Transport in nanofluidic systems: a review of theory and applications

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*New Journal of Physics* 12 (2010) 015004 (23pp)
Received 26 May 2009
Published 22 January 2010
Online at [http://www.njp.org/](http://www.njp.org/)
doi:10.1088/1367-2630/12/1/015004

**Abstract.** In this paper transport through nanochannels is assessed, both of liquids and of dissolved molecules or ions. First, we review principles of transport at the nanoscale, which will involve the identification of important length scales where transitions in behavior occur. We also present several important consequences that a high surface-to-volume ratio has for transport. We review liquid slip, chemical equilibria between solution and wall molecules, molecular adsorption to the channel walls and wall surface roughness. We also identify recent developments and trends in the field of nanofluidics, mention key differences with microfluidic transport and review applications. Novel opportunities are emphasized, made possible by the unique behavior of liquids at the nanoscale.

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1. Introduction

The field of microfluidics has seen rapid development in the past 20 years. A variety of phenomena have been investigated in depth in microfluidic structures, such as transport, mixing, dosing and separation. At the same time, many relevant new applications have been developed, especially in the fields of analytical and clinical chemistry and biochemistry. More recently, partly due to the increased sophistication of cleanroom equipment, research has moved on to nanofluidic phenomena. Nanofluidics is generally defined as the study of fluid motion through or past structures with a size in one or more dimensions in the 0–100 nm range. Apart from the impetus from technology, several factors have contributed to this development. An important motivation has been the desire to replace entangled polymers (which are typically used for gel-based DNA separations) with engineered solid state versions [1]. The free volumes in such polymers typically have dimensions of a few nanometers up to a micron, which can be reproduced with micromachining. Some research has also been purely curiosity-driven, looking for new phenomena when fluidic dimensions go down to or below the characteristic dimensions that determine mechanical (the fluidic slip length) or electrochemical (the electrical double layer (EDL)) behavior. Fluid interactions with the wall are most prominent in nanofluidic systems because of the large surface-to-volume ratio, and give rise to unique phenomena. Finally, nanofluidic devices can provide new tools to investigate fluid behavior on the nanometer scale and thereby enable verification of computational techniques coupling macroscopic continuum descriptions with microscopic molecular dynamics descriptions.

In the last decade the number of publications on nanofluidics has doubled every two years, indicating its increasing importance and increasing interest among researchers. In recent years, several reviews in the nanofluidics field have appeared [2]–[7]. Nanofluidics in general was reviewed in [3]. Technological issues were discussed in [2, 4, 5] and recently two excellent reviews dedicated mainly to electrokinetic transport in nanochannels have also
The purpose of this paper is to review the basic principles of transport of both liquids and dissolved molecules or ions at the nanofluidic scale and from this perspective to review recent applications in nanofluidics. In the first section, the theory and models used to describe transport in nanochannels are related. In this section key differences with transport in microchannels will be addressed. In the next section, developments and trends in nanofluidic transport are discussed. This section is divided into two subsections: flow detection and applications. Finally, there is a conclusion and a look at future devices employing nanofluidic transport.

2. Theory

Modeling of transport in nanofluidic systems differs from microfluidic systems because changes in transport caused by the walls become more dominant and the fluid consists of fewer molecules. This has consequences for the applicability of models used to describe microfluidic transport. Therefore, in this section we present different models used in microfluidics and discuss their applicability for nanofluidic transport. Also, electrokinetic transport differs from that in microfluidic systems because the influence of the EDL is more prominent. Finally, because of the large surface-to-volume ratio in nanofluidic systems a subsection dedicated to wall effects is included.

2.1. Continuum or discrete modeling

Since a cubic nanometer of a typical solvent such as water contains less than 50 molecules, the discrete nature of molecules can become important when considering nanofluidic transport. This means that modeling such a system by applying continuum equations may lead to errors and individual molecules and interactions among them need to be considered. This can be done by employing molecular dynamics simulations, wherein only van der Waals and electrostatic interactions are considered. There has been an enormous increase in the number of publications using molecular dynamics simulations since the pioneering work of Alder and Wainwright [8], with a notable influence on nanofluidic transport [9]–[29]. The reason for this is probably twofold. Firstly, technology for fabricating nanofluidic devices has matured considerably in the last decade, whereas before nanofluidic phenomena were mainly studied in membrane science [30] and in colloid and interface science [3, 31]. Secondly, computational capacity has increased exponentially, resulting in the ability to simulate the behavior of millions of molecules, instead of the several hundreds of Alder and Wainwright. However, as pointed out by Succi et al [32], when considering fluid transport the difference between continuum modeling and discrete modeling is small and is usually limited to the irregular behavior of the first few molecular layers in the liquid. In the following subsection more comparisons are made between continuum and discrete modeling. Consequences for both liquid and electrokinetic transport are discussed. For more information on different modeling techniques for fluid mechanics we refer to [33].

2.2. Transport equations

2.2.1. Liquid transport. As is known from microfluidics, the physics describing transport in fluidic channels diverges somewhat from that used in modeling macroscale device behavior.
That is, the ratios of competing physical processes change as a function of characteristic device length, causing different physical processes to be dominant at different length scales. One method of estimating the order of magnitude of the influence of different processes on transport is by using dimensionless numbers. Dimensionless numbers originate from well-known equations describing flow, such as the Navier–Stokes equations. In [34], the most important dimensionless numbers for mass transport in nanofluidic systems are reviewed. The main conclusion that can be drawn from applying dimensionless numbers to nanofluidics is that gravitational and inertial forces are dominated by viscous and surface tension forces. Since in this paper only single-phase transport is considered, the effects of surface tension forces in nanofluidics will not specifically be considered. In [35], a review of multiphase flows in nanochannels can be found. The fact that viscous interactions dominate over inertial forces is expressed in a low Reynolds number and already applies to the microfluidics length scale. Since Reynolds numbers typically encountered in microfluidic systems are smaller than 1, flow at the microscale is generally accepted to show laminar viscous or simply Stokes flow. For nanochannels with one dimension smaller than 100 nm this rule of thumb holds for velocities even beyond 1 m s\(^{-1}\), which are highly unlikely for nanochannels with zero or little slip velocity at their walls [36].

However, to apply Stokes flow for modeling liquid transport in nanochannels, the assumptions made for the derivation of the full Navier–Stokes equations also need to be examined. These assumptions are as follows. Firstly, the fluid is assumed to be a continuum. Secondly, viscosity is assumed to be independent of the shear rate (i.e. the fluid is Newtonian). Furthermore, the fluid can be assumed to be incompressible (the equations are often then referred to as the Navier–Stokes equations for incompressible flow). Well known and frequently used equations for calculation of fluidic resistance in microfluidics are, among other assumptions, all based on an assumption of incompressible flow. In the following an analysis of the applicability of continuum modeling to nanoscale transport is given. A length will be given below for which the applicability of continuum modeling needs to be carefully deliberated. This length refers to the smallest dimension of a nanofluidic device or of a part of interest of a larger system. It serves as a rule of thumb and is by no means an absolute lower boundary of applicability of continuum modeling. The applicability of continuum theory is often checked by introducing the Knudsen number. For gases, this is the ratio of the mean free path of a molecule and the system characteristic length, \(L\),

\[
Kn = \frac{l}{L}.
\]

In liquids, however, the molecules are densely packed and a mean free path is not a meaningful quantity. For liquids, therefore, \(l\) is defined as the interaction length. This interaction length is based on the number of molecules with which a molecule of interest interacts. As a rule of thumb we use 10 molecular lengths for \(l\). If we substitute \(l\) in equation (1) with the interaction length for water and define a \(Kn\)-value of 1 to correspond with the transition between continuum and discrete flow, the continuum approach can be applied to channels or processes inside a larger channel with a characteristic length down to \(\sim 3\) nm. Later in this paper, we show that this rule of thumb value for transition in behavior appears to be very close to theoretical and empirical values found in the literature.

The next assumption for the Navier–Stokes equation is that the liquid is Newtonian. As mentioned above, interactions of solute molecules with the walls are dominant in nanofluidics, and shear rates might therefore become more important for the description of liquid flow.
behavior. As proposed and checked via molecular dynamics simulations by Loose and Hess [38], liquids are Newtonian up to strain rates twice the molecular frequency, $1/\tau$, which is defined below.

$$\gamma = \frac{\partial u}{\partial y} \geq 2 \frac{1}{\tau}, \quad \tau = \sqrt{\frac{m\sigma^2}{\varepsilon}}. \tag{2}$$

Here $\gamma (s^{-1})$ represents the shear rate, $u$ and $y$ represent the axial velocity and the perpendicular coordinate, respectively; $\tau$ is the timescale on which molecular movement occurs; $m (\text{kg mol}^{-1})$ represents the molecular mass; $\sigma$ (m) is the molecular length scale and $\varepsilon$ ($\text{J mol}^{-1}$) equals the product of Avogadro’s number, $N_A$ (mol$^{-1}$), Boltzmann’s constant, $k$ (JK$^{-1}$) and the absolute temperature $T$ (K) and represents the molecular energy scale. The above is based on the Lennard–Jones model [39]. In [40]–[55], the Lennard–Jones parameters for water are determined using different water models. From this the average $\sigma$ and $\varepsilon$ are determined to be $3.16 \times 10^{-10}$ m and $690 \text{ J mol}^{-1}$, respectively. This results in a molecular characteristic time of the order of a picosecond and a maximum shear rate of $1.24 \times 10^{12}$ s$^{-1}$. This compares approximately to a gradient in velocity of 400 m s$^{-1}$ across a single molecular layer. Since encountered velocities in nanochannels with zero slip at their walls (the zero slip condition will be explained below) are typically much smaller (i.e. of the order of 1 mm s$^{-1}$), it is unlikely that the Newtonian assumption will be broken. However, although this observation is already based on molecular interactions, Qiao and Aluru [11] show in molecular dynamics simulations that for a channel having a width of 4–5 (∼1.5 nm) molecular layers the Newtonian assumption does break down. The induced flow rates presented in [11] are, however, unpractically high, and cause much higher shear rates than are experimentally possible.

Finally, since the pressure differences required to drive liquids through nanochannels are high, the influence of incompressibility also needs to be assessed. The compressibility of water [56] predicts approximately 1% volume decrease of water per 20 MPa, which for a constant cross-section results in a 1% decrease in water column length. This is quite small and will only have an effect at high applied pressures (>10 MPa) if the influence of changes in dynamical pressure variations on transport are assessed.

The conclusion drawn from the above analysis is that for channels with both perpendicular dimensions at least 10 nm, Stokes flow can be applied reasonably well. For systems or parts of systems smaller than 10 nm, the individual nature of molecules may need to be taken into account (more discussion about this can be found below). Mathematically, Stokes flow is described as

$$\eta \nabla^2 u + f = \nabla P. \tag{3}$$

Here $\eta$ (Pa s) represents the viscosity, $u$ (m s$^{-1}$) the linear velocity, $f$ (N m$^{-3}$) a body force exerted on the liquid molecules and $\nabla P$ (Pa) the applied pressure gradient. For $f$ in equation (3) any force acting on the volume of liquid inside the channel can be substituted. For example, to obtain $f$ when an electric field is applied, the electric field strength is multiplied by the net charge inside the channel volume to obtain the Coulomb force.

For Stokes flow, the velocity profile of a cross-section perpendicular to the channel wall is governed solely by viscous forces, is continuous and can be described by neighboring laminae of approximately equal speed shearing along one other. As in microchannels, each channel geometry has its own velocity profile and therefore its own equivalent fluidic resistance. Here, only the solutions for the velocity profile, $\tilde{u}$, and the fluidic resistance, $R$, between two infinite
parallel plates and inside a cylindrical capillary will be given, which are commonly referred to as Poiseuille flow \[57, 58\].

\[
\begin{align*}
\text{Parallel plate} & \quad \text{Cylindrical capillary} \\
 a: \text{ half distance between plates} & \quad a: \text{ radius} \\
 b: \text{ width of the plates} & \quad b: \text{ radius} \\
 \tilde{u} = \frac{1}{2}(x^2 - a^2) & \quad \tilde{u} = \frac{1}{2}(r^2 - a^2), \\
 R = \frac{3\eta L}{2a^3b} & \quad R = \frac{8\eta L}{\pi a^4}.
\end{align*}
\]

The velocity profiles and fluidic resistances of more exotic channel geometries can be found in textbooks such as \[57\]–\[59\].

For nanofluidic devices or parts of interest of larger systems smaller than \(~10\) nm, some of the above assumptions do not apply and the influence of individual molecules may need to be considered. This can be done either in a molecular dynamics fashion or by discretizing important parameters such as the viscosity per molecular layer adjacent to the channel wall. In this case, the former method has the advantage that no assumptions are made concerning the shape of the flow profile and other macro parameters such as, for example, viscosity, but this also has the disadvantage of a large number of degrees of freedom which requires greater computational time. The latter had the advantage of fewer degrees of freedom, meaning larger systems can be considered. However, it has the disadvantage that assumptions are made about the viscosity distribution \textit{a priori}. Qiao and Aluru \[11\] discuss both possibilities using both molecular dynamics simulations and continuum modeling in the case of electro-osmotic flow. The general trend following from \[11\] is that continuum modeling tends to overestimate flow rates in the case of electro-osmotically driven flows. The reason for this is that water and ion layering and thus density changes at the walls are not taken into account. This in turn gives rise to an overestimation of mobile counter-ionic charge concentrations and, according to several other sources \[13\], \[60\]–\[62\], also to an increase in viscosity. Zhang \textit{et al} \[63\] report on similar density and corresponding viscosity changes for pressure-driven flow. Their conclusion is that in nanofluidic systems of a five molecular layer diameter or smaller, viscosity changes are very dominant and will alter the Poiseuille flow profile drastically. Another important conclusion from their work is that in systems consisting of a denser liquid (e.g. electrolytes) the effects are more pronounced. These computational results compare well to the empirical findings of Israelachvili and Pashley \[64, 65\]. In their experiments Israelachvili and Pashley observed discrete water layering by fluctuations in surface force obtained via surface force measurements on KCl solutions at mica surfaces.

Although continuum modeling might not always give accurate results, it is a good tool for estimating the order of magnitude of different competing physical processes. As a result it is useful in assessing different methods of generating fluid transport in nanochannels. It must be remarked that the above considerations only apply for ideally flat walls with no slip conditions and without surface adsorption. In section 2.3, the influence of the walls is taken into account and deviations from the above described behavior are treated, these mainly caused by a nonzero velocity at the walls.
2.2.2. The EDL. The previous subsection showed that deviations from continuum theory describing liquid flow can be found in systems smaller than 10 nm. In this subsection, the influences of confinement on ionic distribution will be shown. In this subsection, glass walls and aqueous solutions around neutral pH are assumed. Since a glass wall at its interface consists of amphoteric silanol (SiOH) groups it can be (de)-protonated as a function of pH, which is typically described using a site binding or dissociation model, as described in [66, 67]. This causes the walls to be charged which can be described by a constant wall potential model, a constant surface charge density model or a constant surface charge density model which takes the chemical equilibrium into account [68]. In this subsection, we will mainly use the constant wall potential model, and the other boundary conditions will be treated in the next subsection where wall effects are discussed.

To determine the concentration of ions inside a nanochannel the potential profile in the so-called EDL needs to be calculated. This is usually done by coupling the Poisson with the Boltzmann equation, as shown in equation (5)

\[-\nabla^2 \psi = \frac{e}{\varepsilon} \sum_i c_i z_i \exp\left(\frac{-z_i e \psi}{kT}\right).\]

(5)

Here, \(\nabla^2 \psi\) (V m\(^{-2}\)) represents the divergence of the gradient in electrostatic potential, which can for parallel flat walls be reduced to the second derivative with respect to the perpendicular coordinate \(y\) (m) (i.e. \(d^2 \psi/dy^2\)); \(\varepsilon\) (F m\(^{-1}\)) represents the permittivity of the liquid; \(e\) (C) is the unit charge; \(c_i\) (mol m\(^{-3}\)) and \(z_i\) (.) are the concentration and the ionic valence of the \(i\)th ionic species, respectively; \(\psi\) (V m\(^{-2}\)) represents the electrostatic potential and \(k\) (J K\(^{-1}\)) and \(T\) (K) represent Boltzmann’s constant and temperature, respectively. For low potentials (i.e. assuming \(z e \psi \ll kT\)) the typical length of an EDL can be defined and is named the Debye length, \(\lambda_D\). It can be seen as the distance from a charged surface where the potential has decayed a factor 1/exp (1) and is often used as a rule of thumb.

\[\lambda_D = \sqrt[\varepsilon kT]{\sum_i N_A c_i z_i^2 e^2}.\]

(6)

Here, \(N_A\) (mol\(^{-1}\)) is Avogadro’s number and the rest of the variables and constants are defined as above. For systems with walls that are separated over a distance of the order of \(\lambda_D\), ion enrichment and exclusion effects are particularly strong (though they can already have a noticeable influence on transport in systems with walls separated further). In such systems, the concentration of ions that are oppositely charged to the wall or counter-ions can be orders of magnitude larger than that for ions of equal charge or co-ions. Plecis et al [69] considered ion enrichment and exclusion in detail, providing both theory and experimental results. This situation is generally referred to as double-layer overlap. If the EDLs hardly overlap, which is defined as \(8\lambda_D \leq h\), and the electrolyte is symmetric (i.e. \(z_+ = z_-\)), the electrostatic potential perpendicular to two infinite parallel walls can be described as a superposition of the potential distributions of both walls as follows [7]

\[\psi(y) = \frac{4kT}{ze} \left[\tanh^{-1}\left(\tanh\left(\frac{ze \zeta}{4kT}\right) \exp\left(-\frac{y}{\lambda_D}\right)\right) + \tanh^{-1}\left(\tanh\left(\frac{ze \zeta}{4kT}\right) \exp\left(-\frac{h-y}{\lambda_D}\right)\right)\right].\]

(7)
Here, \( y \) (m) is the coordinate in the direction perpendicular to the channel wall and \( \zeta \) (V) equals the potential at the wall. Equation (7) is named the Gouy–Chapman equation. To calculate the potential profiles in the case of an asymmetric electrolyte, Gouy and Chapman developed special functions that make equation (7) compatible for calculations with asymmetric electrolytes. The solutions are repeated in, for example, [7, 61]. If one does not want to perform numerical simulations but still wants to know the potential distribution in systems with strongly overlapping EDLs (i.e. \( 2\lambda_D \gtrsim h \)), the Debye–Hückel approximation can be applied [61, 69, 70]. This is a linearization of the Poisson–Boltzmann problem and is by definition only valid for \(|\zeta| \leq 25\text{ mV}\).

\[
\psi(y) = \frac{\zeta \cosh(((h/2) - y)/\lambda_D)}{\cosh(h/2\lambda_D)}. \tag{8}
\]

From equation (8) the ionic distribution of ionic species \( i \), \( \tilde{c}_i \) (mol m\(^{-3}\)) can be easily calculated using the Boltzmann equation

\[
\tilde{c}_i = c_i \exp \left[ -\frac{z_i e \psi}{kT} \right]. \tag{9}
\]

To assess the error introduced due to the use of the Debye–Hückel approximation for calculating the predicted ion concentrations and potential distribution at zeta potentials higher than 25 mV, Conlisk [71] made an extensive comparison between the analytical results obtained by applying this approximation and numerical results. The conclusion is that errors of up to 30% are predicted for zeta potentials higher than 25 mV.

2.2.3. Electro-osmotic flow. In nanochannels, axial liquid transport can be induced by applying an axial electric field, just as in microchannels. This field displaces the counterions and, because they are solvated, drags solvent molecules and produces liquid transport in a process called electro-osmosis. For nanochannels without double-layer overlap, the well-known Helmholtz–Smoluchowski equation can be applied to determine the flow velocity in the electroneutral bulk. This is a linear analytical solution of the Poisson–Boltzmann and the Stokes equation

\[
u = -\frac{\varepsilon \zeta E}{\eta}. \tag{10}
\]

The flow profile in the non-electroneutral double layer is defined by introducing a potential-dependent scalar into equation (10), resulting in equation (11)

\[
u = -\frac{\varepsilon \zeta E}{\eta} \left[ 1 - \frac{\psi(y)}{\zeta} \right]. \tag{11}
\]

As proposed by Burgreen and Nakache [70], this scalar can be integrated over the double layer thickness resulting in a proportionality constant, \( G \), that describes reduced flow as compared to non-overlapped electro-osmotic flow as a function of the amount of EDL overlap.

\[
G = \frac{2\lambda_D}{h} \int_0^{h/2} \frac{\psi(y)}{\zeta} \, dy. \tag{12}
\]

\( G \) has to be calculated numerically, which has been done by Burgreen and Nakache. Infinite series solutions of the problem are given by Levine et al [72]. A comparable proportionality constant is determined for 40 and 100 nm channels both numerically and experimentally by Pennathur et al [73, 74] for a range of different electrolyte concentrations and hence amounts of EDL overlap.
2.2.4. Ionic and molecular transport. Ionic transport, $J$ (mol s$^{-1}$ m$^{-2}$), is usually assessed by the Nernst–Planck equations (13)

$$J_i = -D_i \left( \nabla c_i + \frac{z_i q}{kT} c_i \nabla \psi \right) + c_i u. \quad (13)$$

Here, $D_i$ (m$^2$ s$^{-1}$) is the diffusion constant and $c_i$ (mol m$^{-3}$) represents the molar concentration. The first term represents the contribution of diffusion and electro-migration to the molar flux. The second term represents convective contributions and can in the case of electro-osmotic flow be used to assess the ionic transport by substituting equation (11) into (13). Due to the difference in ionic distribution between microchannels or reservoirs and nanochannels, which is caused by the presence of the EDL as discussed above, a number of specific transport phenomena occur. At the interface between micro and nano a flux gradient exists for ionic species due to their sudden spatial change in concentration, which will give rise to the so-called concentration polarization. On the one side of the nanochannel the salt concentration will increase and on the other side decrease. This phenomenon, long since established in membrane science and colloid chemistry, has also been demonstrated in nanochannels [75]. Another phenomenon that becomes important in small channels is surface conduction. Since the ionic concentration in the EDL is higher than in the liquid bulk, the contribution of the conduction in the double layer, the so-called surface conduction, increases on downscaling. This phenomenon, also widely known in physical and colloid chemistry, has recently also been investigated for nanochannels [76].

Apart from the molecular charge, transport of all molecules, including charged molecules through nanochannels, is affected by the molecular size with respect to the lateral channel dimensions, and also by considerations of molecular entropy. Molecules can be excluded from channels by ion exclusion, by steric hindrance or because of the cost in internal entropy. On the basis of these three factors, nanochannels work as molecular sieves, much like membranes. These aspects have recently been reviewed by one of the authors [77] and also extensively by the group of Han [78]. More details are given in the section on molecular separation.

2.2.5. Modeling ionic transport. The theory concerning electrokinetics given above boils down to two equations, namely the Poisson–Boltzmann to describe the EDL and the Nernst–Planck to describe ionic transport. Both equations are continuum equations and should thus be tested on their applicability to ionic transport in nanochannels. This can be done by comparing continuum results with molecular dynamic results. Furthermore, the Nernst–Planck equation is valid for a dilute electrolyte solution (i.e. ions do not influence each other) and, just as the Poisson–Boltzmann theory does, considers ions to be ideal point sources with an infinitely small size. Over the years different patches have been developed to overcome these assumptions. The limitation imposed by the dilute electrolyte assumption is usually circumvented by using empirical activity constants instead of concentrations [34, 79]. These activity constants are strongly dependent on ion type and concentration and are used to model the decrease in effective migrational transport rate. The influence of a finite ion size is in the case of EDL theory often implemented by a Stern modification [34, 79]. By using the Stern modification one assumes that ions are hydrated and because of that have a minimum distance of approach to the wall surface. Here, the Stern model stems from the more elaborate Helmholtz model which is shown in combination with the diffuse Gouy–Chapman model in figure 1. Other models that take the finite size and the interaction of different ions into account are those that model steric effects.
Figure 1. Generally accepted model of the double-layer region under conditions where anions are specifically adsorbed. Here, $M$, IHP and OHP stand for metal, inner Helmholtz and outer Helmholtz plane, respectively. $\Phi$, $q$ and $\sigma$ represent electrostatic potential, amount of charge and charge density, respectively. $x_1$ and $x_2$ represent the typical distances of the IHP and OHP, respectively, from the metal surface. The indices i and d stand for inner and diffuse layer, respectively (reprinted from [79]).

A recent review of these models and the implications for the Poisson–Nernst–Planck equations by Kilic et al is found in [80, 81]. The question as to whether electrokinetics in nanochannels ought to be modeled taking molecular dynamics into account is answered in [11, 82]. The general conclusion is that molecular behavior should be taken into account to model electrokinetics in systems consisting of 10 molecular layers ($\sim$3 nm) or less. The reason for this is that strong density fluctuations of species (i.e. water molecules and ions) in the first few molecular layers adjacent to the wall cause strong deviations from Poisson–Boltzmann theory. Furthermore, using the results from molecular dynamics simulations and inserting them as lumped parameters into the Poisson–Boltzmann and Stokes equations (the modified continuum model mentioned in section 2.2.1) is beneficial in modeling electrokinetic behavior in larger nanofluidic systems (3–10 nm).

2.2.6. Modeling molecular transport. Molecular transport can also be modeled using the Nernst–Planck equations. However, diffusion and migration often need to be assessed separately, employing modified diffusion and electrophoretic mobility constants. For example,
Balducci et al [83] describe modified diffusion of double-stranded DNA molecules in 100 nm high nanoslits. Ajdari and Prost present a model to account for the modified electrophoretic mobility of DNA molecules [84]. Salieb-Beugelaar et al report on retardation effects in the electrophoretic transport of 48 bp DNA molecules in 20 nm high nanoslits at higher electric fields (>30 kV m\(^{-1}\)) [85]. In all cases, interactions with walls and entropic effects have to be taken into account as they influence the three transport mechanisms. The same is true for convection, which is of course known from chromatography. Once modified transport constants are found, their influence can be assessed by substitution into (in the case of diffusion and electrophoresis) and scaling (in the case of convection) of the Nernst–Planck equations.

2.3. Wall effects

As mentioned in the introduction, effects that happen at the channel walls become increasingly important when decreasing channel height. Typical examples of these effects are the occurrence of EDLs, slip [36, 86] and specific adsorption effects [87]–[91]. Moreover, surface roughness can also have a pronounced effect on transport properties. For example, Qiao et al [17] performed molecular dynamics simulations and found that surface roughness can strongly affect electro-osmotic flow (causing up to 50% decrease in velocity). Another example is the large flow enhancements found by Cotin–Bizonne [92] that occur because of increased slip due to air trapped at hydrophobic walls caused by a large surface roughness. A wall effect that up to now has hardly received attention in nanofluidic literature is the chemical equilibrium between surface silanol (SiOH) groups and the liquid. The authors strongly believe that this equilibrium will have a profound effect on the so-called gating in nanofluidic transistors, first described in a synthetic nanochannel by Karnik et al [93]. This is because the equilibrium can be shifted by applying a different potential at the wall. This shift in equilibrium will result in a strong release or uptake of protons inside the liquid, thereby changing pH and influencing the resulting wall potential. Indeed, recent experiments reported by Jansen et al [94] indicate a large proton release from nanochannel walls on capillary filling, acidifying the filling solution and titrating its constituents. Moreover, since protons are highly conductive, proton uptake or release by the wall can strongly affect the conductivity of the liquid, as discussed by van der Heyden et al [68]. These authors found that replacing the constant potential or constant surface charge condition with a chemical equilibrium condition leads to the best fit with the experimental surface conduction data.

In the following sections, the influence of slip and adsorption effects on transport will be discussed.

2.3.1. Liquid slip. In this subsection, the influence of a nonzero velocity of liquid molecules at the channel wall (also known as liquid slip) will be discussed. Whereas no slip represents a situation where the liquid in the first molecular layer is stagnant and all other molecules are sheared past the first molecular layer, the first molecular layer does move in slip flow, though with strong friction with the wall. The lower this friction with the wall—achieved, for example, by employing very hydrophobic walls—the less force is needed for a given flow velocity. Therefore, slip is very important in nanofluidics since it drastically reduces the required pressure in pressure-driven flows. Whitby and Quirke review very low-friction flows in carbon nanotubes and nanopipes and discuss several approaches to a functional device in [95].
Figure 2. Three cases of slip flow past a stationary surface. The slip length $b$ is indicated. Drawing after Lauga et al [101].

It has been predicted theoretically for some time that electro-osmotic flow would also be strongly enhanced in the case of slip, and recently the first experimental evidence for this was found [96]–[98]. A theoretical case has also been made for strong flow enhancements in the case of diffusio-osmosis [99]. The fact that the effects of slip are far more pronounced in nanochannels than in microchannels can be seen in equation (14), which describes the average fluid velocity due to an applied pressure gradient in a rectangular channel of width $\gg$ height [100],

$$u = \frac{h^2}{12\eta} \left( -\frac{dP}{dx} \right) \left( 1 + \frac{6b}{h} \right).$$

Here a pressure difference, $dP/dx$, is applied in the axial direction of the channels. $b$ represents the slip length and is defined in figure 2. Comparable equations can be written for electro-osmotic flow and diffusio-osmosis, the difference between them being that the channel height is replaced by, respectively, the Debye length and a length characterizing a molecular adsorption layer.

Recently, one of the authors discussed the consequences of liquid slip on micro- and nanofluidics [36]. For reasons of clarity a figure from this paper is repeated, originally published in [101].

In figure 2, the consequences of slip for the velocity of the liquid are clearly shown. The case on the right is particularly informative, because it represents a situation where liquid does not experience any friction with the wall and could theoretically be accelerated to the speed of light.

Parameters that are known to influence slip in nanochannels are surface roughness and hydrophobicity [92, 102]. Generally, the slip length is increased for increasing hydrophobicity and decreasing surface roughness when the channel walls are hydrophilic. There is, however, convincing evidence that surface roughness in the case of hydrophobic channels leads to greater slip lengths (several tens of microns as compared to around 20 nm for smooth hydrophobic channels) because of air trapping in surface inhomogeneities [92]. For more detailed information on slip flow, refer to [36] and references therein.

2.3.2. Wall adsorption. In nanofluidic channels where the lateral dimension is often orders of magnitude smaller than the axial dimension, the effects of lateral diffusion are much more pronounced than in microfluidic channels. On transport through a nanochannel the frequency with which a molecule hits a wall by lateral diffusion is greatly increased with respect to
microchannels, since this frequency scales with $1/h^2$. The tendency of molecules to adsorb on the channel wall material when they encounter it can lead to a large decrease in the transport rate of such molecules in a process equivalent to liquid chromatography [103]. This observation is reflected in the number of publications that have appeared in recent years concerning modified transport in nanochannels of mainly cationic molecules [87]–[91], [104]. On diffusion of adsorbing molecules through a nanochannel, the reduced transport rate is accompanied by a sharply defined diffusion front. Karnik et al [89] demonstrate that this effect can be used to precisely pattern the surface of nanofluidic channels. The same phenomenon had previously been described by Delamarche for microchannel patterning [105]. Karnik et al also present an analytical model to account for altered diffusion, introducing a modified diffusion constant that describes the change in transport as a function of cross-sectional area, perimeter, surface density of adsorbed species and the concentration of the molecule under consideration at the channel entrance. Experimental evidence for transport rates in nanochannels supports this, and for proteins and positively charged dyes diffusion constants were reported that were from four orders of magnitude [88] to as much as eight orders of magnitude [87] lower than tabulated bulk values. These dramatic changes will, for example, have a profound influence on using such molecules as tracer molecules to assess the flow velocity, rendering this approach practically impossible.

3. Applications

In this section, several applications of transport in nanochannels are treated. Technology concerning the fabrication of nanofluidic devices employing transport will not be treated here, since several extensive reviews on this subject have already appeared [2, 4, 5]. Since in most cases transport needs to be assessed, in the first subsection flow detection methods are reviewed concerning their applicability to flow at the nanoscale. In the next subsection, several applications found in the literature are looked at. Common applications range from pumping and transport control to energy conversion and separation of analytes.

3.1. Flow detection

In this subsection, the detection of transport in nanochannels is discussed. Whereas flow detection in microchannels has often evolved from macro-scale methods, flow detection in nanochannels has been expected to run into more fundamental problems, such as the minimum spatial resolution of around 300 nm for visible light [106]. This limiting spatial resolution prevents the detection of flow profiles across the height of the channel, but could possibly be improved by combining evanescent wave illumination and particle image velocimetry (PIV), as first discussed by Zettner and Yoda [107]. Recently, Bouziques et al applied total internal reflection fluorescence (figure 3) to perform PIV in a 200 nm thin layer adjacent to a microchannel wall [96]. Limited spatial resolution is, however, not the only problem experimental nanofluidics researchers must encounter. Since transport in microchannels is often assessed by particle-based visualization techniques (such as PIV), effects posed by the channel walls will certainly influence transport of such particles. Since nanochannel walls are often negatively charged, introduced particles have to be negatively charged to prevent them sticking to the wall and consequently clogging the channel. This complicates introducing such particles into nanochannels, since equally charged particles and walls lead to a high possibility of

New Journal of Physics 12 (2010) 015004 (http://www.njp.org/)
exclusion of the particle, dependent on the ionic strength. Electrostatic repulsion from the walls will furthermore cause particle enrichment in the center of the channel. Using physiological-strength electrolytes, this limits the applicability of such techniques to channels larger than $\sim$10 nm. Another very obvious problem is the limit on the minimum size of the particles currently available, which is around a few nanometers.

Moreover, there is also a limited applicability of tracer molecules to visualize microchannel flows. As mentioned in the previous section for particles, molecules of opposite or neutral charge adsorb to the wall. Same-charge molecules, however, can be excluded, resulting in concentration reductions of several orders of magnitude, as discussed in section 2.2.2, resulting in the need for a very low detection limit of the detector used (mostly fluorescent). To further complicate matters, neutral fluorescent molecules tend to be insoluble in water, greatly limiting their application. Modeling of the reduced transport properties with the model of Karnik et al, as discussed in section 2.3.2, could provide a way to indirectly determine flow properties using positively charged dye molecules. It should be noted, however, that adsorption of positively charged dye molecules to the wall is likely to decrease electro-osmotic flow drastically by decreasing the wall potential.

The other flow-sensing methods employed in microchannels found in the literature [106] are time-of-flight techniques, such as the heating of a small cross-sectional segment of liquid and subsequent detection downstream. Here, the distance between the heat actuator and detector, divided by the time between the application of the heat pulse and the detection, is a measure of the time-and-space-integrated velocity of liquid in the channel. The applicability of this technique to nanochannel flows is questionable, since the induced temperature gradient is likely to be diminished by heat transfer to the walls, which is very efficient in large surface-to-volume ratio systems. Finally, Mela et al [108] apply the current monitoring technique successfully to assess nanochannel electro-osmotic flow. This technique is also a time-of-flight technique and works by measuring the time it takes to refresh an electrolyte of a given strength with another one having a different strength by measuring the current along the channel. This technique is
often applied as a calibration technique for other flow-visualization techniques [106] and was first described by Huang et al [109] to assess the electro-osmotic flow rate in capillary zone electrophoresis. This technique is, however, only useful in obtaining a temporal and spatial average. Furthermore, its applicability is limited to electrolyte strengths and channels that are high enough for surface conduction not to determine the axial conductivity of the channel. Stein et al [76] show that surface conduction for 70 nm channels already becomes dominant for salt concentrations below 4 mM. Extrapolating the experimental data in [76] limits the applicability of the current technique to monitor nanochannel flows for physiological solutions to a channel height of approximately 5 nm.

3.2. Liquid transport (pumping)

As discussed in the introduction, pumping of liquids in nanochannels is preferably performed by electrokinetics, among other reasons because of its beneficial scaling behavior. This observation is reflected in the focus on electrokinetics encountered in recent reviews of nanofluidics [2], [5]–[7]. Whereas most publications address flows with zero slip at the walls, Muller et al [98] predicted that hydrodynamic slip will strongly enhance the magnitude of electro-osmotic flow in nanochannels, since the effect will scale with \( b/\lambda_D \) (with \( b \) the slip length and \( \lambda_D \) the Debye length) instead of with \( b/h \) as for pressure-driven flow (with \( h \) the channel height). This prediction was recently both theoretically and experimentally supported by Bocquet and co-workers, who found an increase of the electro-osmotic flow velocity at hydrophobic surfaces by a factor of two (figure 3, right-hand side) [96]. A much smaller number of articles has been published in which pressure-driven flow is employed [110]–[113]. These, except for [113], have an electrokinetic angle, because they consider power generation by generating streaming currents.

Several other driving forces are proposed in the literature [114]–[118]. An example of a more exotic driving force is diffusio-osmosis [99], [118]–[121]. Here, liquid transport is generated by a concentration difference between two ends of a channel or two sides of a particle. This concentration difference causes two types of transport named chemi-osmosis and electro-osmosis, caused by diffusion and migration of net charge, respectively. Transport in the latter case is caused by a difference in cationic and anionic flux, thereby inducing a potential gradient along the channel. This potential gradient in turn induces fluid motion in the channel equivalent to electro-osmosis except without the need for an externally applied potential difference. The flow speeds attained are of the order of \( \mu m s^{-1} \), which is probably the reason diffusio-osmosis has received less attention in the literature than electro-osmosis. An interesting development in the field is the introduction of liquid slip to diffusio-osmosis-driven pumps. Ajdari and Bocquet [99] theoretically proposed diffusio-osmosis as a viable pumping method in nanochannels, under the condition of a certain amount of liquid slip. In that case the diffusio-osmotic flow velocity would be amplified by a factor \( b/L_m \), where \( L_m \) is a sub-nanometer molecular length scale. A 100-fold amplification of the diffusio-osmotic flow velocity would then be possible.

Eijkel et al [114] communicate their findings on liquid flow in 500 nm high all-polyimide channels induced by pervaporation or osmosis of the solution through the thin channel roof. Due to the use of a large pervaporation area, the measured flow rates are up to 70 \( \mu m s^{-1} \). The pervaporation of water induces fluid flow by the movement of water from high chemical potential in the channel to low chemical potential in the atmosphere, as in trees, and osmosis.
induces fluid flow by water movement from low salt concentration to high salt concentration. This is a typical example of a technique that exploits the large surface-to-volume ratios in nanochannels, since pervaporation is a function of surface and the effect for equal pervaporation rates is more pronounced in small volumes.

Soare et al [116] describe theoretically a system with active deformable walls to drive liquid through a nanochannel. And in an extraordinarily simple experiment by Huh et al [122], PDMS nanochannels are deformed to pump liquid. Nanochannels in Poly Di Methyl Siloxane (PDMS) are created by applying mechanical stress to thickly oxidized PDMS layers. Cracks that are created in this manner have a controllable width and height of 688 and 58 nm, respectively, and are triangular shaped. This shape in combination with the use of extra-stiff PDMS probably helps this device from sticking irreversibly. Liquid pumping in these channels can be obtained by applying a relatively small pressure (22–42 kPa) to the PDMS. Here, lower applied pressures can be used to control flow velocity and higher pressures to completely close the channels. This technique could have an impact on nanofluidics comparable to that of Quake and Scherer’s systems on microfluidics [123], because of the relatively easy fabrication and the potential for massive parallelization. All other techniques exploit the dominance of surface tension and viscous forces over inertia in nanofluidic channels. For example, Tas et al [117] use capillary filling to induce liquid movement in small microchannels in a technique that could potentially be scaled to nanoconfined channels. Pumping is performed by first replacing water with gas by inducing a slight gas over-pressure, and then replacing gas with water by capillary pressure. A structural asymmetry in the system provides directionality to the pumping.

Another, more exotic, way of exploiting surface tension and viscous forces is one where liquid flow is induced in a lipid nanotube between unilamellar vesicles [115]. This is done by continuously manipulating the shape of one of the vesicles using a micromanipulator, with this changing the surface tension, causing a lipid flow in the nanotube from high to low surface tension, which consequently drags the liquid in the nanotube along by viscous forces.

3.3. Control of molecular transport

In this subsection, transport control of dissolved molecules in nanofluidic channels is discussed. By transport control we mean here active control over the transport of ionic or molecular species inside the liquid. In microchannels, transport control is often (of course with the notable exception of separation techniques like chromatography and electrophoresis) concerned with flow control [124], where only the transport of the liquid is actively controlled and the ionic-molecular species inside it passively follow the flow lines. In nanochannels, however, active control of the transport properties of different ionic and/or molecular species becomes feasible. The reason for this is twofold. Firstly, nanochannels have a size that is of the order of the EDL, making selective transport properties based on charge possible. Secondly, (bio)-molecules often have a size in the nanometer range, making selective transport properties and thus separation based on size a possibility. Both reasons are founded on the molecular filtering or sieving properties that nanochannels have, properties they share with membranes and filters [77]. Since in the following subsection separation is treated, in this subsection the discussion will be restricted to ways of controlling the transport properties inside nanochannels.

Flow control techniques in nanochannels are, as with the pumping techniques described above, dominated by electrokinetics [2], [5]–[7]. The possibility of controlling the transport
parameters of different ionic species inside the liquid inside a nanochannel was mentioned above. Examples of experimental papers exploiting this possibility are [104], [125]–[127].

Interesting to note is that though in all four articles different methods of gaining control over the transport properties are employed, all are based on electrostatics. Kuo et al [126] and Schoch et al [104] approach the problem mainly by altering the electrostatic potential by changing the chemical parameters pH and electrolyte strength. The main difference between the two is that Kuo et al use a membrane and Schoch et al a specifically engineered nanochannel. Karnik et al [125] gain control by actively varying the electrostatic potential at the wall of a nanochannel using electrodes buried in the wall. This modifies the double-layer charge, changing the electro-osmotic mobility, and could eventually lead to flow inversion at high applied positive voltages (i.e. in the case of a negatively charged wall). The effects are strongest at pH values close to the point of zero charge of the wall (around pH 2 for glass walls). The reason for this is that the chemical buffer capacity for protons of the walls is smallest in this region [128]. Finally, Miedema et al [129] present the most direct method of transport control, by altering the polarity of several surface groups inside a biological porin and thereby creating a nanofluidic diode. A trend in nanofluidics in recent years is to manufacture the fluidic equivalent of well-known electrical circuit elements such as diodes [129]–[132] and transistors [93, 125], [133]–[136]. This preferentially leads to large system integration on a single chip, as is known from electronic chips, which could for example be very beneficial for otherwise time- and analyte-consuming screening of new drugs [137]. Other examples of transport control by electrostatics work by changing important chemical parameters such as pH and/or background concentration [104, 126], [138]–[140]. Finally, Powell et al present the controllable oscillating transport of ions through nanoscale pores by the transient formation and re-dissolution of nanoprecipitates [141].

### 3.4. Energy conversion

Energy conversion from the liquid mechanical to the electrical domain is a topic of great recent interest. In the 1960s, Osterle [142] and Burgreen and Nakache [143] published theoretical studies on the potential of energy conversion in nanofluidic structures, but predicted low conversion efficiencies. Recently, the search for sources of ‘green’ energy has encouraged researchers to try to find solutions for this low efficiency [110]–[112], [144]–[146]. An advantage of fluidic energy conversion is its potential for massive parallelization on a relatively small surface area, thereby promising a high power density. In particular, the use of liquid slip has been indicated as a promising way to increase efficiency [146].

### 3.5. Separation

As it is not the main aim of this paper to review separation in nanodevices, and this subject would indeed deserve a separate review, we will discuss it here only briefly. Reviews of separation in nanoengineered devices have recently appeared [77, 147], also providing some background theory. Phenomenologically, the same forces are encountered as in microscale systems, namely hydrodynamic forces, electrostatic forces, van der Waals forces, solvation forces (like hydrogen bonding) and entropic forces. The use of micro- and nanotechnology now allows for better control of the separating structure, enabling improved separation performance or even entirely new separation methods.
Hydrodynamic forces are mainly employed in separation systems to transport the analytes from the injection point to the detection point, but a parabolic flow profile can also be used to perform hydrodynamic chromatography using the different average speed of large and small species in such a flow. Blom et al [148] showed hydrodynamic chromatography in channels of 1 µm height, separating beads of the order of 10 nm. Stein et al [113] showed a size-dependent transport rate of DNA in nanochannels by pressure-driven transport of DNA, which they ascribed to a process similar to hydrodynamic chromatography. Ogston sieving (sieving based only on molecular size) can be regarded as a variant of hydrodynamic chromatography in a sieving matrix. The group of J Han has demonstrated a device that performs this type of sieving in a continuous-flow fashion [149].

Electrostatic forces are employed in the direction of main transport (electrophoresis), but they will also always be present in the double layer, acting perpendicular to the transport direction. In the latter case they alter the rate of passage of charged analytes through a sieve. Since the electro-osmotic flow profile in a nanochannel approaches a parabolic shape, this modifies the transport rate of the counter-ions residing close to the wall with respect to co-ions residing in the middle of the channel. As a result, the effective electrophoretic mobility is affected, as demonstrated by Pennathur et al [73, 74].

Several groups have demonstrated electrophoretic separation of DNA in nanochannels [150]. Cross attributed the observed separation of 2–10 kb-long DNA molecules in 19 nm-high nanoslits to a differential friction with the walls [151]. Pennathur et al observed electrophoretic separation of DNA oligomers (10–100 bp) in 100 nm deep channels [152]. The observed dependence on ionic strength suggested an important role for the EDL field. Salieb-Beugelaar and Teapal et al observed a mobility of long DNA (48 and 2.8 kbp) in 20 nm nanoslits that depended on the DNA length and strongly on the applied field, with transient trapping observed at higher fields [85]. In view of the applied field strengths (up to 200 kV m⁻¹) dielectrophoresis and steric trapping were suggested as explanations.

In general, the inevitable increase of entropy during a separation decreases the resolution obtained. In the case of the self-diffusion of the DNA molecule, however, entropy can be used for separation. Nanofluidic confinement removes entropic freedom from a DNA molecule, and as a result DNA tends to remain in a space where it can freely self-diffuse, or to move to such a space if part of its chain already resides there. This ‘entropic trapping’, which is also known from large-pore gels [153], has been employed in nanofluidic devices for DNA separation in both batch-like and continuous formats [78, 149], and was also employed in an entropic recoil device [154]. Timescales for separation, however, are long because diffusional steps are necessarily involved. A very eloquent view of separation by exploiting changes in entropy is expressed by Austin [155].

Leinweber et al [156] showed that entropy can also be counteracted electrochemically in a nanofluidic continuous flow de-mixing device. On the application of an axial electrical field, de-mixing was observed at electrode islands embedded in the channel wall, separating ionic analytes in concentrated and diluted streams in the flow direction.

Liquid chromatography can benefit greatly from micromachining, which provides an entirely regular packing of the separation channel, which considerably decreases peak broadening. The group of Desmet has advanced considerably in this area [157, 158], continuing the work begun by Regnier et al [159]. They employ micromachining to pack a separation channel with pillars of width and spacing of the order of 500 nm, and provide the necessary nanoporosity of the separation matrix by the use of porous silicon.
A drawback of nanofluidic separation systems is their low sample throughput, which gives rise to detection problems. This problem can be addressed in several ways. A continuous flow format can be adopted, which improves the quantity of separated analyte at the cost of analysis time \([78, 147, 149, 160]\). Alternatively, the concentration polarization caused by a nanochannel can be employed to pre-concentrate analytes in a (perpendicular) microchannel \([161]\). In both cases, the spatial architecture of the systems involved is only practicable because of the use of micromachining methods, allowing ‘smart design’ that is non-random down to the 50 nm scale \([162]\). Another answer to the detection problem might be the use of parallel separation channels with parallel detection in each channel to avoid band broadening.

4. Conclusion and outlook

In conclusion, we have shown by reviewing both the experimental and the theoretical literature that liquid flow and electrokinetics in nanochannels concerning aqueous electrolytes can often be modeled using continuum theory (i.e. the Stokes and Nernst–Planck equations for the liquid flow and electrokinetic problems, respectively) for channels with a size down to 10 nm. For smaller channels or parts of interest of larger systems, the application of continuum theory needs to be carefully deliberated. Moreover, we present several important consequences for transport of an increasing surface-to-volume ratio for decreasing channel height/diameter. We reviewed liquid slip, chemical equilibria between solution and wall molecules, adsorption of molecules to the channel walls and wall surface roughness.

The applications of transport in nanochannels range from pumping and transport control to energy conversion and separation. The high surface-to-volume ratio in all these applications plays a dominant role, causing the transport to be determined by interactions between the liquid and/or molecules inside it and the walls, and sometimes also causing problems like adsorption. It was also seen that in nanofluidics transport control of individual-charged molecules becomes feasible, in contrast to microfluidics. At downscaling the double-layer thickness approaches the channel height, and liquid transport and charge transport become increasingly coupled. As a result liquid displacement is accompanied by a net charge displacement that induces potential and/or pressure gradients that strongly influence transport properties. On the basis of recent developments, we expect that nanofluidics will play an important role in a number of fields, both fundamental and applied.

On the fundamental level single-molecule studies will probably benefit from the ease and precision of confinement in nanofluidic channels, and the relatively easy way in which different geometries can be sculpted by micromachining. Applications in (bio)analytical chemistry, especially with regard to separation, are likely to follow. Concerning single cell studies, it can be envisaged that the extremely small cell volumes can be addressed using nanofluidic dosing or extraction systems. Finally, for energy conversion from the mechanical to the electrical domain, nanofluidic solutions have potential when liquid slip can be implemented.

Acknowledgment

The Dutch Technology Foundation STW is gratefully acknowledged for financial support via a Nanoned grant.
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