Microfluidics: Basic Issues, Applications, and Challenges

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Introduction

The ability to create structures and patterns on micron and smaller length scales has triggered a wide range of scientific investigations, as well as the development of many devices to transport and manipulate fluids and pattern surfaces. The engineering paradigm, therefore, turns to design, manipulation, and control on length scales that are increasingly approaching the molecular. These types of investigations involving fluids, broadly identified under the theme of microfluidics, have rekindled interest in a classical area of fluid dynamics: low-Reynolds-number flows. The objective of this article is to highlight some avenues of research and development in microfluidics. Given the limited format of this article, extensive referencing is not possible, but research papers with novel ideas in this field are appearing at a rapid pace. One particularly interesting aspect of the research is the imaginative use of engineering, chemistry and physics to achieve devices with specific functions.

Modern developments in the design and utilization of microfluidic devices for fluid transport have found many applications, ranging from the life sciences industries for pharmaceuticals and biomedicine (drug design, delivery and detection, diagnostic devices) to industrial applications of combinatorial synthesis (such as rapid chemical analyses and high throughput screening). In other branches of medicine, new paradigms for noninvasive diagnostics and surgery are enabled by small (possibly implanted or ingested) microdevices. As an example of the rapidly increasing demand for biomedical microdevices, the biochip market was $400M in the year 2000 and is expected to increase fivefold by 2005 (Jain, 2000). Other areas of applications for microdevices for the transport of liquids and gases include the aerospace and automotive industries, microreaction engineering, printing, and optical applications. Novel electrical devices assembled using microfluidic components are also a possible area for technological innovation. Two recent articles in the *AIChE Journal's* "Perspectives" column provide examples of some of these applications (Jensen, 1999; Langer, 2000).

Generally, microfluidics refers to devices or flow configurations that have the smallest design feature on the scale of a micron or larger. Frequently, this means rectangular channels with cross-sectional dimensions on the order of tens or hundreds of microns. For most cases involving the flow of small molecule liquids like water, this scale is well suited to the standard continuum description of transport processes (such equations of change as the Cauchy stress equations supplemented by appropriate constitutive equations and body forces), even though surface forces play a more important role than is usual. The development of mechanical structures on the nanometer length scale is another area of rapid progress. Since many of these nanofabrication processes take place in the liquid state, the understanding of "nanofluidics" is a research challenge that will likely involve contributions from continuum, statistical, and molecular mechanics. In general, the design paradigm faced by the engineer is *scale-down* rather than the more familiar scale-up.

Micro- and nanodevices are useful because they allow manipulation with fast response times, they can handle small fluid volumes, sense and control flows and pattern substrates on small length scales, and, what promises to be very important, they can selectively address the cellular scale. Traditionally, silicon micromachining methods have been used to make micron-scale electrical and mechanical devices from silicon and glass. More recently, elastomeric materials have been used (McDonald et al., 2000). The latter systems offer potential advantages of faster design times, low cost, the ability to fabricate nanoscale features, and the possibility of deformable shapes (Quake and Scherer, 2000). Both fabrication techniques will likely continue to play important roles in future applications.

Many challenging research and design questions are posed by micro- and nanofluidic systems. Because the field has seen rapid recent development, several review articles have already been written (e.g., Gad-el-Hak, 1999; Ho, 2001). Most of these articles have focused on specific microdevices (Ho and Tai, 1998; Quake and Scherer, 2000; Whitesides and Stroock, 2001), such as the design of valves, pumps, actuators, mixers and reactors, sensors, and three-dimensional networks of channels. Many of these ideas are important in light of the development of the lab-on-a-chip concept (or micro-total-analysis systems), where transport processes, including mixing, reactions, separations, and manipulation of particles, are being applied on smaller scales than traditional engineering technologies. Another area of significant interest is in active control, for example, manipulating the boundary layer in high-speed flow; these applications are of less interest to most chemical engineers and will not be discussed further.

In addition to the design of new devices, there are research questions raised concerning transport processes, in particular the motion of particles in small devices, and the impact of surface forces. It is useful to consider "particles" in a broad sense and so distinguish (I) small organic molecules (a few Angstroms in size), (II) protein molecules (typical sizes about 20-50 Å), and large biopolymers such as DNA, (III) suspended solid particles or cells (typically 1-10 µm) or nanowires (tens of nanometers in diameter but typically microns in length) (Huang et al., 2001), and (IV) fluid droplets or gas bubbles with radii comparable to the channel, but with lengths possibly larger. In addition, surface forces are very important and often dominant on the small-scale characteristics of microdevices. These forces include van der Waals forces, forces associated with charged Debye double layers common when ionic solutions are present, and surface tension, which is typically significant when fluid-air or fluid-fluid interfaces are present. One can manipulate such surface forces by patterning substrates on length scales from microns to submicrons, and the laminar flow in microchannels is particularly useful here (so-called laminar flow patterning). As recently explained by Zhao et al. (2001), surface micropatterning of the walls of a microchannel directs streams of fluid based on wettability and so maintains continuous contact between gas and liquid streams. Surface patterning via laminar flow in microchannels is also potentially very useful in other small-scale coating processes (Darhuber et al., 2000), which represent a further application of design and control using microfluidic principles. Figure 1 shows one view of the range of length scales to be considered in microfluidics applications and studies.

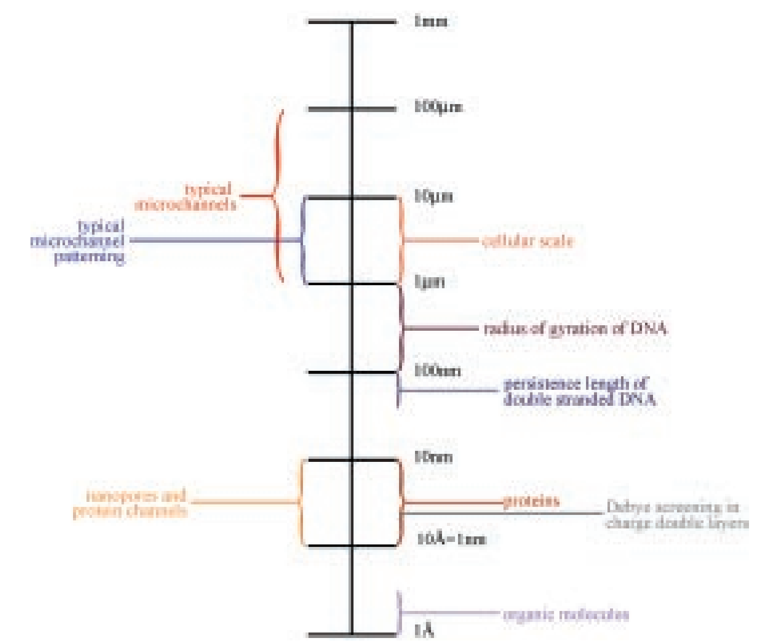

Figure 1. Microfluidics devices require the integration of understanding of a range of scales, from the micron size of most channels and delivery devices possibly down to the sizes approaching the molecular. An understanding of dynamical processes requires consideration of additional length scales including surface and manufacturing roughness, the extent of the influence of van der Waals forces and double-layer screening, and the radius of gyration, as well as the extended length, of biopolymers.

Low-Reynolds-number flow in microdevices

Typical applications are concerned with gases, water, or other aqueous solutions. The channels manufactured to date have dimensions $\ell \approx 1$–300 µm, and flow speeds u, though varying widely, and at least for liquids they are possibly in the range up to cm/s, which yields a Reynolds number $\Re = \rho u \ell / \mu < 30$ where ρ and µ denote the density and viscosity of the fluid. In many cases, $\Re < 1$ so that viscous forces dominate the response. For other cases, although the Reynolds number is not actually less than 1, it is in such a range that the flow remains laminar.

Investigations of low-Reynolds-number hydrodynamics naturally fall into the fluid dynamics realm of long interest to the chemical engineering community (Happel and Brenner, 1983; Kim and Karrila, 1991); indeed in the 1970s, G. K. Batchelor coined the term *microhydrodynamics* to describe this flow regime. The most important new themes introduced by the small length scales of microfluidic devices are the significant role of surface forces (surface tension, electrical effects, van der Waals interactions, and surface roughness), complicated three-dimensional geometries, and the possibility that suspended particles have dimensions comparable to the microchannels. One of the challenges is to creatively use or tailor these effects to produce functional devices.

Fluid motions in these small-scale systems are driven by the following.

1. *Applied Pressure Differences.* The velocity distribution is parabolic (or nearly so) across the channel, as familiar from the classic Poiseuille flow.

2. *Electric Fields.* The flow is referred to as electro-osmotic when bulk fluid motion is driven by stresses concentrated in charged (Debye double) layers near boundaries—the velocity profile is generally uniform—or electrophoretic when directed motion of charged particles occurs. For these cases, the response is expected to scale linearly with the electric field. In the case of dielectrophoretic responses, where motion occurs essentially because an electrical dipole interacts with the gradient of the electric field, the response is expected to be proportional to the square of the electric field.

3. *Capillary Driving Forces Owing to Wetting of Surfaces by the Fluid.* This leads to pressure gradients in liquids, so it is similar in many ways to item 1, though the shape of the interface may itself be important.

4. *Free-Surface Flows Driven by Gradients in Interfacial Tension (Marangoni Flows).* These can be manipulated using the dependence of surface tension on temperature or chemical concentration (for a clever application of the latter, see Gallardo et al., 1999).

Only a few examples of centrifugal driving forces have been described, and buoyancy effects are small owing to the small length scales of these configurations. The influence of bends in microchannels is important since bends occur frequently when maximizing the use of space in a design of a microdevice. In addition, one should distinguish single-phase flows from two- or multiphase flows. It should then be evident from Figure 1 and items

1–4 above that as the length scale of the geometry is reduced, additional length scales associated with surface forces become more significant in the overall response. As an example of considerations potentially relevant as the scale is reduced and additional forces are significant, Chang (2001) discusses electrokinetically driven multiphase flow in microchannels.

Some discrepancies have been reported between flow measurements made in small channels and expectations from classical theory based on solutions to the Navier-Stokes equations. However, a careful consideration of the experimental results for pressure-driven flows of liquids demonstrates that, in fact, in almost all cases there are no significant discrepancies (The pressure drop per unit length is as correlated in friction factor charts, Sharp et al., 2001). It is clearly important to recognize the significant influence geometry plays in low-Reynolds-number flows, as the familiar Poiseuille formula (or a lubrication calculation) makes clear. For example, since the pressure drop as a function of flow rate varies as the inverse *fourth* power of the radius, a small change in the dimension transverse to the flow, say due to manufacturing imperfections or objects adhering to the boundary, produces large changes in the flow.

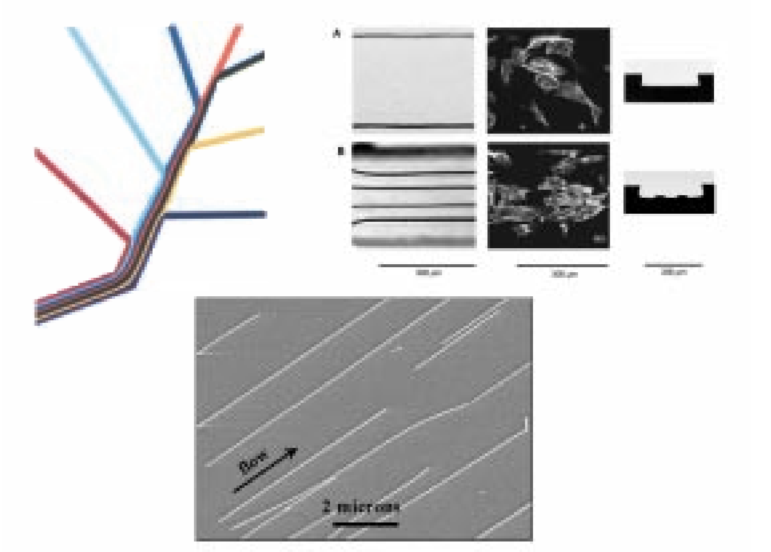

Figure 2. Examples of microfluidic manipulations that include surface patterning and particle positioning.
(a) Multiphase laminar flow in microchannels (Kenis et al., (1999); image copyrighted by Felice Frankel): these systems can be used for microfabrication such as carrying out chemical reactions that pattern or chemically etch surfaces. (b) Alignment of BCE cells on topographical features created by laminar flow etching such as shown in (a): (A) Control experiment. BCE cells grown in a channel with no topographical features. The cell body as well as the actin stress fibers have random orientation. (B) BCE cells grown in channels with approximately 60 micron wide ridges and grooves. The lefthand side micrograph is a phase-contrast image of the cells after they were fixed and stained with phalloidin to visualize the actin cytoskeleton. The righthand side micrograph is an epi-fluorescence image that shows the actin fibers of the same cells. The cell bodies, as well as the actin stress fibers, align at the edge of the ridges. (Takayama et al., 2001). (c) Nanowires deposited in nearly parallel arrays along the surface of a microchannel using pressure-driven flow. Such nanostructures can be assembled into functional electrically conducting networks (Huang et al. (2001)). The scale bar is 2 microns.

For gases, theory is in excellent agreement with experiment if compressibility and finite wall slip (owing to the mean free path being comparable to the channel dimensions) are properly accounted for (Arkilic et al., 1997). Furthermore, it is worth recognizing that electrical effects due to charged double layers can be difficult to quantify, in particular since charge inhomogeneities may occur. Also, at the scale of tens or hundreds of nanometers, at least for surfaces that are essentially atomically smooth, there is evidence for slip (Pit et al., 2000). Thus, it is our understanding that for small molecule liquids such as water, the familiar continuum description remains an appropriate starting point for analysis of microdevices, with appropriate consideration being given to electrical effects, slip, etc., as indicated briefly before.

Transport Phenomena

Individuals microdevices have a specified objective. Better understanding of the local fluid dynamics can in principle produce novel, better and more efficient designs. Among the themes to consider when thinking about design and performance of microdevices are transport, mixing, separation and manipulation of particles, and the influence of surface forces as devices are scaled down.

The systematic analysis of transport in scale-down of microdevices should bring to mind a familiar feature of engineering education: dimensional analysis. Since the Reynolds numbers is generally small, it itself does not usually appear as a parameter. Instead, geometric features and ratios can matter in dictating the details of the flow, and other dimensionless ratios, typically involving surface, electrical and/or thermal forces, are important when characterizing the details of transport processes. For one view of these ideas from the perspective of colloidal systems, see Russel et al. (1992).

Dispersion. The interplay of convection and diffusion is crucially important in many applications, especially those involving chemical reactions. The spread of an injected (Brownian) solute in a pressure-driven Poiseuille flow generally occurs much more rapidly than predicted if only molecular diffusion is considered. This Taylor-Aris dispersion occurs because thermal fluctuations (i.e., molecular diffusion) allow suspended particles to sample streamlines that have different speeds. Since dispersion is often to be prevented, electroosmotic flows are useful since such flows have uniform, or nearly uniform, velocity profiles, which limit spreading to that by molecular diffusion alone. Of course, to utilize device volume more effectively the channels are curved (often highly) and some designs now utilize three-dimensional networks, which produce (unwanted) dispersion even in electroosmotic flows.

An area of current research seeks to understand the detailed fluid flow in the entire microchannel network in order to produce designs that minimize this hydrodynamic dispersion. Also, over short time scales, suspended particles cannot diffuse across the entire channel, so the Taylor-Aris dispersion mechanism is not appropriate and instead dispersion (and so chemical reactions) is controlled by the local features of the velocity distribution in the channel; this produces spreading at different rates near the walls of the channels (regions of large gradients) compared to the center of the channel (Ismagilov et al., 2000).

Separation Processes. There are well known methods using cross fields (electric, thermal, etc.) to produce or enhance spreading of an injected solute in the flow direction and this axial spreading naturally aids separation processes. Such well-known field-flow-fractionation methods are similar to Taylor-Aris dispersion and apply to microchannels as well. It is also possible to modify surface properties of microchannels to effect interactions between particles and surfaces that can further impact separations. Here, it is worth recognizing the possible influence of hydrodynamic interactions when charged particles move in the neighborhood of boundaries, which has been characterized recently to understand the "attraction of like-charged" colloidal particles (Squires and Brenner, 2001). In addition, microfabrication techniques have been used to manufacture an array of closely spaced posts that separate large biopolymers according to size during electrophoresis (Duke and Austin 1998).

Mixing. Mixing is important but appears more difficult at small scales because the familiar use of turbulence is unavailable. Often molecular diffusion alone is not sufficient given the flow speeds and channel lengths used (not the Taylor dispersion limit mentioned above). It is intuitively reasonable that enhancing the mixing of two fluids or a tracer in a fluid will be aided substantially by chaotic particle paths of the fluid itself. Perhaps more surprising is the realization that simple laminar flows often have sufficient ingredients to produce chaotic mixing flows, i.e., laminar chaos. Here, research drawing the connection between mixing and nonlinear dynamics will likely be useful (Ottino, 1989). Microdevices are currently being designed to take advantage of these manners of mixing, including the demonstration of passive micromixers (Liu et al., 2000). Also, peristaltic mechanisms, which produce bulk motion by some form of time-dependent boundary perturbation, may prove to be useful.

Polymers. Several questions stand out when considering the presence of polymers (e.g., DNA) in microchannels. On the one hand, the presence of a small amount of polymer is known to modify the rheological response of the bulk flow and so results from the non-Newtonian fluid mechanics literature must be applied or determined for the flow configurations typical of microchannels. On the other hand, microflows can be used to manipulate polymers. For example, the polymers can be sorted, stretched, bound to surface groups, possibly identified in a number of different ways and manipulated by externally applied fields. As an example, Babcock et al. (2000) discuss both the microscopic and macroscopic responses. Finally, the typical sizes of polymers can be comparable to the microchannels themselves and understanding and characterizing transport properties of confined polymers undergoing flow is an active area of research.

Outlook and potential research directions

Many microfluidic devices have been developed in the past several years. These systems are rapidly being applied in the biomedical, pharmaceutical and printing industries, to name just a few. It is natural to think that these systems will be integrated with "smart materials and devices" (e.g., Langer, 2000). The ability to pattern substrates, implement the lab-on-a-chip concept, control and enhance chemical reactions and heat transfer, manipulate particle position, orientation and transport rates, develop mixing and separation processes, among others, will offer both research and engineering opportunities in the future and hopefully be among the successful technologies utilizing microfluidic principles and devices. The importance of scaling down devices, as well as characterizing and understanding the interplay of fluid flow, surface forces, and potentially statistical and molecular interactions, are among the research questions that will need to be addressed.

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