1 Introduction and Overview

1.1 Micro- and nanofluidics

Analyzing and computing fluid flow at small scales is becoming increasingly important because of the emergence of new technologies such as the ability to construct microelectromechanical systems (MEMS). These systems may be used for drug delivery and its control; DNA and protein manipulation and transport; and the desire to manufacture laboratories on a microchip for rapid molecular analysis, requiring the modeling of flows on a length scale approaching molecular dimensions. On these small scales, new flow features appear that are not seen in macroscale flows.

Because of the large surface-to-volume ratio in nanochannels, surface properties become enormously important. Because the pressure drop $\Delta p \sim 1/h^3$, it is prohibitively large for a nanoscale channel. Thus fluid, biomaterials such as proteins, and other colloidal particles are most often transported electrokinetically, and the art of designing micro- and nanodevices requires a significant amount of knowledge of fluid flow and mass transfer (biofluids are multicomponent mixtures) and often heat transfer, electrokinetics, electrochemistry, and molecular biology. To efficiently manufacture laboratories on a microchip, the analysis and computation of flows on a length scale approaching molecular dimensions, the nanoscale, are required.

The common thread is micro- and nanofluidics. Thus micro- and nanofluidics play the role of unifying the fields of fluid mechanics, heat and mass transfer, electrostatics and electrodynamics, electrochemistry, and molecular biology. In particular, nanofluidics opens the door to uncovering the structure and conformation of biomaterials, such as proteins, through molecular simulation.

The objective of this book is to introduce the reader to micro- and nanofluidics, the basic mechanics of modeling fluid flows and heat and mass transfer, that is, at very small scales. The emphasis is on those systems that have biological and chemical applications. These systems are commonly at the microscale, with length scales $\sim$100 μm or 100×10^{-6} meters, and the 100 times smaller nanoscale, at length scales $\sim$100 nm or 100×10^{-9} meters. In many of these systems, transport is from the microscale to the nanoscale and back to the microscale.

Microfluidics in general consists of three distinct components:

1. Modeling: computational and theoretical
2. Fabrication
3. Experimental methods

The emphasis will be on modeling because of the limitations of experimental methods at the micro- and nanoscale, although experimental methods are also discussed, where appropriate; Bohn (2009) discusses some of the experimental methods used to probe single molecules. Because this is primarily a book about modeling, fabrication methods are not discussed.

Government research programs, such as the Defense Advanced Projects Research Agency (DARPA) and Simulation of Biological Systems (Simbiosys), (which ran from 2002 to 2005), deal with the development of microsystems that can be used to identify many types of molecules through their transport characteristics. The ultimate goal of the program was to develop computer-aided design tools (CAD) for applications to chemical–biological warfare defense, infectious disease monitoring, and drug delivery.

The governing equations of fluid flow on a length scale orders of magnitude greater than a molecular diameter are well known to be the Navier–Stokes equations, which are a statement of Newton's law for a fluid. Along with conservation of mass and appropriate boundary and initial conditions in the case of unsteady flow, these equations form a well-posed problem from which, for an incompressible flow (constant density), the velocity field and pressure may be obtained.

Applications in the biomedical field involve, for the most part, internal flows in micro- and nanochannels and tubes. The fluids are generally electrolyte mixtures, with, perhaps, a biomolecular component, usually some protein (say, albumin). Thus mass transfer occurs, and because many biomolecules (e.g., most proteins) are charged, there is an electric field as well. The determination of the identity and rates of transport of ionic and biomolecular species is one of the purposes of many micro–nanoscale devices.

Because micro- and nanofluidics usually involves the transport of charged species, its study requires a multidisciplinary approach. Thus the study of fluid flows at the microscale and nanoscale most often requires expertise in electrochemistry, surface chemistry, electrostatics and electrokinetics, molecular biology, heat and mass transfer, and macro-scale fluid mechanics. To design devices having micro- and nanoscale features requires a team approach involving chemists, biologists, medical practitioners, engineers, and systems analysts. As one might guess, each of these disciplines speaks a somewhat different language, and it is only with some effort that these technical language barriers can be overcome.

There are a number of textbooks on various aspects of electrokinetic phenomena, including the fluid mechanics of electrokinetics; for more details, see Chang and Yeo (2010), Masliyah and Bhattacharjee (2006), Karniadakis *et al.* (2005),

Bruus (2008), Kirby (2010), Tabeling (2005) and Li (2004). All the aforementioned books are essentially monographs written primarily for advanced graduate students beginning their research careers.

It is with this interdisciplinary view of micro- and nanofluidics that our journey begins. We start in this chapter by presenting some examples of micro- and nanofluidic devices, followed by a working definition and a bit of the history of nanotechnology. Then a broad discussion of the fields of fluid mechanics and heat and mass transfer is presented. This is followed by a discussion of electrostatics and the character of electrolytes (charged fluid mixtures). Micro- and nanofluidics often deals with mixtures of liquids and solid particles. If the particles are less than a micron (10^{-6} m) but larger than about 1 nm, the mixture is termed a *colloidal mixture*. Finally, we introduce some of the basic concepts of molecular biology. One of the major objectives of this book is to show how micro- and nanofluidics unifies the fields of the thermal sciences, electrochemical systems, and molecular biology. The unifying features of these fields are described next, followed by a discussion of a typical design procedure. The chapter concludes with two short sections on unit systems and notation, the latter being a very important section. In short, all notation is local.

1.2 Some micro- and nanofluidic devices

In this section, we qualitatively describe several micro- and nanofluidic devices and their applications. An interesting application of microtechnology is small drug delivery devices. These devices can deliver very small and precise doses of medicines quickly and efficiently. Some devices may also be used as biomolecular separators because different species (often electrically charged) and biomolecules travel at different speeds in these channels, due primarily to their differences in size, charge, and shape. Devices of this sort perform analyses faster and are more efficient in a wide variety of applications, including water quality, medical diagnostics, and applications associated with national security such as sensing chemical and biological toxins.

As you reflect on the art of designing micro- and nanodevices, think of the fact that this activity requires a significant understanding of fluid flow and mass transfer and, often, heat transfer and electrokinetics. Mass transfer is especially relevant to biofluids because they are multicomponent mixtures.

A specific example of this sort is an *electro-osmotic pump*, or sometimes *nanopump*, which is used to induce transport of charged molecules. Such a device is depicted in Figure 1.1(a). This biomedical device is useful for the delivery of various types of proteins, such as albumin and immunoglobulin, both of which have many biomedical uses (Peters, 1996). Nine channels are shown in the depiction, but an actual device may employ 20,000–40,000 channels. In general, in biomolecular transport and analysis systems, it is essential to have lots of little channels to distinguish the very small molecules that are being analyzed.

The device depicted in Figure 1.1(a) is often called a *synthetic nanopore membrane*. In biology and chemistry, the term *membrane* is used to describe a thin sheet of porous material that can be either natural (the outer skin of a cell is a membrane) or synthetic.

What is Lab-on-a-chip?

The ability to fabricate devices on the micro and nanoscale has led to the development of devices that can identify different molecules, separate these molecules, manipulate them, and transport these molecules. What had once required a laboratory and large samples can now be done at very small scales.

The generic name given to these types of devices is "Lab-on-a-chip (LOC)," which refers to a type of processing. The key feature of LOC is that the various steps in a diagnostic procedure "the laboratory" are integrated on to one small devices "the chip." These devices have also been called micro total analysis systems (μ TAS) and the two terms are most often taken to be equivalent. Most LOC applications have a biochemical component to them.

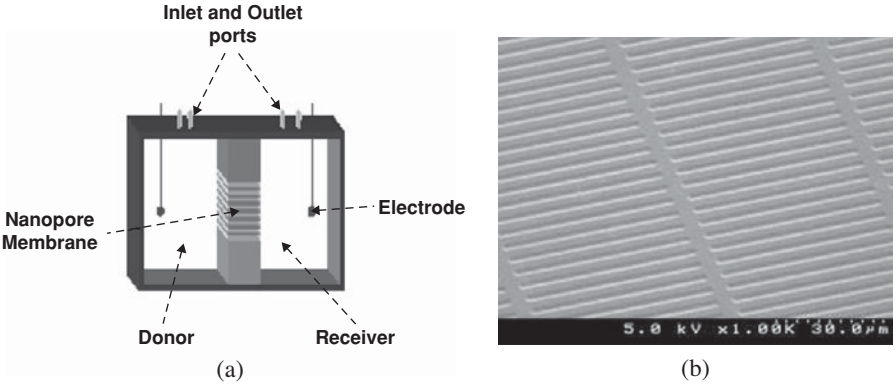
Such systems work because in a large or small sample the following general principles regarding the molecules under consideration here apply: Molecules can be identified by properties, such as how they appear under the action of a laser. Molecules of different size and electric charge characteristics move at different speeds allowing them to be separated based on a simple criteria. Molecules may be modified by inducing chemical reactions with other molecules. And finally molecules can be moved from one place to another by the bulk motion of the fluid.

Lab-on-a-chip devices are being developed for bacteria screening, cancer detection, and unicellular exploration.

Such LOC systems have several advantages that make them attractive in biomedical applications:

1. Lower equipment costs and power requirements because of the small length scales,
2. reduced separation and reaction times again because of the small length scales,
3. LOC typically require nano- to picoliter (vs. mL for comparable macroscale analyses) volumes of analyte and reagents, reducing chemical costs and biochemical hazard and waste disposal problems;
4. integrating sophisticated chemistry procedures within a single system, LOC can be used by nonspecialists to perform complex analyses.

The devices from within the chemistry and biochemistry industries described earlier were created using MEMS technology. The broad range of micro- and nanodevices of this sort are commonly referred to as a *lab on a chip*: a device that incorporates all the steps of chemical–biochemical analysis to perform a given measurement. Sometimes these systems are called *micro total analysis systems*, or μTAS.

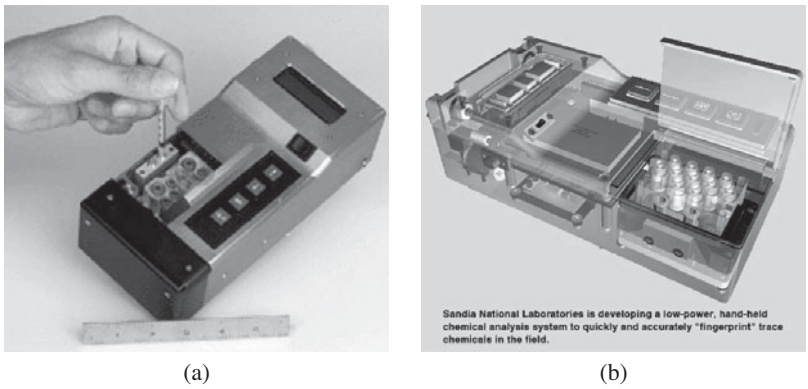


(a) (b)

Figure 1.1 (a) Drawing of a nanopump containing a nanopore membrane. (b) Scanning electron microscope (SEM) image of a synthetic nanopore membrane. From Conlisk *et al.* (2009).

As an example of a lab on a chip, Sandia National Laboratory has developed a fully integrated chemical analysis system that has the ability to determine constituents of gas and liquid samples within 1 min (Figure 1.2) through integration of sample collection, separation, and detection steps. It is made up of a compact power source, lasers and photodiodes, a microprocessor, and micro-sized injection and separation channels. In contrast, much of the current chemistry–biochemistry analysis labs consist of equipment as large as a microwave oven for each of the analysis steps.

The use of lab-on-a-chip devices in a chemical–biochemical analysis lab reduces equipment costs but can also reduce the cost of other resources. The advantages of a lab-on-a-chip device are comparable to the advantages of miniaturization seen in the computer industry. For example, when reducing the size of a computer chip, the distance electrons need to travel is much shorter, reducing the processing time. This same principle applies to microfluidic devices: reducing the size of a channel reduces the distance molecules need to travel, therefore



(a) (b)

Figure 1.2 Sandia National Laboratory fully integrated chemical analysis system that can be held in one hand. (a) Final product. (b) Cutaway image of the device, showing many of the components.

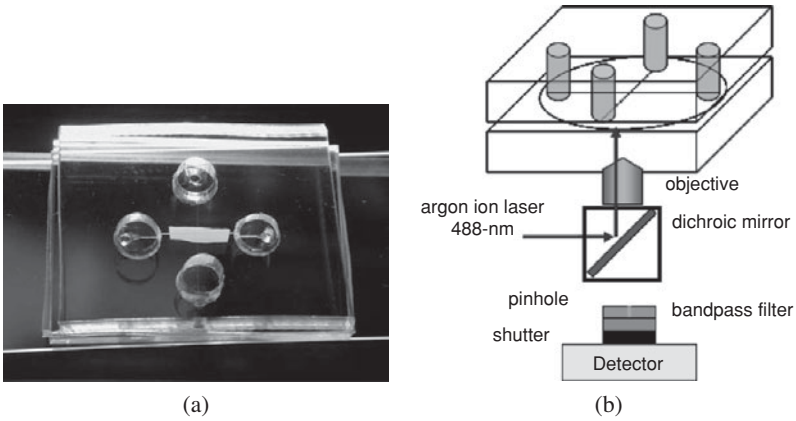


Figure 1.3 (a) Chip used for attomole level chemical detection courtesy of Professor Paul Bohn. (b) The detection system from Kuo *et al.* (2003).

reducing processing time. These devices are highly portable and also require much less *reagent*, or sample, the chemical compound used to detect and identify an analyte. For a standard analysis experiment, microliters or larger of reagents are used for each experiment; however, with lab-on-a-chip devices, only nanoliter or picoliter volumes may be required for each experiment. Think of the savings in chemical use and the environmental benefits of reduced chemical and biotoxic waste.

A number of security applications are associated with these devices. Nanocapillary array membranes of approximately circular cross section (Kemery *et al.*, 1998) are being used to detect biological warfare agents in concentrations at the attomole (10^{-18} mole) level. Such a system is depicted in Figure 1.3. Channels on the order of 10–100 nm are employed to manipulate these biochemicals, which must be handled in very low concentrations. A molecule is identified by a laser-induced fluorescence signal, and the device can identify molecular size and charge based on its transfer characteristics through the channel. A similar device can be employed with an enzyme sample (Gong *et al.*, 2008).

The nanocapillary array membranes (NCAMs) used in the 3-D configuration shown in Figure 1.3 function in the same manner in which individual transistors function in integrated circuits: by controlling the temporal and spatial delivery of ultralow-volume fluid packets. Achieving an all-electronic fluidic switching network with no moving parts is an enabling development for 3-D integrated microfluidic devices. In nearly all cases of multidimensional chemical analysis, the chemical sample needs to be processed through multiple sequential chemical unit operations. These might include separation of a desired component from a raw mixture, subsequent chemical processing (derivatization) to visualize the compound, and placing it in the right spatial location for detection and/or further characterization. In simple 2-D (planar) structures, the management of chip real estate soon becomes a design challenge. Going into the third dimension makes

it possible to save real estate and achieve highly compact and efficient designs. Furthermore, there is the possibility of using the individual nanopores to carry out enhanced chemical reactions by taking advantage of the small distances to improve the efficiency of chemical turnover. In this sense, the NCAMs are more than just simple fluidic switching elements; they can be thought of as attoliter-scale chemical reactors with on-demand delivery (or generation) of reagents and removal or collection of products.

Ion Channels

The basic units of all living organisms are cells. In order to keep cells functioning properly there must be a continuous flux of ions in and out of the cell and its components. The cell and many of its components are surrounded by a plasma membrane which provides selective transfer of ions through *ion channels*. The ion channels are embedded in the cell membrane, are usually negatively charged and are about 10 angstroms in diameter. The polarity of the plasma membrane makes it challenging for molecules to move in and out of cells and its components. Thus ions (Ca^{2+}, Cl^{-}, K^{+}, Na^{+}, H^{+}, Mg^{2+}, HCO^{3-}, $PO_4{}^{2-}$) must selectively move through the membrane via protein channels electrokinetically through a combination of electro-osmosis and electromigration. Both of these fluid dynamic phenomena are discussed in Chapter 9 and ion channels are described in more detail in Chapter 8.

Very recently, on April 26, 2009, new ion channels that govern the function of the inner ear were found in a very surprising place! (http://medicalnewstoday.com/articles/147506.php)

In contrast to the synthetic devices described earlier, natural nanochannels exist in cells for the purpose of providing nutrients and discarding waste; in that sense, they function as natural pumping systems. That is, these natural nanochannels, called *ion channels*, act as electro-osmotic pumps that contain perhaps thousands of nanopores – a natural nanopore membrane. Peter Agre of Johns Hopkins and Roderick MacKinnon of Rockefeller University won the 2003 Nobel Prize in Chemistry for their work on understanding how natural ion channels work.

1.3 What is it about the nanoscale?

Why is everything different at the nanoscale? Or is anything different at all? As the typical length scale of the channel approaches the microscale level and beyond to the nanoscale level (Table 1.1), conventional means of moving fluids, such as with a pressure gradient, become ever more difficult, and the character of the surfaces bounding a fluid becomes ever more important. Consider the channel depicted in Figure 1.4(a). In micro- and nanofluidics, the surface-to-volume ratio is very large, making the nature of the surface (e.g., its charge, roughness, and

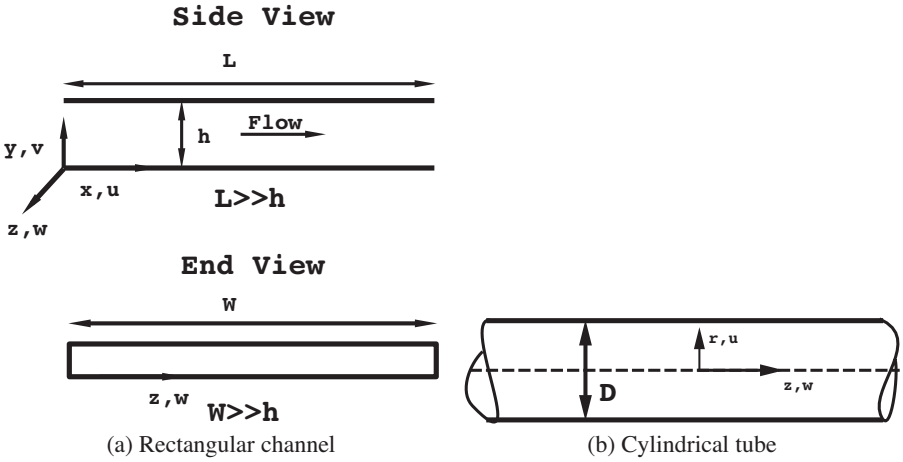
Table 1.1. SI units of length measurement

Factor	Prefix	Symbol
10^{9}	giga	G
10^{6}	mega	M
10^{3}	kilo	k
10	deka	da
10^{-1}	deci	d
10^{-2}	centi	c
10^{-3}	milli	m
10^{-6}	micro	μ
10^{-9}	nano	n
10^{-10}	angstrom	A
10^{-12}	pico	p
10^{-15}	femto	f
10^{-18}	atto	a

whether it is hydrophobic or hydrophilic) very important. The surface-to-volume ratio for a channel having dimensions $(L, h, W) = (1\text{ m}, 1\text{ m}, 1\text{ m})$ is

$$\frac{S}{V} = 2\left(\frac{1}{W} + \frac{1}{h} + \frac{1}{L}\right) = 6\text{ m}^{-1} \tag{1.1}$$

On the other hand, for a channel having dimensions $(L, h, W) = (3\ \mu\text{m}, 1\ \mu\text{m}, 40\ \mu\text{m})$ which is typical of a class of nanopore membranes, the surface-to-volume



(a) Rectangular channel (b) Cylindrical tube

Figure 1.4 (a) Geometry of a typical channel. In applications, $h \ll W, L$, where W is the width of the channel and L is its length in the primary flow direction. Variables u, v, w are the fluid velocities in the x, y, z directions. (b) Sketch of a cylindrical pore having velocities (u, v, w) in the (r, θ, z) directions.

ratio is

$$\frac{S}{V} \sim 2 \times 10^6 \text{ m}^{-1} \tag{1.2}$$

For a 20 nm channel, $(L, h, W) = (3\ \mu\text{m}, 20\ \text{nm}, 40\ \mu\text{m})$, the surface-to-volume ratio is even higher:

$$\frac{S}{V} \sim \frac{2}{h} \sim 40 \times 10^9 \text{ m}^{-1} \tag{1.3}$$

Because of the large surface-to-volume ratio, a surface roughness, for example, of 5 nm in a 1 μm channel, is negligible, whereas in a 10 nm channel, that same roughness can have a profound effect on the flow. The same situation occurs for a cylindrical tube (Figure 1.4(b)). In this case,

$$\frac{S}{V} = \frac{1}{R} = \frac{2}{D} \tag{1.4}$$

where R is the radius of the tube.

Several comments can be made about fluid flows in channels under 1 μm in minimum dimension:

1. Surface properties of a channel or tube, such as electrical surface charge density and roughness, become very important because of the large surface-to-volume ratio.
2. Significant increases in flow rate may be attained if the surfaces of the channel are hydrophobic (water hating); that is, significant fluid slip may occur at the wall. This occurence is termed *induced slip* or *apparent slip*.
3. The continuum approximation may break down, especially for gas flows.
4. Pressure-driven flow is only viable at very low flow rates, on the order of nL/min or 10^{-9} L/min, in nanoconstrained channels because of the very large pressure drops required otherwise, on the order of atmospheres.
5. Molecular diffusion, which is very slow at the macroscale, is fast at the micro- and nanoscale, the time scale being $t \sim L^2/D_{AB}$.

From the second comment, it is thus seen that for liquids, whether there is slip or no slip at the wall can be a function of surface chemistry, whereas in gases, slip is entirely controlled by the magnitude of the Knudsen number, the ratio of the mean free path to the characteristic length scale. However, it should be mentioned that liquid flows remain in continuum even for channels whose smallest dimensions approach 10 nm.

As mentioned, it becomes increasingly difficult to pump liquids by pressure in nanoscale channels. To see this, let us compare the pressure drop for *electro-osmotic flow* with the corresponding pressure drop for *pressure-driven flow* or *Poiseuille flow*. The *volume flow rate* in electro-osmotic flow may be estimated by

$$Q_e = CU_0hW \tag{1.5}$$

where U_0 is the electro-osmotic velocity scale and is independent of h (as we will see), C is a constant that depends on the concentration of the electrolyte, and W is

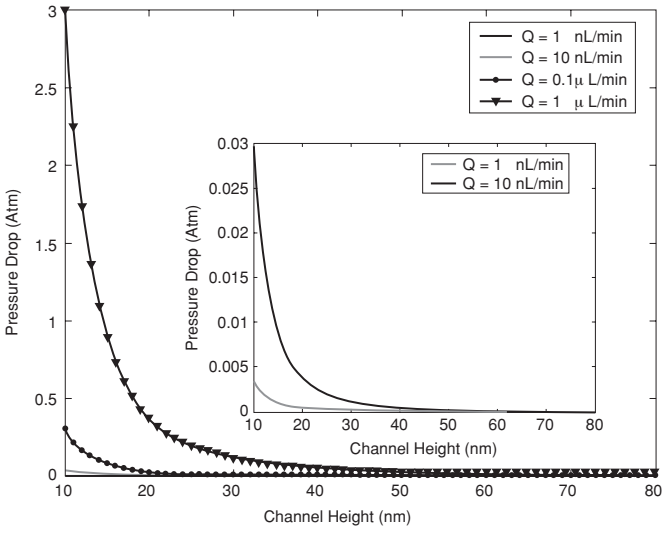


Figure 1.5 Pressure drop as a function of channel height to achieve a volume flow rate of $Q = 10^{-6}$ L/min and several values of the flow rate on the μL scale typical of many existing systems. Here L = liter; 1000 L = 1 m^3. The applied electrical potential for $Q = 10^{-6}$ L/min is very small.

the width of the channel. The velocity scale U_0 turns out to be directly proportional to the imposed electric field, and thus the flow rate is proportional to h. Conversely, for Poiseuille flow, the volume flow rate in a parallel plate channel is given by

$$Q_p = \frac{Wh^3}{12\mu L}\Delta p \tag{1.6}$$

where Δp is the pressure drop. This means that pressure-driven flow requires large pressure drops, as depicted in Figure 1.5; note that at a channel height of 10 nm, 3 atm of pressure drop is required to drive a flow of $Q = 10^{-6}$ L/min, which is a characteristic flow rate in drug delivery applications. However, if the flow rate is $Q = 10^{-9}$ L/min, the pressure drop is not nearly as large. Three atmospheres is a large pressure drop in a liquid, and clearly a relatively large pump would be required to provide this pressure drop. This is a major consideration when designing a nanopore membrane for the applications discussed previously.

As has been seen, it is often not feasible to transport fluids in nanochannels using an imposed pressure drop; electro-osmosis and electrophoresis are often used for transporting both charged and uncharged species and biomolecules. That is, electrokinetic phenomena play a crucial role in micro- and nanofluidics. Moreover, it is important to note that at present, velocity, temperature, and concentration profiles across a channel cannot be measured in channels having at least one dimension under about 1 μm (Sadr *et al.*, 2006; Breuer, 2005). Thus, to understand the physics of flows at those scales, modeling is not only necessary but also essential in describing the important features of the flow within a microdevice having nanoscale features such as a nanopore membrane.