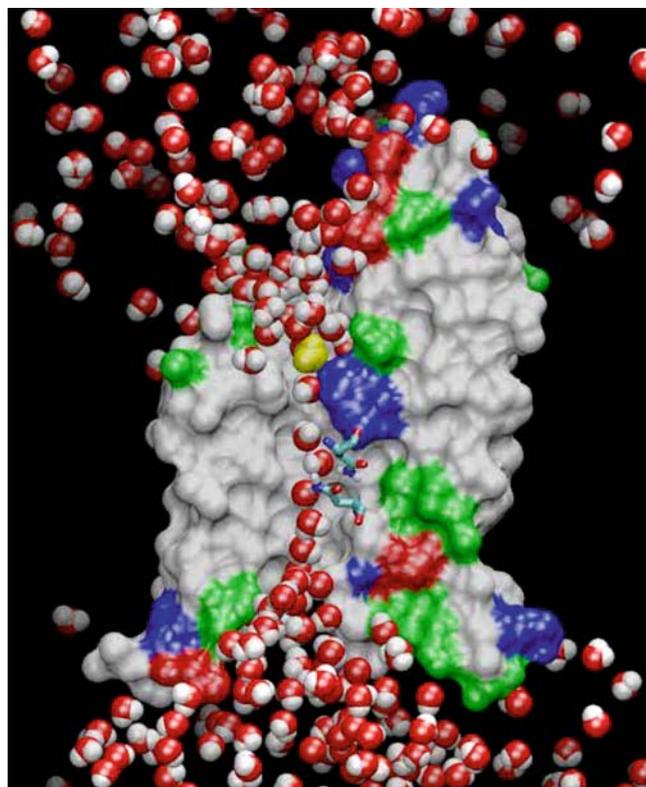

Fig. 3 Snapshot of the single water file moving through an aquaporins molecule residing in the liquid bilayer of a cell. This image is a still from the movie published at http://www.ks.uiuc.edu/Research/aquaporins/

vich 1962; Probstein 1994). When double-layer overlap occurs, more or less large corrections are necessary. For the static situation, they were already derived in the 1950s as an extension of the DLVO theory. In the 1960s, theoretical papers appeared presenting electrokinetic theory for nanoslits and nanochannels (Burgreen and Nakache 1964; Rice and Whitehead 1965). They modelled the electroviscous effect, predicted the electro-osmotic flow profile in such channels (which tends to become parabolic) and gave corrections for the contribution of surface conductivity to the total conductivity (Lyklema 2001). This work was later extended for a larger range of experimental circumstances by the application of numerical simulation tools (Levine et al. 1975; Fievet et al. 2000). The macroscopic equilibrium distribution of ions between two systems with different concentrations of fixed charge was derived by Donnan (1924) ("Donnan equilibrium"), and can conveniently be found in physicochemical or colloid chemical textbooks. A Donnan equilibrium will exist between the solution in a channel with overlapping double layers and a connected reservoir. It is important to realise that it also entails the creation of an osmotic pressure difference.

Considering two-phase flow on the nanoscale and adsorption and film flow on solid surfaces, a large body of experimental and theoretical knowledge has been accumulated in the old Soviet Union, which was recently made more available (Churaev 2000). An interesting discussion is, for example, going on concerning the thickness of stationary water films adsorbed on glass or quartz surfaces. Consensus seems to have been reached that surface cleanliness plays an important role. Thus, it was reported that, at high relative humidity, films of more than 100-nm thick can be formed on freshly cleaned surfaces, but that a few days storage in air will reduce the maximal thickness to less than 10 nm (Gee et al. 1990; Churaev 2003). Much theory on two-phase and three-phase flow (of importance for the petrochemical industry), including the contributions of corner flow and film flow to the hydraulic conductivity in pores, can also be found in soil science (Tuller and Or 2001; Ransohoff et al. 1987). A unified mathematical theory on the long-scale evolution of moving thin liquid films is presented by Oron et al. (1997).

In this theoretical context, it is interesting to mention the recent use of a dusty liquid plasma to model fluids on the nanoscale (Morfill et al. 2004). Though this method will not be accessible to many, the charged microparticles visualised in the streaming plasma on the microscale can possibly act as an analogue computer for the kinetic movement of liquid molecules on the nanoscale.

4 Phenomena

As a result of the palette of forces that act on the nanoscale, a whole range of phenomena specifically occurs on this scale. As already mentioned in the intro-

duction, these phenomena have been discovered in many disciplines through the years, and many devices and apparatus are based on them. In nature, this is the scale of the cell machinery and the cell processes are governed by them (Ciofalo et al. 1999). This section will present an overview; we are by no means pretending that it is exhaustive since the literature presents us with a truly dazzling array. Phenomena and examples will be taken both from the classical disciplines where nanofluidics was implicitly present (including biology) and from "modern" nanofluidics.

4.1 Surface-energy-related phenomena

When devices are scaled down to nanometre dimensions, the surface-to-volume ratio increases and surface-related phenomena will become increasingly dominant. An interesting phenomenon observed during two-phase flow in nanochannels is the generation of capillarity-induced negative pressure (Tas et al. 2003). Negative pressure in first instance sounds impossible, and, in fact, it is impossible for gases where zero pressure at vacuum is the lowest attainable. Liquids and solids however can be put under tension, i.e. they can exist at negative pressures (Imre et al. 1998). Such pressures were observed in devices where the thin channel roofs were deformed by the negative pressure in a capillary liquid plug. Figure 4 shows the tongue-like shape of the meniscus observed in 100-nm high nanochannels due to the bending of the
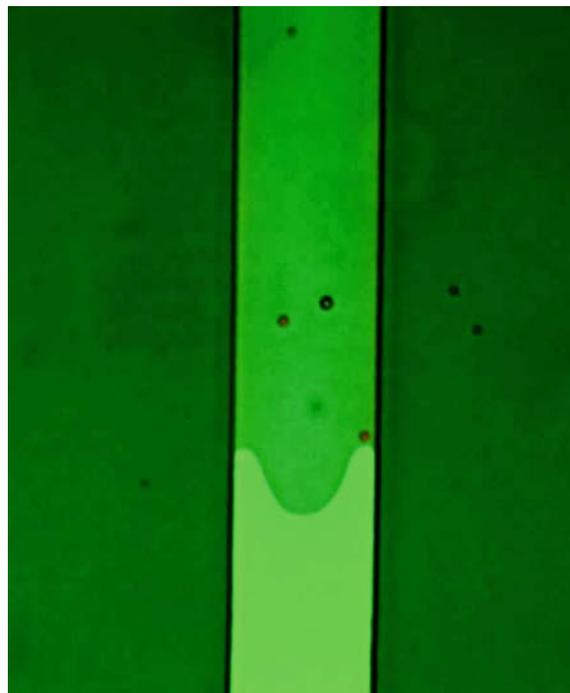

Fig. 4 Optical micrograph of a water plug (*dark colour*) in a 108-nm high thin-roofed nanochannel. The strange meniscus shape is due to deflection of the channel roof by the large negative pressure (−17 bar) in the water plug

830-nm thick and 10-μm wide silicon nitride capping layer under the influence of the negative liquid pressure. Calculating the pressure from the meniscus curvature using the Young–Laplace equation, a value of −17 bar was derived. According to the Kelvin equation, the negative pressure will be inversely proportional to the capillary height (Mercury et al. 2003). In micromachining, the large negative pressures that can be generated in thin layers of drying water can cause stiction (Tas et al. 1996).

Interestingly, the water behind a meniscus with a 50-nm radius is at equilibrium with water vapour of 98.9% relative humidity, according to the Kelvin equation (Derjaguin and Churaev 1974). At a higher relative humidity, atmospheric water will, therefore, condense in the nanochannel, a phenomenon called "capillary condensation." The thermodynamic energy of water in pores or channels is determined by the capillary pressure and the osmotic pressure, and, in soil chemistry, it is customary to use the matric potential ($J kg^{-1}$) to describe the resulting liquid water energy (Tuller and Or 2001). In thermodynamics (J/mol) and in biology (J/m^3 or water potential), other units are customary to express the specific water energy. Movement of water in films, corner flows or bulk as a result of gradients in the water potential is much investigated in soil chemistry (Tuller and Or 2001; Or and Tuller 2003) and in physical and colloid chemistry, where nanocapillaries provide a good experimental model (Churaev 2000). The subject of negative pressure is also intimately connected with cavitation in liquids. Cavitation is generally thought to occur when seeding nanobubbles expand (Trevena 1987). However, bubbles of sufficient size cannot occur in nanochannels of constant cross section and contact angle, where all bubbles, ultimately, will collapse (Tas et al. 2003). Cavitation has also been studied with the SFA by creating large negative pressures (Chen and Israelachvili 1991).

In the Nanoscale forces section, we already mentioned the slip flow that can occur at the (sub) nanometre scale. Slip can occur both at atomically flat surfaces, e.g. at high shear rates (Zhu and Granick 2001) and at hydrophobic rough surfaces where air pockets can remain (Vinogradova 1999; Watanabe et al. 1999), or a very thin vapour layer can adhere (de Gennes 2002). Interestingly, MD simulations of the movement of single water files through (6, 6) carbon nanotubes indicate that slip will also occur at this scale because the water molecules interact more strongly with each other than with the walls (Kalra et al. 2003). In these simulations, the flow resistance actually proved independent of nanotube length for lengths from 1 nm to 4.5 nm.

The liquid/solid contact angle depends on both the surface material and its roughness. Even when the material is only slightly hydrophobic, the introduction of surface roughness can result in a contact angle close to 180° (Bico et al. 1999). In non-equilibrium situations, even hydrophilic materials can behave strongly hydrophobic if they have a high roughness (Herminghaus

2000). When the effect is combined with a low roll-off angle of water drops, it is called superhydrophobicity or the "lotus effect" (Marmur 2004). Microstructuring or nanostructuring can be used to create such surfaces, and it is best to combine roughness on different length scales (Lau et al. 2003). In nature, Lotus leaves use this effect for self-cleaning, since the rain drops that roll off the leaves take dust particles and microorganisms along (Barthlott and Neinhuis 1997). Interestingly, the beetle Stenocara living in the arid Namib desert has specially designed wing surfaces both for condensing and transporting liquid. Morning fog condenses on rough hydrophilic bumps on the wings and the drops formed subsequently roll down waxed microstructured superhydrophobic patches for drinking (Parker and Lawrence 2001). Figure 5 shows the beetle and the different areas on its back.

Experiments conducted in our laboratory on microstructured surfaces demonstrated that roughness gradients can result in the spontaneous movement of water drops (R. E. Oosterbroek, personal communications). The surface tension is a function of temperature (the thermocapillary effect) and the local electrical field (giving rise to the electrowetting phenomenon) (Verheyen and Prins 1999), and structures have been made that exploit this effect for the movement of droplets (Cho et al. 2002; Kataoka and Troian 1999).

4.2 Shear-related phenomena

As mentioned in the previous section, strong shearing can cause cavitation, occurring either at the liquid/solid interface or in the liquid itself (Chen and Israelachvili 1991). Interestingly, the snapping shrimp is thought to induce water cavitation by the shearing induced by the extremely fast closure of its claws (Versluis et al. 2000) (see Fig. 6). Shear forces will also extend polymer and DNA molecules in solution (Perkins et al. 1994; Adjari et al. 1994; Manneville et al. 1996; Bakajin et al. 1998). They can easily break long DNA (Thorstenson et al. 1998) and denature proteins (Maa and Hsu 1997), and are used for cheap random DNA fragmentation. An excellent review on the mechanics of biomolecules can be found in Bao (2002).

4.3 Electrical double-layer-related phenomena

A large number of phenomena will occur on double-layer overlap in nanochannels or nanoslits, as mentioned in the previous section. The phenomena are observed when studying nanochannels, nanopores, bundles of nanopores, membranes, sols, gels and soils (membranes or soils are in a first-order approximation often modelled as a bundle of capillaries). Due to the increased surface-to-volume ratio, the contribution of the surface conductivity (the conductivity through the electrical double layer) becomes larger on downscaling
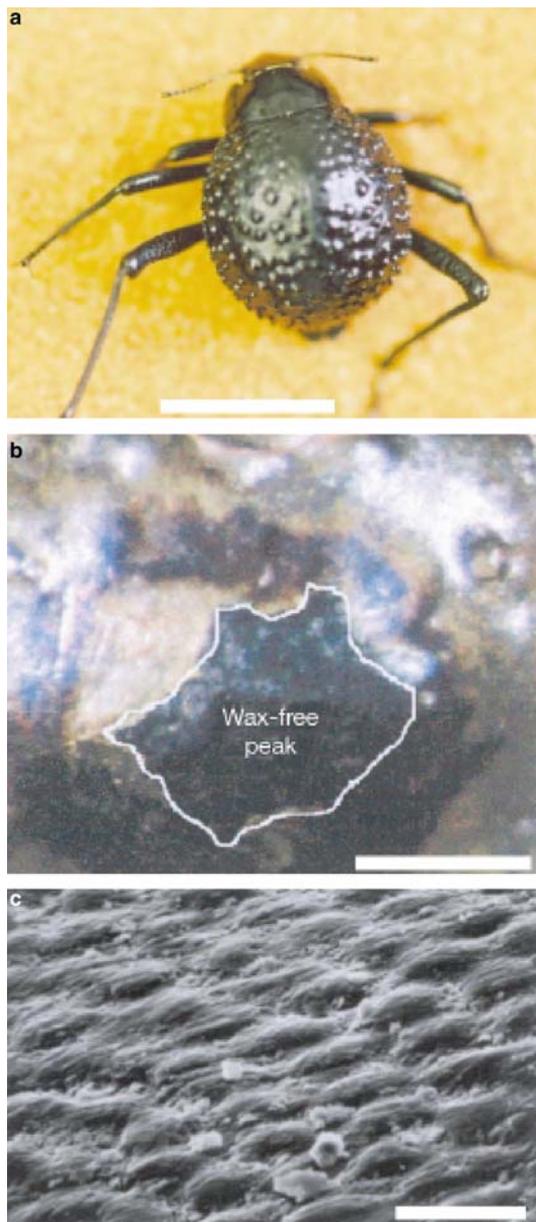
Fig. 5a–c The Stenocara beetle (a), the wax-free condensing areas on its wings (b) and waxed superhydrophobic wing areas (c). Scale bars: (a) 10 mm, (b) 0.2 mm, (c) 10 μm. Reprinted with permission from Parker and Lawrence (2001)
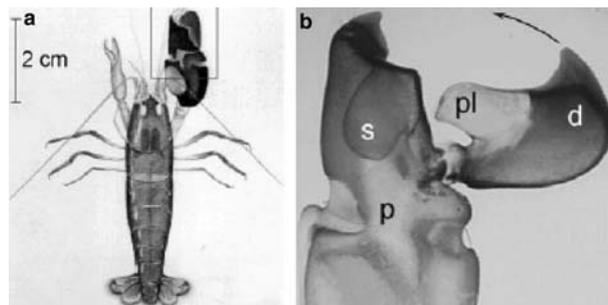

Fig. 6 a The snapping shrimp *Alpheus heterochaelis*. b During the rapid closure of the claw, the plunger *pl* moves into the socket *s* and a high velocity water jet is formed that causes cavitations in the sea water by expansion of even sub-micron bubbles (negative pressure generated, approximately −3 bar). Reprinted with permission from Versluis et al. 2000

(Lyklema and Minor 1998; Lyklema 2001), an effect which has also been experimentally observed in nanochannels (Stein et al. 2004). When double-layer overlap occurs, the streaming potential will decrease and the pore conductivity increase (Fievet et al. 2000). In addition, co-ions will be excluded from the channel (or membrane), counterions are enriched and a Donnan equilibrium will be established between the channel solution and its connected reservoirs (Fievet et al. 2000). When double-layer overlap occurs in soils and in gels, they will swell because of the osmotic pressure resulting from the high concentration of counterions. This effect also contributes to the mechanical strength of cartilage (Sun et al. 2004). Hydrostatic pressure will, therefore, be built up in nanochannels on double-layer overlap.

In the kidney, the negatively charged albumin is prevented from passing from the blood to the primary urine by the basal membrane. It is thought that, apart from size filtering, co-ion exclusion by the negatively charged membrane contributes to this effect (Benthansen et al. 1993). In a very comparable experiment with nanochannels, the wall charge on nanotubes was seen to influence the transport of proteins with different charges in a different way (Ku and Stroeve 2004). Semipermeability was also demonstrated in nanochannels using fluorescent molecules and Fig. 7 shows the accumulation of fluorescent dye on one side of a semipermeable 60-nm high nanochannel carrying current (Pu et al. 2004). In
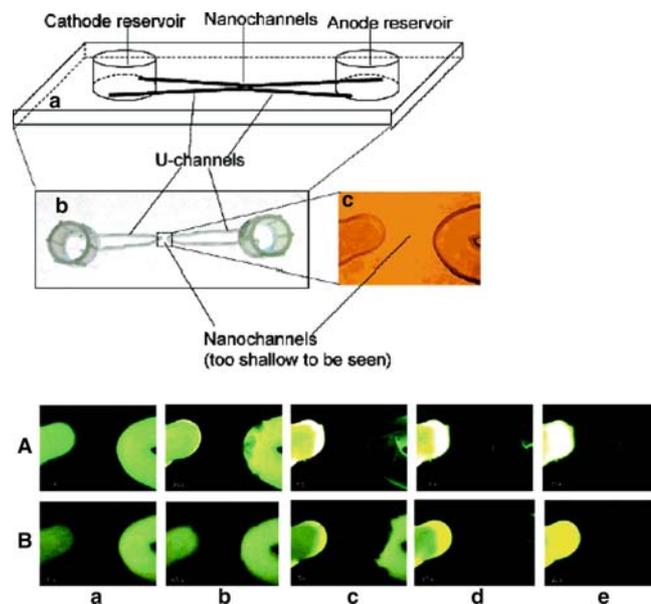

Fig. 7 *Top* Nanochannel chip layout. *Bottom* When a voltage is applied between the reservoirs, salt (as indicated by the fluorescent dye) is accumulated at the side where the positive counterions inside the channel are transported to. On the other side, ion depletion occurs. Reprinted with permission from Pu et al. (2004)

semipermeable membranes with still smaller pores, the effect is used for desalination (Probstein 1994). The semipermeability of nanochannels has also been employed for the injection of one microfluidic channel through a nanoporous membrane into another microfluidic channel with the channel layers and membrane in a 3-D stack (Kuo et al. 2003; Cannon et al. 2003).

Even without double-layer overlap, the electrical field inside a nanochannel can still have an effect on dissolved molecules, e.g. changing the conformation of charged macromolecules when they approach the wall. In fact, biomolecules like DNA and proteins almost always carry charge and create a double layer around them. Double-layer interaction with the wall can lead to attraction and possibly adsorption or repulsion. Much information about the charging and interaction behaviour of biomolecules can be found in the book of Tanford (1967). Conformational changes occur on protein adsorption, sometimes accompanied by ion inclusion (Norde 1986).

An extra degree of freedom will be introduced if the wall charge can actively be modified during the experiment. A nanochannel with a surface potential that could capacitively be actuated by metal electrodes insulated from the channel solution (a liquid channel FET) was demonstrated in the 1990s (Gajar and Geis 1992). In microchannels, this effect is generally used to modify electro-osmotic flow (Schasfoort et al. 1999). Recently, the same effect was used to electrically switch the filtering behaviour of nanoporous membranes (Schmuhl et al. 2004).

A "hot" research area is that of rectification of a net-zero force (thermal motion or an imposed oscillating (time-averaged zero) force field) by means of a spatially asymmetric potential ("ratchet") (Ajdari et al. 1994; Magnasco 1993) to obtain vectorial movement. The technique has been used to transport micronsize colloidal particles through a silicon wafer with asymmetric pores by applying an oscillating pressure difference (Kettner et al. 2000) or an oscillating electrical field (Marquet et al. 2002). More recently, the latter system was scaled down and it was shown that potassium ions can be transported against their concentration gradient through a conical surface-charged nanopore (tapered from 2 nm to 500 nm) when subjected to an oscillating (time-averaged zero) electrical field (Siwy and Fuliński 2002). Furthermore, simulations predict that an asymmetric nanopore will rectify an oscillating pressure difference to create net liquid flow (Hod and Rabbani 2003).

4.4 Size-related phenomena

Yet another set of phenomena is related to molecular size and steric repulsion. The result is size exclusion, which is widely used in membranes with pores of various sizes, from angstroms to micrometres. It should be kept in mind that at pore widths on the order of the Debye length, electrical forces always occur simultaneously. Another way to use molecular size exclusion is perpen-

dicular to the direction of transport. This is done in classical size exclusion chromatography, where columns are packed with nanoporous particles, increasing the retention volume and retention time for small analytes, but not for large ones. Molecular sieves also work on the steric exclusion principle, but are generally applied to smaller molecules. As pointed out by Giddings, size exclusion is also influenced by changes in entropy (Giddings 1991). A flexible molecule that has many conformational states is, for example, less likely to enter a pore than a rigid molecule of the same size, even when both have the same average radius.

Size exclusion on the sub-nanometre scale plays a role in the water channels that offer a low resistance passageway for water through cell walls. These channels are generally called aquaporins (Clapham 2003), and ions will not pass through them because they would have to shed their water shell, which is energetically too unfavourable.

However, natural evolution was also able to develop K^+ channels with a high selectivity for K^+ over Na^+ while both have water shells. In this case, it is thought that both electrostatic forces and steric forces play a role in achieving selectivity (Clapham 2003). The size of molecules that can be manipulated in nanosystems differs widely from 0.3 nm for the water molecule to 3.4 μm for the length of a fully stretched 10-kbp DNA molecule. Figure 8 shows a bar scale with a number of molecules and structures of interest drawn along side. It will be clear that several orders of magnitude are covered and that the manipulation of every group of molecules will demand nanostructuring on a different specific size. Thus, micrometre-long DNA molecules can be fractionated using structures with micrometre-sized features. Because DNA, at the same time, has a small cross section, its passage through 1.5-nm diameter nanopores can also be studied, as will be discussed in a later section.

4.5 Entropy-related phenomena

An entropy increase can drive a system in a certain direction, and, on the nanoscale, several phenomena have been shown to relate to entropy changes. Flexible molecules, such as DNA molecules, have many more possible coiled states than elongated ones, and entropy, therefore, drives them to a coiled state (Strick et al. 2000; Bustamante et al. 1994). As a result, DNA molecules will
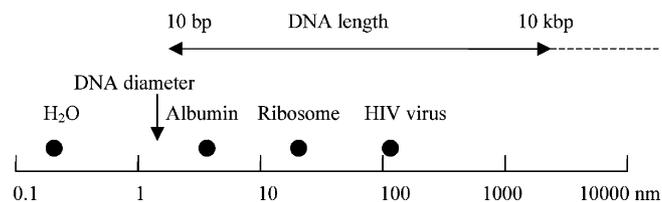

Fig. 8 Typical dimensions of a number of molecules studied. Each molecule will need a structure of specific dimensions suitable for its manipulation

prefer to stay in larger cavities instead of migrating into smaller ones, to maximise entropic energy gain (Muthukumar and Baumgartner 1989). This will affect DNA separation in gels (Arvanitidou and Hoagland 1991) and in nanomachined entropic traps (Han et al. 1999), and will also drive DNA out of small cavities if it gets caught (Turner et al. 2002). Figure 9 shows the relaxation of DNA that was stretched by hydrodynamic shear from the stretched state back to the coiled state, regaining entropy (Wong et al. 2003). DNA can also be stretched by confinement in 2-D nanochannels if the diameter of the channel is less than the persistence length of DNA, which is about 50 nm (Tegenfeldt et al. 2004a).

Entropy gain also drives diffusion, and this diffusional movement can be rectified using so-called Brownian ratchets. Micromachined Brownian ratchets, which are repetitive asymmetrical structures able to apply an asymmetric force field to a liquid, can, therefore, be used for the separation of molecular species on the bases of their diffusion coefficients. All Brownian ratchets manufactured to date had a typical length scale larger than 1 micrometre (see, e.g. Bader et al. 2002), and much improvement can, theoretically, be expected in separation performance when the ratchets can be scaled down to nanometre size. Interestingly, the Brownian ratchet concept has also been demonstrated in the 2-D confinement of a lipid membrane using barriers 25-nm high (Oudenaarden and Boxer 1999). As mentioned in the next section, one of the theories explaining active transport in cells is also based on rectified Brownian motion (Kitamura et al. 1999).

4.6 Molecular-structure-related phenomena

Perhaps the ultimate challenge for nanofluidics is to harness interactions on the single molecular scale. This is routinely used, for example, in pharmacology, where drugs are designed specifically to fit in a certain receptor cavity. The drugs then have their effect on the human body by a massively parallel action in many cells. The aquaporins we mentioned in the previous section conduct water molecules but not protons, which is thought to result from the intricate electrical and spatial properties of the channel, concerning interactions of single water molecules with the amino acids constituting the
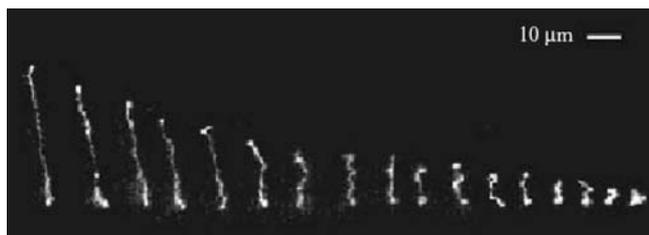

Fig. 9 Relaxation of a YOYO1 coloured T2 DNA molecule (164 kbp) gaining entropy after hydrodynamic stretching. Each image is separated by 2.5 s (from left to right). Reprinted with permission from Wong et al. (2003)

walls (Tajkhorshid et al. 2002; Clapham 2003; de Groot and Grubmüller 2001). Water conductance through a single aquaporins channel is about 10^9 molecules per second, and it would be possible to imagine a structure with many channels in parallel conducting water but not protons. The nanotechnological manufacturing of functional nanopores is still very much in its infancy, but a few successes can already be pointed out. In a so-called bottom-up approach, ion channels have been synthesised by self-assembly of cylindrical octapeptides (Hartgerink et al. 1996) (see Fig. 10, top). The resulting tube-like structures were shown to have bactericidal properties, making the bacterial wall permeable to ions (Fernandez-Lopez et al. 2001) (see Fig. 10, bottom).

Another important issue when it comes to pumping is whether to perform active transport. In the cell, active transport is provided by molecular motors like kinesin (Svoboda et al. 1993) and actin/myosin (Astumian and Bier 1994), which burn ATP. Cellular ion pumps were already mentioned, and they also "run" on ATP. One theory on the functioning of these motors states that they rectify the ubiquitous Brownian motion by means of molecular ratchet structures (Astumian and Bier 1994; Ajdari and Prost 1992). Technological nanopumps manufactured thus far have relied on an external, macroscopically applied source of energy, like an oscillating electrical field (Siwy and Fuliński 2002).

5 Applications of nanofluidics

A number of applications of nanofluidics have already been mentioned in the previous sections, like the use of charged polymers for lubrication, the lotus effect for self-cleaning surfaces, membranes for filtering on size or charge (e.g. for desalination) and nanoporous materials for size exclusion chromatography. Furthermore, we mentioned a number of exemplary natural phenomena, like (again) the lotus effect for tidy plants and thirsty beetles, biolubrication, snapping shrimps, passive selective transport in aquaporins and active transport in ion channels, molecular motors like kinesin and charge-based filtration in the kidney basal membrane. The old adage "natura artis magistra" in this respect certainly applies to nanofluidics. In this section, we will mention some more applications of modern nanofluidics and discuss some ongoing investigations that might lead to new applications.

5.1 Separation science: size fractionation in regularly structured microarrays

An important area of application for nanofluidics is separation science. In classical separation science, nanometre-sized structures are often employed, e.g. nanoporous materials as column packing in size exclusion chromatography, nanoporous gels for DNA separation and nanoporous silica packings for HPLC. In all

Fig. 10 The hydrogen-bonded tubular architecture of the self-assembled eight-residue cyclic D,L-a-peptides (*top*), and modes of membrane permeation accessible to peptide nanotubes (*bottom*). Reprinted with permission from Fernandez-Lopez et al. (2001)
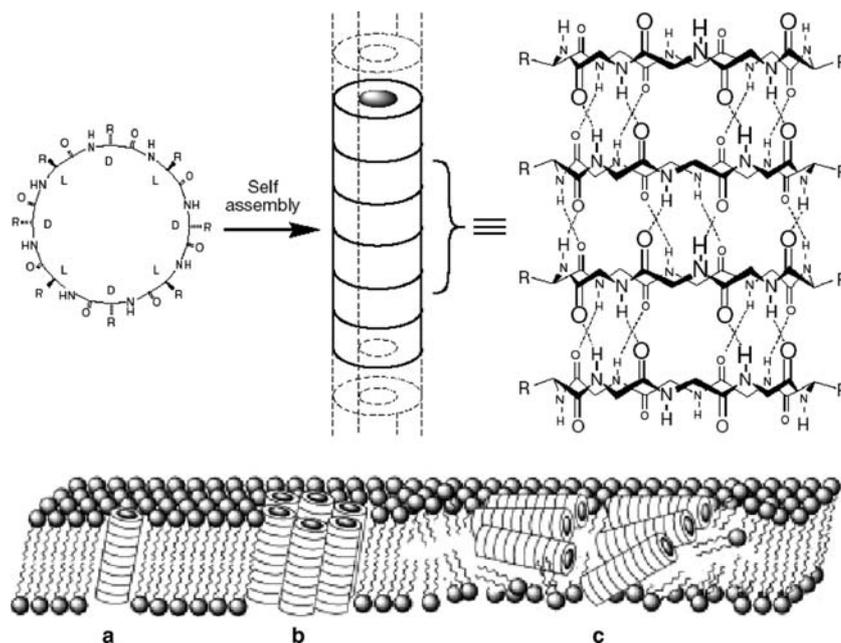
these systems, the nanostructuring is random, and the separation, therefore, is accompanied by spatial averaging. By using micromachining, it is possible to make regular microstructures or nanostructures, and a number of innovative lab-on-a-chip devices have demonstrated that this opens up entire new fields. The devices considered contain structures in the low micrometre range, but are still included here because their principle of operation, namely, the performance of a continuous sequence of identical separation operations on single molecules, can no doubt be extended to smaller length scales. The micrometre length scale they now employ is actually optimal for the separation of the high molecular weight DNA molecules that they are applied for.

In the first place, as we already mentioned above, a number of devices have been demonstrated that employ arrays of regularly spaced (sub-)micrometre obstacles for continuous flow separations. These devices are especially suitable for the separation of long (>10 kbp) DNA, where the best classical results are obtained using pulsed field gel electrophoresis (PFGE) (Kim and Morris 1995). The first such micromachined device was published in 1992 and employed an obstacle course with 1-μm wide posts spaced 2-μm apart for electrophoretic DNA separation (Volkmuth and Austin 1992). Though separation performance was not on a par with PFGE, the device provided much insight in the motion of DNA molecules in confining (gel-like) matrices because of its regular geometry (Volkmuth et al. 1994). DNA could be seen getting hooked on posts and delayed. A much more powerful mode of operation of the same regular array was presented later when DNA separation was performed by applying two alternating electrical fields of different directions and magnitude (Fig. 11) (Huang et al. 2002). Large DNA molecules can only follow the strong component while small DNA molecules travel in the direction of the sum vector. This device was christened

the "DNA prism" and showed good separations of long chain DNA in 15 s. It operates in a continuous flow, which is a large advantage since a continuous stream of analyte can be obtained. Another impressive analytical device that uses a regularly structured microarray was recently published and is shown in Figs. 12 and 13 (Huang et al. 2004).

It employs a regular array of posts where each new line of posts is shifted for a fraction of the inter-post spacing. Particles that just fit between the posts will "go with the flow" and move diagonally through the device, while smaller particles will move with the average hydrodynamic flow, which is straight down. Separations were demonstrated for polystyrene spheres with diameters from 600 nm to 1000 nm in 40 s in continuous flow. A unique property of this separation principle is that it does not depend on diffusion like the related principles of hydrodynamic and size-exclusion chromatography (Blom et al. 2003), but instead depends on steric and hydrodynamic effects. This means that the resolution improves with flow speed. The presented devices employ micrometre-sized obstacles and work probably by electrical repulsion and steric exclusion forces. It is exciting to think of the possibilities when the devices are scaled down and other forces are employed. In classical separation science, where no regular spacing occurs, these separation principles are out of reach.

5.2 Separation science: ratchets

Several applications of the ratchet in separation science have already been mentioned (Bader et al. 2002; van Oudenaarden and Boxer 1999). In general, there are two types of ratchet, as depicted in Fig. 14 (Astumian and Bier 1994). One type (Fig. 14b) is much like the ratchet from our everyday experience, namely, a rectifying

Fig. 11 a Schematic of the behaviour of short and long pieces of DNA. The short DNA can follow the sum vector of both the strong and weak fields, but the long DNA can only follow the vector of the large field since it gets caught behind the pillars; **b–d** fluorescence micrographs of DNA separations under different field strengths and continuous flow; **d** all four DNA lengths (61, 114, 158 and 209 kb) are collected in different channels. Reprinted with permission from Huang et al. (2002)
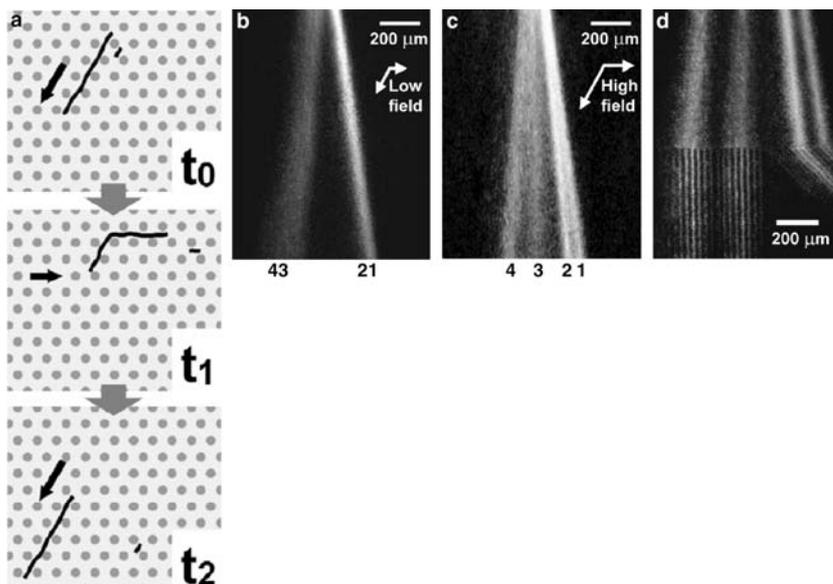
structure where movement is easier in one direction than the other because a larger force is necessary for one direction compared to the other. This type of ratchet uses an oscillating time-averaged zero force as its input (e.g. an E-field or a pressure gradient), which it rectifies (Magnasco 1993). The other type (Fig. 14a) is more subtle and employs a periodic change of the height of the ratchet teeth (Ajdari and Prost 1992). This type of ratchet uses Brownian motion as its input ("Brownian ratchets") and switches from the state where the energy barriers (ratchet teeth) are lower than the thermal energy kT, to a state where they are higher. Because of the spatial asymmetry of the teeth, a net transport of particles takes place.

All analytical Brownian ratchets produced up until now had micrometre-scale structures and the separation performance was not on par with classical methods, e.g. for DNA separation. Forces employed were dielectrophoretic (Rousselet et al. 1994) and electrostatic (Bader et al. 2002). Large improvements are, however, to be expected for Brownian ratchets on downscaling to the nanometre range, since diffusion time scales with the inverse of the square of the typical length. Two intriguing
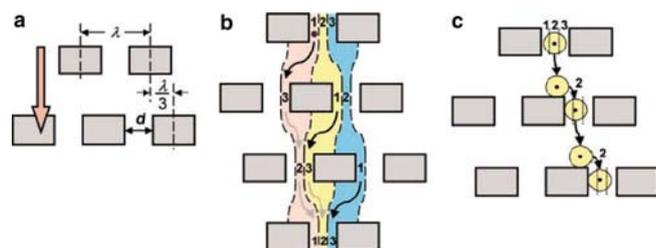
applications of nanoscale rectification ratchets were already mentioned, namely, the asymmetric nanopores for ion (Siwy and Fuliński 2002) and liquid (Hod and Rabbani 2003) transport. It is to be expected that exciting devices can be produced when more nanoscale ratchet devices are produced, since nature employs the concept as well for transport and pumping, rectifying the abundant kT noise at the molecular level (Magnasco 1993).

5.3 Separation science: entropic principles

It is energetically favourable for a DNA molecule to be in the coiled state since this maximises its entropy

Fig. 12a–c Continuous particle sorter. Principle of operation: **a** design: a row of obstacles, gradually shifted in the flow direction; **b** small particles will move with the flow lines and won't be displaced horizontally; **c** particles with a size on the order of the gap will be continuously displaced. Reprinted with permission from (Huang et al. 2004)
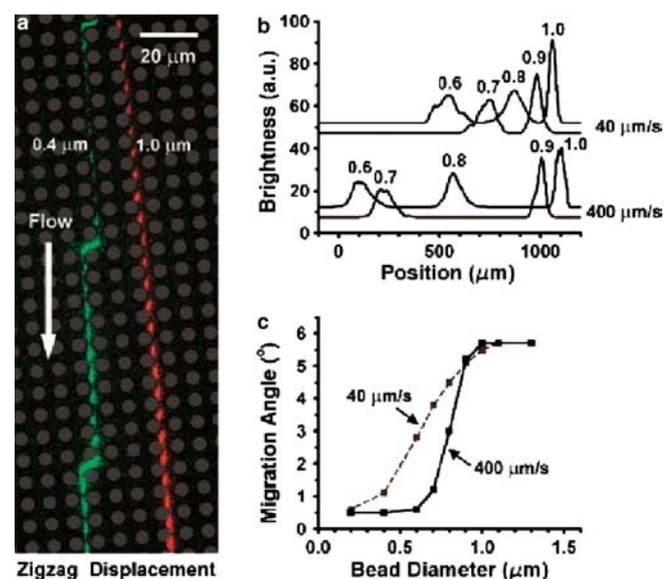
Fig. 13a–c Continuous particle sorter. **a** 400-nm polystyrene beads move straight down, while 1-μm particles deviate. **b** Separation of four different sizes of beads; crucially, separation improves with flow speed since separation depends on viscous sorting and not on diffusion. Reprinted with permission from Huang et al. (2004)
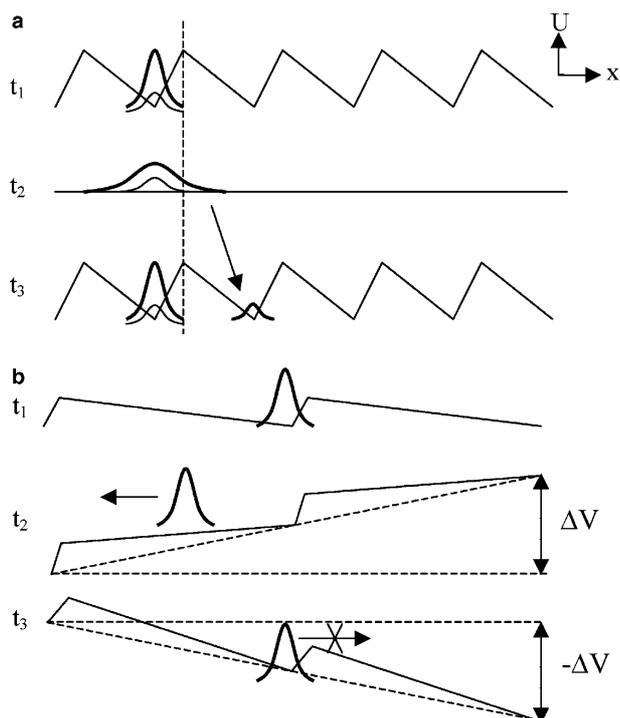
Fig. 14a, b Two types of ratchet devices. **a** Brownian ratchet, employing a time-varying asymmetric potential profile to rectify Brownian motion (Gaussian distribution curves of slow and fast diffusing species are drawn). **b** Rectifying ratchet, employing an asymmetric potential profile U rectifying an oscillating net zero force $F(t) = -dV/dx$
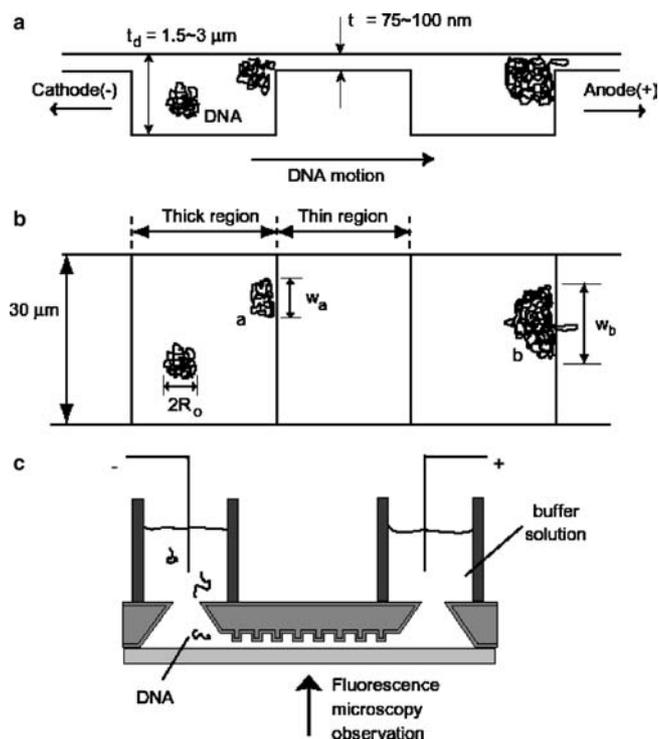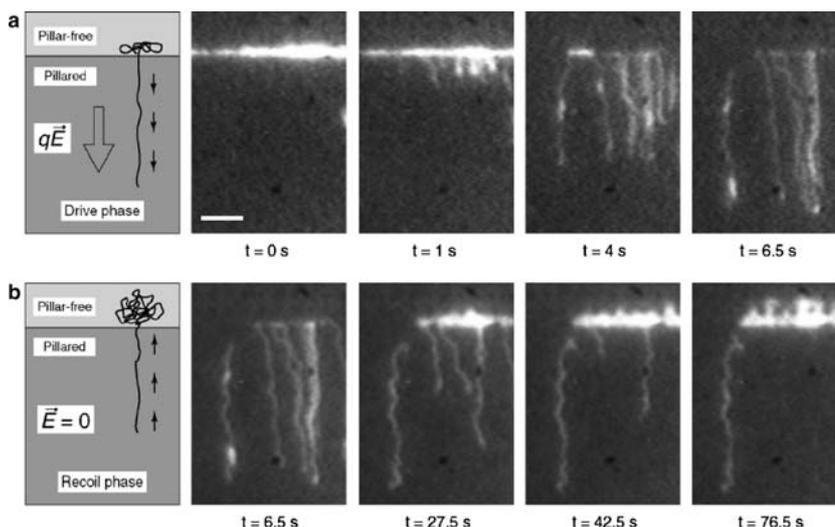

Fig. 15a–c Nanofluidic separation device with many entropic traps. **a** Cross-sectional schematic diagram of the device. Electro-phoresed DNA molecules are trapped whenever they meet a thin region because their radius of gyration (R_o) is much larger than the thin region depth (here, t_d and t_s are the thick and thin region depths, respectively). **b** Top view of the device in operation. Trapped DNA molecules eventually escape, with a probability of escape proportional to the length of the slit that the DNA molecule covers (w_a and w_b). Larger molecules have a higher escape probability because they cover wider regions of the slit ($w_b > w_a$). **c** Experimental setup. Reservoirs are made at both ends of the channel and are filled with DNA solution. Reprinted with permission from Han and Craighead (2000)

(Bustamante et al. 1994). Two separation devices employ this tendency, namely, the entropic trap (Han et al. 1999) and the entropic recoil device (Turner et al. 2002). The entropic trap device (see Fig. 15) uses a sequence of micrometre-deep channel regions and 90-nm deep channel regions.

When DNA is transported through the device by electrophoresis, it is caught in the entropy wells of the deep regions and only moves through if, by thermal movement, a sufficient part of its chain moves into the shallow region. Since the chance of this happening is bigger for longer DNA molecules, these move faster through the array. The entropic recoil device (see Fig. 16) employs a channel with alternating densely pillared and open areas, along which, intermittently, an electrical field is applied. Only the DNA molecules that, during the field pulse, have entirely moved into the pil-lared area will remain there; the other molecules, by recoil, will move back to the original empty channel section. As a result, short DNA moves faster than long DNA.

5.4 Single molecule studies: the benefits of confinement

As already mentioned, much effort has been devoted to studying the properties of single DNA molecules, including the determination of the base sequence, and

the reader is referred to some excellent reviews (Strick et al. 2000; Tegenfeldt et al. 2004b; Chu 2003). Nano-fluidics has great benefits for these studies, since it can provide a confinement for the DNA molecule. Thus, it has been demonstrated that DNA sizing can be performed by stretching the DNA in 2-D nanochannels and measuring the length (Tegenfeldt et al. 2004b; Tegenfeldt et al. 2004c). DNA can even be further confined by pulling it through the 1.5-nm diameter pore of the α hemolysin protein (Kasianowicz et al. 1996; Meller et al. 2000) (see Fig. 17).

In the latter case, the measured signal is the modulation of the cross-pore DC resistance. The duration of the resistance modulation was shown to contain information on the chain length and the intensity of the modulation information was shown to contain information on the identity of the bases passing through the pore. Single nucleotide resolution might not be impossible using this device (Deamer and Branton 2002). A review on this method, which can be called Coulter counting for nanoscale objects, has recently appeared (Henriquez et al. 2004). An alternative to spatial con-

finement of the molecule is spatial confinement of a light source. Such confinement can be obtained using zero-mode waveguides (basically, subwavelength holes in a metal film) emitting an evanescent field. Using such a light source, the activity of a single DNA polymerase could be studied at high concentrations (see Fig. 18) (Levene et al. 2003). A first prototype of a nanomachined 2-D slit with near-field optical illumination for DNA stretching and fluorescence detection of specific sites has also appeared (Tegenfeldt et al. 2001). Crucial for such a device is the optical resolution, since this will, for example, allow the fluorescence label study of the approximately 20-nm long control factors (Tegenfeldt et al. 2004b).

5.5 Information technology

From an information technology point of view, small liquid volumes may be considered to carry information on two different levels. The first bulk-like one is that such a volume may be acidic (say a logic "1") or basic ("0"). It has been shown that some basic logical operations (AND and OR) can be implemented in a particular fluidic manifold (Mela et al. 2003. Now, although these logic operations are limited in speed, they may compare favourably with their electronic counterparts in terms of energy dissipation. A perhaps even more tantalizing thought is that each tiny liquid volume still may contain billions of molecules that, on their turn, may represent complex data. One example is the famous DNA computer solving a particular class of mathematical problems, exemplified by the so-called travelling salesman problem (Adleman 1994; Lipton 1995). Such combinatorial problems lend themselves well for a massively parallel approach, although publications up to now have been rather theoretical. The question that remains is whether downscaling such microfluidic approaches to the realm of nanofluidics is beneficial or not. On the one hand, diffusional processes responsible for the interaction of molecules scales with the inverse of the dimension squared; on the other hand, the number of molecules present scales with the third power of the dimension. Nevertheless, the great and tantalizing property of liquid volumes is the third dimension that gives such an enormous boost to the number of molecules and the amount of information. A central problem is how to control, manipulate and access this information. For (ss)DNA, *reading* the base sequence of single molecules is the subject of various research groups. The most promising approach is to create a nanometre-sized hole, pull the molecule through it and try to resolve the base sequence either by optical or electrical (a sort of nanoCoulter counter) way. In some respect, such a single DNA molecule can be seen as a nano version of the good old wire recorder used for music recording. *Writing* information into (ss)DNA molecules is equivalent to controlled DNA synthesis. The ultimate speed at which this can be realised is limited by the reaction kinetics, and, in order to reach that point, diffusion of individual bases to the DNA "under construction" should be as fast as possible. With downscaling of individual plug sizes of base trains to the nanometre domain, and while keeping a flow velocity of several millimetres per second, the different bases can be brought to the DNA molecule with a frequency on the order of megahertz. Although this is fairly slow compared to other information carriers, massively parallel operation could still give this approach an advantage.

6 Problems and issues

6.1 Detectability

Most applications of nanofluidics will concern chemical or physical analysis and, therefore, will need some form of detection. In chemical analysis, detection will become very problematic when low concentrations are present together with small detection volumes. A cube of
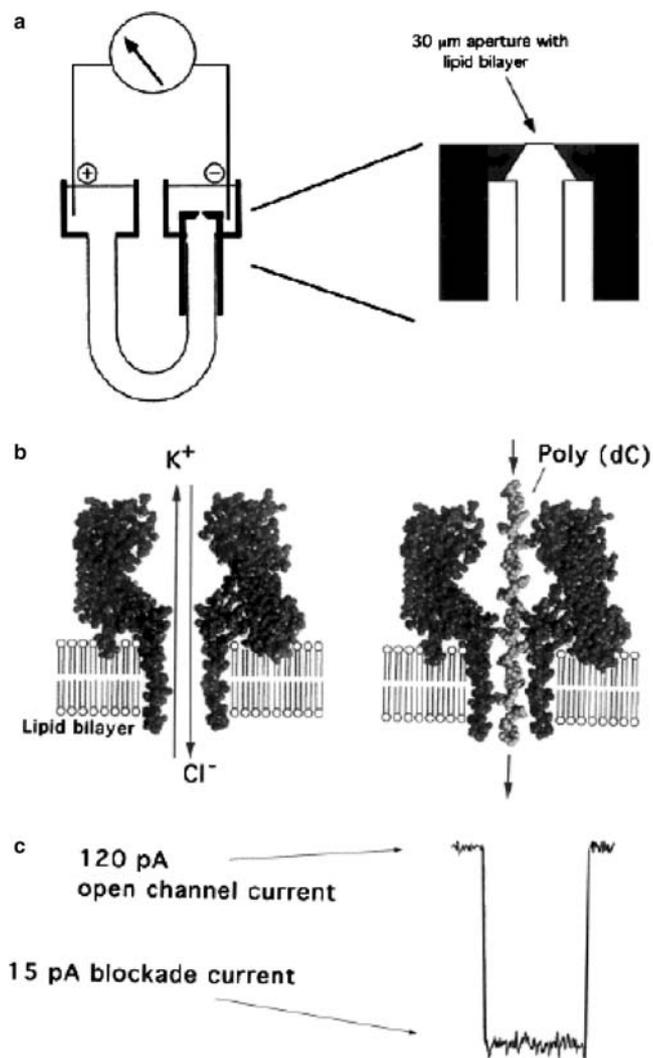
Fig. 18 Schematic of a metallic "nanopore" or zero-mode wave-guide containing an isolated DNA polymerase enzyme. The engineered nanostructure isolates the fluorescent excitation to a nanometre-scale volume surrounding the enzyme. Transient fluorescent bursts represent incorporation events of fluorescently labelled individual bases. Reprinted with permission from Levene et al. (2003)

Fig. 17 a Nanopore support device with hemolysin subunits incorporated in the lipid bilayer. b The hemolysin nanopore is shown as a cross section; a synthetic poly(dC) DNA strand traversing the pore is shown on the *right*. c When a single-stranded nucleic acid molecule traverses the pore, a transient blockade of ionic current results, during which the ionic current is reduced from 120 pA to 15 pA. Reprinted with permission from Deamer and Branton (2002)

100×100×100 nm will, e.g. contain only six molecules at an analyte concentration of 1 µM, which means expensive single molecule detection methods are necessary. Massive spatial parallel structuring is a possible solution to this problem, which can be possible using micromachining methods. However, if band broadening is to be avoided, the structures should spatially be highly homogeneous. A more robust solution is therefore offered by continuous flow structures like the DNA separation devices already mentioned. In this case, the separation can benefit from nanoscale structuring while the detection can benefit from the time integration. In (bio)physical analysis, spatial information is often necessary, e.g. to know the location of control factors on DNA or, even more ambitious, to know the location of each base pair. Near-field optical microscopy offers a
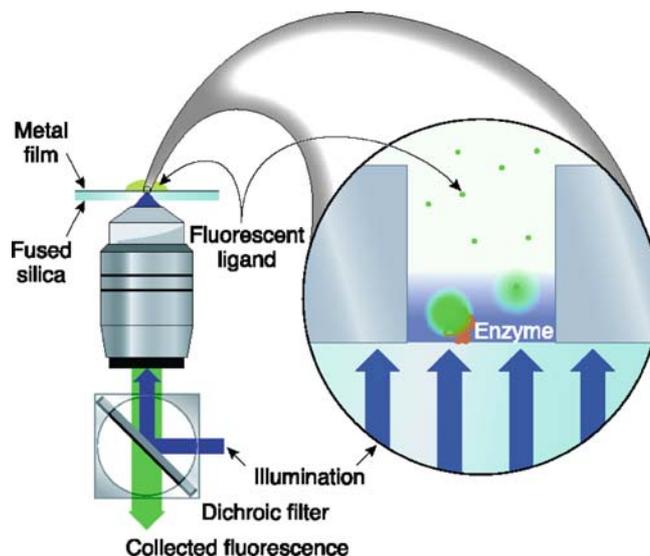
possible solution to meet the former objective, at present, offering a resolution of about 50 nm (Richards 2003). This method is well suited for integration in nanofluidic systems, as has already been demonstrated (Tegenfeldt et al. 2001; Levene et al. 2003). It has been mentioned earlier that conductometric detection is close to meeting the former objective, allowing single base detection during DNA transport through a nanopore (Deamer and Branton 2002). Many other detection methods might offer sensitive detection on the nanoscale, but are outside the scope of this paper. Some reviews on detection in microfluidic devices will be useful for the nanofluidic regime as well (Vilkner et al. 2004; Reyes et al. 2002; Auroux et al. 2002; Schwarz and Hauser 2001).

6.2 Fouling and stability

In nanochannels, molecules will always be very close to the wall and adsorption of proteins, especially the amphiphilic proteins, will easily occur, as described by the DLVO theory. A layer of polyethyleneglycol (also called polyethyleneoxide) is generally recommended to avoid adsorption (Tegenfeldt et al. 2004b) and can be vapour-deposited (Popat and Desai 2004). The working mechanism is thought to be entropic stabilization of the PEG coils (Alexander–de Gennes theory) as well as the stabilisation derived from their excellent hydration (Morra 2000). An issue that will be encountered in two-phase flow when proteins are present is the denaturation at the liquid–water interface (Clarkson et al. 1999). Also, high shear rates have to be avoided to maintain protein

(Maa and Hsu 1997) and DNA stability (Thorstenson 1998).

7 Concluding remarks

The field of nanofluidics has very broad roots in many disciplines, and the phenomena that are encountered touch many aspects of physics, chemistry and biology. The applications of nanofluidics presented in this paper mainly concerned separation science and we saw that, in the past few years, several fundamentally new modes of separation were accessed. Two fundamental reasons seem to lie at the basis of this: first, we have now entered the domain where the analyte size is on the order of magnitude of the device features. Second, absolutely regular structures can now be manufactured, which repetitively perform exactly the same operation on the particles to be separated. It has already been possible to demonstrate the first point by the devices for DNA fractionation because micromachining was sufficient for the separation of (micrometre-sized) large DNA molecules. The second reason actually makes material what always was the conceptual basis of classical separation science, namely, that a continuous separation consists of a sequence of single separation steps ("plates"). In a number of nanofluidic separation devices, we can now actually explicitly identify this sequence of plates in time or space. The precise control over time and space offered by nanomachining, therefore, holds great promise for the battle against band broadening.

A second area of nanofluidic applications has recently been the study of fundamental properties of liquids and molecules, e.g. in biophysics and fluid mechanics. Here, nanofluidics offers the possibility to confine molecules to very small spaces, or to subject them to controlled forces. In these areas, nanofluidics is very much used as an engineering tool to extract fundamental knowledge.

What about the future? We will try to identify a few phenomena and forces that are still untapped. An important phenomenon that has been hardly used is specific interaction as occurring, for example, with antibodies or ion pumps. The challenge here is to devise structures that harness these specific molecular interactions, if possible, on a continuous and highly parallel scale. The body does this in a continuous fashion, e.g. in its molecular machines, and in a highly parallel fashion, e.g. in muscle contraction. Will this be possible by technical means as well? Then, this could, for example, contribute to tissue engineering, but also to actuation or separation in microsystems or nanosystems. As another example of an untapped phenomenon with possible analytical applications, will it be possible to manufacture structures that molecularly exclude protons as aquaporins do or ions as ion channels do? Can we employ these in nanofluidic systems in a controlled way for separations? A totally different and even more speculative question is whether it will be possible to apply massively parallel nanofluidic systems for computational purposes, as briefly discussed above. Other questions still concern the use of predominantly physical phenomena, such as slip flow in small nanochannels or the negative pressures occurring in two-phase flow in such channels. Can nanofluidics play a role in research on friction and lubrication? And again, turning to single-molecule analysis, will we be able to manufacture structures that write DNA and read it, e.g. nanopores that can read DNA code by having DNA bases incorporated in them like the old head of a wire recorder?

Finally, the conclusion can be that, due to the new nanotechnological tools available in the past 20 years, we have, for the first time, been able to precisely control liquid flow and molecular behaviour at the nanoscale. The new area of nanofluidics applying these tools has already borne some exciting fruits and many more are expected to follow.

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