Microfluid Nanofluid (2005) 1: 301–318
DOI 10.1007/s10404-005-0041-z

REVIEW

David Erickson

Towards numerical prototyping of labs-on-chip: modeling for integrated microfluidic devices

Received: 8 February 2005 / Accepted: 14 March 2005 / Published online: 14 July 2005
© Springer-Verlag 2005

Abstract This review article presents an overview of some of the tools, techniques and applications of numerical simulation for integrated microfluidic devices. Provided is a broad overview of the different areas to which numerical techniques have been applied in the development of these devices from detailed studies of fundamental microfluidic problems (e.g., species mixing and sample dispersion) to unique approaches that take a more global overview of the entire system. While the majority of the work to date has been in these areas, also reviewed is some recent progress into other equally important areas of microscale transport such as thermal analysis and chemical reactivity and specificity. An overview of the advantages and disadvantages of common numerical techniques is also presented along with a brief discussion of some of the existing numerical tools, focusing on those best suited for microscale transport analysis. As microfluidic devices become increasingly complex, optimal fluidic and transport designs become more and more difficult to do experimentally. Thus, it is believed that future demand in the field will be for highly integrated simulation tools that allow users without a significant computational fluids background to "numerical prototype" highly integrated devices.

1 Introduction

Microfluidics may well be to the first half of the 21st century what microelectronics was to the latter half of the 20th century. The development of the integrated circuit allowed electrical devices to shrink from room-sized to pocket-sized, all the time increasing in speed and penetrating into nearly every aspect of our lives. Similarly, it is hoped that many of the large, expensive chemical and biological analyses that are currently being performed can be replaced by integrated microfluidic devices (Erickson and Li 2004a; Vilkner et al. 2004; Paegel et al. 2003), often called labs-on-chip, resulting in a similar revolution.

As a result of this promise, the development of lab-on-chip devices has become a highly competitive field and as such researchers typically do not have the luxury of large amounts of time and money to build and test successive prototypes in order to optimize species delivery, reaction kinetics or thermal performance. Rapid prototyping techniques, such as those developed by Whitesides' group (Duffy et al. 1998; Ng et al. 2002), coupled with the shift toward plastics and polymers as fabrication material of choice (de Mello 2002) have significantly helped to cut cost and development time once a chip design has been selected. Computational and analytical simulation of on-chip processes, however, can serve to dramatically reduce the time from concept to chip even further (Erickson and Li 2004b). Simulation allows researchers to rapidly determine how design changes will affect chip performance, thereby reducing the number of prototyping iterations. Perhaps even more importantly "numerical prototyping" applied at the concept stage can provide excellent estimates of potential chip performance (e.g., rate of surface hybridization of solution phase targets, speed of thermal cycling for PCR or separation performance in capillary electrophoresis) enabling the researcher to take a fruitful path from the beginning.

There are a variety of factors that complicate the numerical simulation of microscale phenomena and thereby distinguish it from its macroscale counterpart. The particular form in which these complications present themselves and the techniques for handling them tend to be application specific, and thus, is tackled in turn throughout this article, they can generally be broken down into four different groups. The first complication, and often most important numerically, is the

D. Erickson
Department of Mechanical and Mechanical and Aerospace Engineering, Cornell University, Ithaca, New York, UK
E-mail: de54@cornell.edu

range of relevant length scales, which can vary as much as seven orders of magnitude (from the double layer thickness, nm, to channel lengths and substrate dimensions, cm). Secondly, the downscaling of the size dramatically increases the relative importance of surface and interfacial phenomena (e.g., the electrical double layer, surface tension and roughness). Rapid and localized changes and fluidic and material properties (e.g., thermal conductivity, viscosity, conductivity) can also occur in many systems, which tend to be particularly important when thermal analysis is of interest. In general, however, the most challenging and interesting aspect of computational simulation for labs-on-chip devices is the range of relevant phenomena, which combines microfluidics, microtransport, microthermal, micromechanics, microelectronics and optics with chemical and biological thermodynamics and reaction kinetics. In general, one must consider all of these aspects in order to provide a complete numerical picture of what is required to engineer a true lab-on-chip.

In this article, we review the use of numerical simulation and computational engineering techniques applied to the design and development of lab-on-chip devices. In general, as many of the relevant phenomena will be covered as possible—from unique approaches to electrokinetics and microscale flow, microscale thermal simulation, and chemical/biological reactions. While not the focus of this article, important analytical works that form the theoretical background of a particular area of interest are also briefly mentioned.

In general, this article is written assuming readers have at least a rudimentary understanding of traditional pressure-driven flow and electrokinetic phenomena. As the range of physical phenomena covered in this article is so large and the number different techniques used to model each situation varies so greatly, a comprehensive review of the governing equations is beyond the scope of this article. Here, the focus is on the applications, the specific numerical tools and approaches used to model the relevant physics. Readers are referred to Erickson and Li (2004b) or Karniadakis and Beskok (2002) as well as classic reference texts on electrokinetics such as Lyklema (1991, 1995) and Hunter (1981) for general fundamental details and the references herein for specific details related to the phenomena of interest.

2 General overview of numerical techniques and tools

Prior to discussing the detailed applications, a brief overview of some of the general numerical techniques and tools used by those currently in the field is warranted. Broadly speaking, techniques for computational analysis can be classified by the particular method by which the governing equations are discretized as finite difference, finite volume, finite element and boundary element methods. The advantages and disadvantages of each of these methods are well documented by others (Ferziger and Perić 2002; Garg 1998; Gresho and Sani 1997) and thus, only a cursory overview is presented here.

2.1 Finite difference method

In the finite difference (FD) technique (Chung 2002), the partial derivatives in the governing differential equations are replaced with Taylor series approximations based on the values of neighboring nodes (Ferziger and Perić 2002). The result is a single algebraic equation for each node which can be assembled and solved reasonably simply using a variety of well-developed direct and iterative solvers. This method has the advantage of generally being the easiest to implement, though, it is practically limited to well-structured grids and thus only advantageous in simple geometries (e.g., capillaries or channel cross sections).

2.2 Finite volume methods

For finite volume (FV) methods (Dick 1996b), the simulation domain is divided into a series of control volumes, each corresponding to a single grid point (node), over which the differential equation is integrated. Similar to FD methods, a single algebraic equation, in which the values of the neighboring nodes appear as unknowns, is then obtained for each control volume (Ferziger and Perić 2002). Unlike FD methods, however, the FV method does not require a structured grid and is thus suitable for more complex and commonly encountered geometries (e.g., looping channels used in on-chip capillary electrophoresis). The major disadvantage with FV methods comes in the definition of derivatives (i.e., as with FD methods, when the grid is irregular, a Taylor series expansion to obtain the derivative is impossible) and the difficulty in converting higher order derivatives into lower order ones (Dick 1996b). The result is that FV methods are best suited to problems where the viscous terms are absent as opposed to the low Reynolds number flows encountered in microfluidics in which these terms are dominant.

2.3 Finite element methods

The finite element (FE) method (Heinrich and Pepper 1999; Reddy and Gartling 2001; Dick 1996a; Gresho and Sani 1997) enjoys many of the same advantages of the FV method, most importantly the ability to handle unstructured grids and irregular geometries. The distinguishing feature of the FE method is that the equations are multiplied by a weight function prior to being integrated over the domain (Ferziger and Perić 2002). The most significant advantage of the FE method from the microfluidicist's point of view is the relative ease and elegance by which the weak formulation allows for the application of boundary conditions and the extraction

of boundary information. This is particularly relevant for the flux or gradient-based boundary conditions that are commonly encountered in applied electrical fields, transport systems with surface phase reactions and thermal analysis involving convective heat transfer. Isoperimetric quadratic elements can also be used to exactly conform to curved fluid–fluid interfaces such as those encountered in surface tension driven flows. A disadvantage of FE methods is the numerical difficulties associated with handling highly irregularly shaped elements (e.g., large aspect ratios or highly curved) or large ranges in element size within a single mesh. In lab-on-chip devices, the relevant length scales can range over seven orders of magnitude, from the double-layer thickness (nm) to channel length (cm) and thus, it is often difficult to avoid using such elements while maintaining a computationally tractable problem.

2.4 Boundary element methods

Boundary element methods (Gupta 1999) attempt to satisfy the governing equations in all elements of the domain through the minimization of certain integrals over the boundary. This technique has not widely been applied to microfluidic systems. However, in principle it does have significant advantages in terms of computational efficiency, as only boundary elements are necessary. The method does, however, have difficulties in handling systems with variable material properties (Garg 1998).

2.5 Computational tools for microfluidics

There are a variety of commercially available codes that have been very successful in modeling microfluidics processes (e.g., Fluent (http://www.fluent.com), FEMLAB (http://www.femlab.com), CFD-ACE+ from the CFD Research Corporation (http://www.cfdrc.com) and Coventor (http://www.coventor.com)). While these excellent tools do present the path of least resistance to high-level numerical analysis, they do in general require the user to posses some background in computational fluid dynamics (a skill not particularly prevalent amongst the chemists, biologists and doctors who dominate the chip development field). Additionally, many of these codes tend to be focused primarily on simulation of fluid flow and to a lesser extent, species transport, which as mentioned above does not provide a complete picture of what is required to engineer a true lab-on-chip. The multiphysics capabilities of FEMLAB, which facilitates the coupling and simultaneous solution of different fundamental equations along with its point and click interface make it likely the best candidate of the widely available tools for comprehensive modeling. In addition to these commercial packages, some research groups have developed their own codes (a much more laborious task), which allows them to be specialized for lab-on-chip development. Our group specifically has pursued the development of a FE-based code termed BLOCS (*Bio-Lab-On-a-Chip Simulation*), which is capable of simulating a variety of on-chip processes by integrating microfluidics, microtransport, and microthermal analysis with biological thermodynamics and reaction kinetics.

3 Microscale flow and species transport simulation

Traditionally, microfluidic simulation has concentrated on the study of fluid flow and species transport in channel structures commonly encountered in lab-on-chip devices using either traditional pressure or electrokinetic phenomena as the primary motive force (see Erickson and Li (2004b) or Hunter (1981)). Many of the most highly cited of these investigations have focused on the application of numerical techniques to the study of such fundamental microfluidic problems as species mixing, controlled sample dispensing and dispersion for on-chip capillary electrophoresis. In addition to providing an overview of these investigations, we also examine some of the other areas to which numerical techniques have been applied, attempting to focus on those which present unique flow patterns and simulation techniques or those which allow the investigator to take a more global overview of the chip, as opposed to concentrating on a specific domain.

3.1 Dispensing, dispersion, mixing and concentration gradients

As alluded to above, some of the first numerical simulations of flow and species transport directly translatable to modern lab-on-chip devices were investigations of electrokinetic-focusing and sample-dispensing techniques based on those popularized by Harrison et al. (1992, 1993). In one of the first of these studies, Patankar and Hu (1998) examined the electrokinetic flow field at a cross intersection, which was followed-up by Ermakov et al. who extended that work to look at species focusing and mixing (1998) and dispensing in similar fluidic systems (2000). In another early study, Bianchi et al. (2000) performed FE-based simulations of electrokinetic flow at a T-junction. Building on those initial studies, Fu et al. (2002a, b, 2003); Lin et al. (2002, 2004a), Ren et al. (2002, 2003) and Jin and Luo (2003) developed advanced numerical simulators and used them to develop a variety of novel and complex pinching and dispensing techniques. Of particular interest are the works of Tang et al. (2002) who modeled and developed an electrokinetic technique for composition modulation in microfluidic systems involving the high-frequency oscillation of the inlet voltages and Chmela et al. (2002) who took a different approach and used fluent-based simulations to design and characterize a pressure-driven flow based sample injection technique. Wolff et al.

(2003) used numerical simulations to design and optimize their ''smoking chimney'' design for hydrodynamic focusing of cells. Sundararajan et al. (2004) presented Coventorware-based simulations to develop a 3-D hydrodynamic-focusing technique, which they then experimentally demonstrated in a PDMS-based chip. FEMLAB-based simulations of isoelectric focusing were presented by Lu et al. (2004) as part of the development of their microfabricated device for subcellular organell sorting.

One problem with traditional capillary electrophoresis systems was that poor heat rejection characteristics led to radial gradients in the buffer viscosity, which in turn resulted in sample dispersion, see Knox and McCormack (1994a, b), thereby limiting the strength of the applied electric field and ultimately the resolution and speed of analysis. The shift toward glass microchips with much better heat-rejection characteristics significantly reduced this problem. However, geometric constraints introduced the new problem of band broadening at looping turns. In addition to several excellent analytical and experimental investigations (Griffiths and Nilson 2000; Culbertson et al. 1998), a series of excellent numerically based studies have examined solutions to this problem typically concentrating on developing novel turn geometries. In one of the most globally applicable of these studies, Molho et al. (2001) coupled numerical simulations with shape optimization analysis to develop a general turn geometry for minimizing dispersions. Recent works by Fiechtner and Cummings (2003, 2004) have demonstrated the use of 2-D numerical solutions of the Laplace equation coupled with a Monte Carlo technique to model diffusion to develop a faceted design technique for minimizing dispersion. Fu et al. (2002c) also considered the issue of band broadening in microfluidic systems. Also of particular note is the work of Bharadwaj et al. (2002) who used numerical simulations as part of their more comprehensive look into the design and optimization of CE chips. A particularly unique part of that study was the inclusion of detector models to better characterize the entire system.

Systems exhibiting spatial gradients in electrolyte conductivity are an important subclass of electrokinetic flows occurring in commonly encountered applications such as field amplified sample stacking and isoelectric focusing. The introduction of a nonlinearity into the coupled electric field, flow and transport system significantly complicates the modeling process and leads to an interesting class of problems. Recent works that have examined this problem include those by Sounart and Baygents (2001) who studied the transport of a sample plug with significantly higher conductivity than that of the bulk fluid, and Ren and Li (2004) who numerically examined the effects of conductivity differences on the sample-injection process. Perhaps the most interesting works conducted in this area are the recent studies on electrokinetic stability in the presence of conductivity gradients perpendicular to the direction of bulk fluid motion by the Santiago group at Stanford University (See Oddy et al. 2001 for an example of how electrokinetic instabilities have been applied to microscale mixing). From this group, Lin et al. (2004b) presented a comprehensive model of the conditions that lead to this instability and nonlinear numerical simulations of the predicted transport field, which agreed well with experimental results. Figure 1 is an illustrative example of the numerical results from this work demonstrating the evolution of flow instability under various applied field strengths. For details of the simulation conditions readers are referred to the aforementioned work by Lin et al. (2004b).

In general, liquid based microfluidic systems tend to be strongly laminar and thus lacking a strong advective (with the notable exception of the electrokinetic instability work) or turbulent enhancement component, species mixing tends to be diffusion based and therefore require either a long dwell time or long channel length. Biddiss et al. (2004) (also see Erickson and Li (2002b)) demonstrated the use of numerical characterization of a surface heterogeneity based electrokinetic micromixer by examining the performance of a series of heterogeneous surface patterns and geometries. Figure 2 compares the numerical predictions with the experimental results obtained in a PDMS/glass chip where the bottom surface has been patterned with a checkerboard surface heterogeniety pattern (which was found through numerical simulation to exhibit the best mixing characteristics for this case). Chung et al. (2004) used the CFD-ACE package to simulate the pressure-driven and relatively high Reynolds number (between 10 and 300) mixing of water and ethanol in a circulating microfluidic system. Jen et al. (2003) developed an interesting twisted microchannel geometry to induce advective mixing in a T-type microfluidic systems simulated using the CFD-ACE package. Wang et. al. (2003) used the MemCFD microfluidics package from Coventor to model the pressure-driven mixing in a microfluidic system with patterned groves on the bottom surface similar to that proposed by Stroock et al. (2002). In another very impressive study, Johnson and Locascio (2002) used the CFD-ACE package to characterize and optimize the use of slanted well designs for microfluidic mixing under electroosmotic flow. The study also investigates the use of the technique for combined mixing while minimizing sample dispersion. Interested readers are also referred to their original work on this design (Johnson et al. 2002). Neils et al. (2004) developed a 3-D combinatorial microfluidic system that produces a series of titrations of different input compounds. In this work, FE simulations were used to characterize the serpentine mixer outlet uniformity. Hong et al. (2004) used the CFD-ACE+ package to simulate their passive micromixing system which consisted of a series of in-plane Tesla structures. Simulations and experimental validation there revealed an increase in the mixing efficiency as the flow rate increased (as the result of enhanced convective effects) unlike traditional passive mixers, which tend to show a decrease. Holden et al. (2003) used the CFD-ACE+

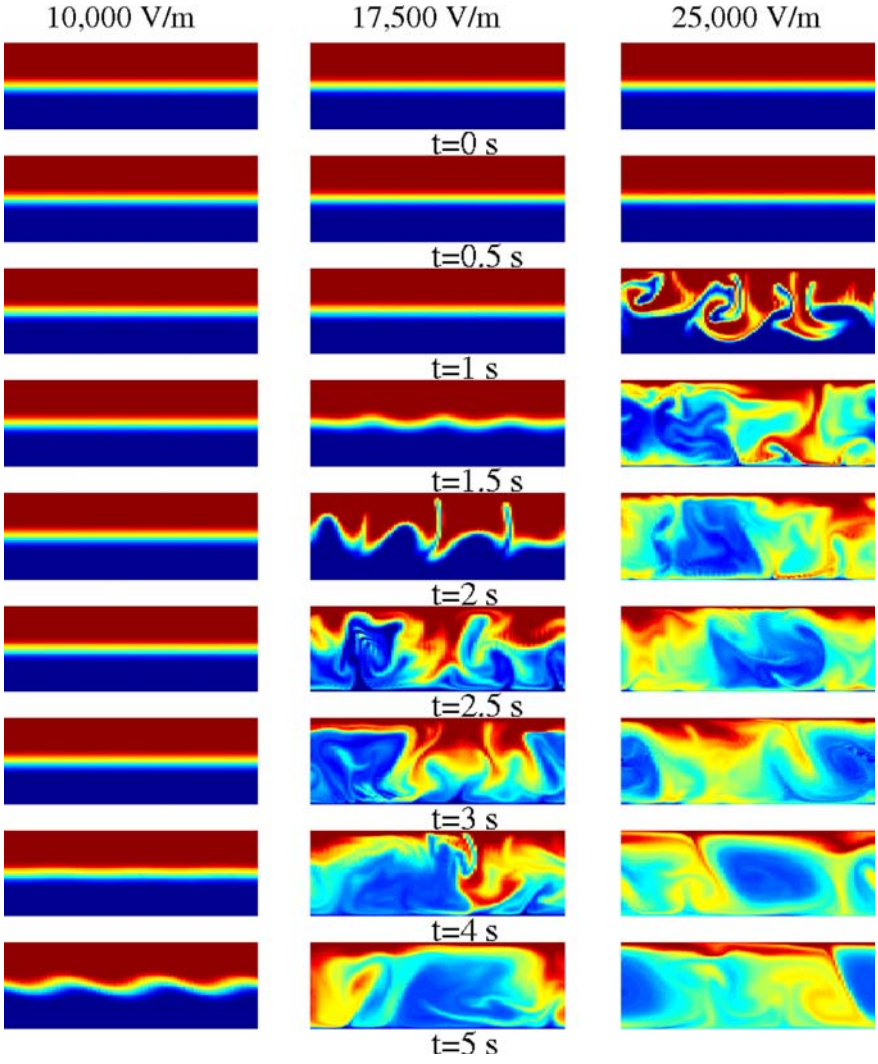

Fig. 1 Sample images of nonlinear numerical simulations of electrokinetic instability in microchannel flows from Lin et al. (2004b). Simulation results shown here are for three different applied fields (columns) at various times (rows). The electric field and bulk flow are directed from left to right. High field is applied at $t = 0$ s. Each image corresponds to a visualization of a passive scalar in a physical domain of 1 mm wide (y) by 3.6 mm long (x); the z (depth) dimension is not modeled in these simulations. (Note that the images have been slightly stretched in the y-direction to give best visualization.) An initial white-noise perturbation with an amplitude of 10^{-5} with respect to the base state is provided. Reprinted with permission from Lin et al. (2004b). Copyright 2004 American Institute of Physics

package to help numerically design their μDD (microfluidic diffusion diluter) device, which consisted of a Y-shaped intersection coupled to an array of parallel microchannels. Schönfeld et al. (2004) used numerical simulations to optimize their split-and-recombine (SAR) chaotic mixer for Reynolds numbers ranging from about 1 to 100 demonstrating that it can be characterized by finite-time Lyapunov exponents. The model was verified experimentally using water-glycerol solutions. Also of interest is the numerically prototyped microscale magnetic stirbar array simulated in CFD-ACE by Lu et al. (2002).

3.2 AC electrokinetics and dielectrophoresis

The development of a series of related applications has led to an enhanced interest in time periodic electroosmotic flows or alternating current (ac) electroosmosis (i.e., electroosmotic flow induced by unsteady applied electric fields). Comprehensive models of AC flow in slit channel geometry have also been presented by Dutta and Beskok (2001) who developed an analytical model for an applied sinusoidal electric field using a nonlinear Poisson–Boltzmann double-layer distribution, and Söderman and Jönsson (1996) who examined the transient flow field caused by a series of different pulse designs. Erickson and Li (2003a) presented a transient numerical and analytical (via a Green's function formulation) model of ac electrokinetic flow through a rectangular channel of arbitrary aspect ratio and excitation waveform. It is shown that the steady time periodic (after the effects of the initial impulse are dissipated) velocity profile is characterized by the ratio of the period of oscillation to the time scale for viscous diffusion and that impulsively started flows exhibit interesting transient behavior resulting in a net positive velocity at the channel midpoint during the initial cycles. González et al. (2000) used a linear double-layer analysis to model flow near a set of parallel electrodes subject to two ac fields, 180° out of phase with each other (also see the experimental investigation by Green et. al. (2000)). Green et al. (2002) also presented a FE simulation of dielectrophoretic and traveling wave forces in systems

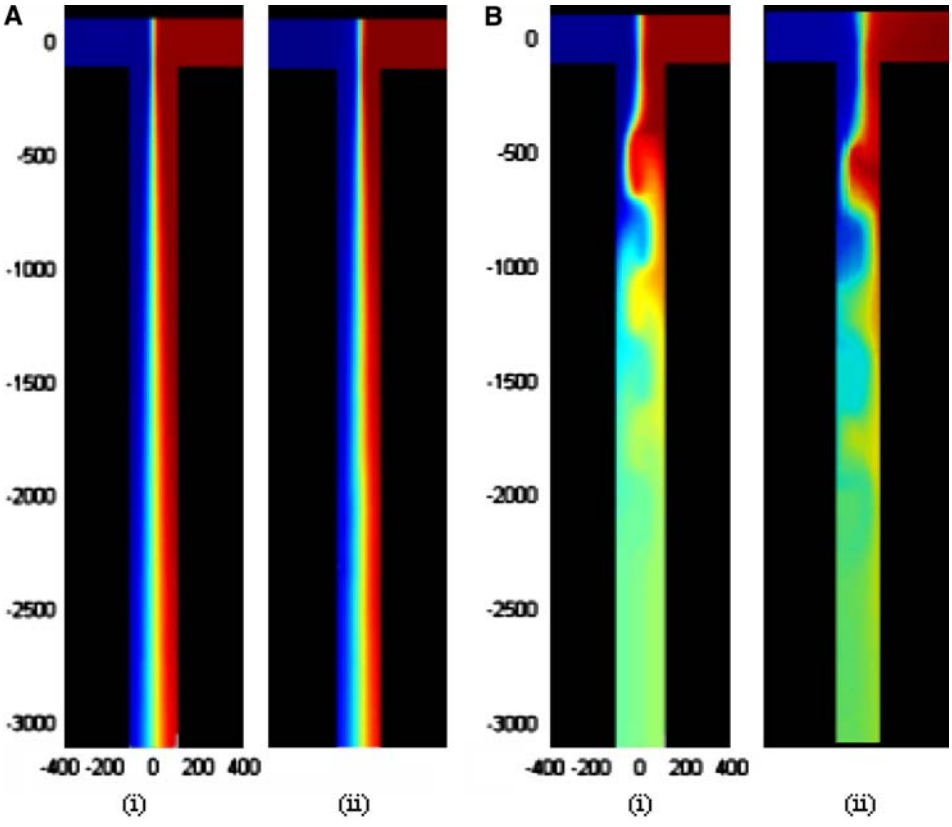

Fig. 2 Comparison of numerical simulations and experimental results for surface heterogeneity enhanced electrokinetic mixing from Biddiss et al. (2004). Images illustrate the steady-state species transport for an applied voltage potential of 280 V/cm for (**a**) the homogeneous microchannel and (**b**) the heterogeneous microchannel as derived through (i) numerical and (ii) experimental analysis. The heterogeneous microchannel system was functionalized with a positive polyelectrolyte in a checkerboard pattern on the bottom glass surface. Numerical simulations were used to determine the geometric properties of the heterogeneity pattern which yielded the best mixing characteristics. Reprinted with permission from Biddiss et al. (2004). Copyright 2004 American Chemical Society

with interdigitated electrode arrays. As part of the development of their dielectrophoretic fluidic system for fractionation of biological cells into subpopulations, Li and Kaler (2004) presented numerical simulations of the local electric fields and force profiles. Meinhart et al. (2003) presented FEMLAB based simulations of flow induced by combined dielectrophoretic and electrothermal forces (see Green et al. (2001) for additional information on electrothermal effects) and achieved quantitative agreement with experimental μ-PIV measurements thereby demonstrating the importance of electrothermal forces on particle motion. For a comprehensive overview of dielectrophoresis, particularly as applied to particle separation methods, readers are referred to the article by Gascoyne and Vykoukal (2002).

3.3 Flow over nonuniform surfaces

One of the challenges of modeling microscale transport is that it is strongly dependent on both the local and global surface properties. Electroosmotic flow tends to be exceptionally sensitive to such heterogeneities as irregularities in the surface charge density by definition affect the electrokinetic body force and lead to induced pressure forces or localized flow circulation. Ajdari conducted a series of pioneering analytical studies examining these effects on electroosmotic flow over nonuniform surfaces (Ajdari 1995) and transverse effects using channel shape and charge-density modulations (Ajdari 1996, 2001). Long et al. (1999) also developed an analytical model for an isolated heterogeneous spot in a flat plate or capillary geometry. The tumbling behavior predicted by these models was later observed in slit microchannels experimentally by Stroock et al. (2000, 2001) who found excellent agreement with their flow model. Readers are also referred to Anderson (1985) as another pioneering work in modeling these effects. Ghosal (2002a) developed a lubrication theory approach to modeling the electroosmotic flow profile in capillaries of varying cross section and surface ζ-potential. Also of interest from this author is the investigation into the effects of analyte adsorption on electroosmotic flow (Ghosal 2002b). Erickson and Li presented numerical models based on a simultaneous solution to the Nernst–Planck, Poisson and Navier–Stokes equations for both pressure driven (2002a) and electroosmotic flow (2003b) over periodically repeating nonuniform surface ζ-potential pattern. In the former of these cases, the presence of heterogeneous patches is shown to induce flow in all three coordinate directions, including a circulation pattern perpendicular to the main flow axis. In the latter cases, the simulations revealed a distinct 3-D flow structure that, depending on the degree of heterogeneity, varies from a weak circulation perpendicular to the applied electric field to a fully circulatory flow system. In addition, the electrophoretic influence of the applied electric field on the net charge density in the double layer is shown to cause a significant deviation from the traditional Poisson–Boltzmann distribution. The effects of

periodically repeating surface roughness on microscale transport processes were modeled by Hu et al. (2003a, b) using a 3-D, FV-based numerical model. Using this model, it was found that the increase of the electroosmotic mobility or the decrease of the electrophoretic mobility could dramatically enhance the uniformity of the concentration field.

3.4 Free surface, capillary and immiscible liquid flows

The development of microfluidic devices that exploit capillary forces as the primary means of fluidic transport (e.g., Duffy et al. 1999) have led to renewed interest in free surface flows. Numerically, the modeling of such systems is complicated by the need to track and maintain a record of the position of each point along the free surface and use that information to apply a surface stress boundary condition that is strongly dependent on the local curvature. To accomplish this, several interfacial tracking techniques have been developed. The Marker and Boundary method used by Tay et al. (1997) to examine underfill wetting for microelectronic packaging is based on the Marker and Cell technique detailed by Welsh et al. (1966). This technique tracks a series of surface markers placed along the interface, which are advected to their new position at each time step based on the previous time step's computed interfacial velocity. Arbitrary Lagrangian–Eulerian (ALE) methods are also commonly used when surface tension effects are important (see Donea et al. (2004) for an overview and Dettmer et al. (2003) for an example). As the name implies, ALE methods exploit the advantages of both Lagrangian and Eulerian frames of reference to simplify the computation and maintain a high mesh quality (versus a purely Lagrangian approach) as the interface moves. They, therefore, tend to be good for modeling relatively large deformation fluid structure interactions such as those occurring within many MEMS devices. The volume of fluid (VOF) technique, largely developed by Hirt and Nichols (1981), tracks the fraction of each phase in every computational cell to extract the interface shape. Tseng et al. (2002) applied the VOF interface tracking technique to the problem of reservoir filling, investigating factors such as the contact angle and reservoir shape. Experimental verification is also presented using a microscale particle image velocimetry setup (μ-PIV). In another interesting study, Lin et al. (2003) also used a VOF technique to model the deposition of fixed size liquid samples onto a bioreactor using a stamper array chip. In general, each of these techniques have their own particular advantages and disadvantages, however, a limitation for capillary driven microfluidic systems is the strong coupling between the computed interfacial shape and the surface stress boundary condition (i.e., slight errors in the interfacial advection velocities can lead to large errors in computed surface curvature) require relatively short timesteps to avoid oscillations and instabilities in the interface position. This, therefore, tends to limit the ability of these methods to track capillary driven flows over long distances, with reasonable computational resources. Many microfluidic systems, however, wet over relatively large areas but have consistent and predictable interfacial curvature. For such cases, Erickson et al. (2002c) developed a volume displacement interface tracking technique, used in conjunction with FE simulations of the flow field and Cox's rule (Cox 1986) for determining the dynamic contact angle and interface shape. This technique was then used to examine the effects of geometric variability on long range wetting behavior.

The ability to create, transport and handle discrete drops on either open surfaces or within closed channels through local manipulation of the contact angle has emerged as one of the most promising new technologies for lab-on-chip devices. Presently, the most commonly used techniques for performing such manipulations are based upon the principals of electrowetting (or electrocapillarity see Quillet and Berge (2001) for an overview) whose origins date back over 100 years to Lippmann's discovery that applied electrical forces that can have significant influence on the local interface conditions (Lippmann 1875). Electrocapillarity is essentially a contact-line phenomenon whereby charge accumulation at the solid-droplet interface induces an apparent local reduction in the contact angle. The use of a microfabricated electrode array therefore permits discrete droplets to be transported, mixed and analyzed thereby creating truly adaptable microfluidic systems (e.g., Srinivasan et al. 2004). Dielectrophoretic forces, which rely on droplet polarizability as opposed to charge accumulation, have also been used to accomplish many of these same tasks (e.g., Schwartz et al. 2004). Likely the most comprehensive numerical simulations of discrete droplet manipulation for lab-on-chip devices were conducted by Zeng and Korsmeyer (2004). In that work, they present an excellent overview of droplet electrohydrodyanmics and use Coventor-based simulations to illustrate such fundamental processes as droplet translocation, fission, fusion and injection. Figure 3 demonstrates the "droplet fission" simulations conducted by Zeng and Korsmeyer (2004) where the electrowetting phenomenon is used to break apart a single droplet into two individual ones. Thermocapillary effects, where differential temperatures are used to induce changes in the local contact angle, have also been examined as a technique for discrete droplet manipulation (e.g., Sammarco et al. 1999). In an excellent study, Darhuber et al. (2003) numerically and experimentally demonstrated the potential of thermocapillary driven flows on lithographically patterned hydrophilic microstripes for lab-on-chip-type applications. The authors have recently expanded on this work to study the mixing properties of such systems (Darhuber et al. 2004).

Flows of immiscible liquids occur in many microfluidic systems and are modeled using many of the same techniques described above to track the moving boundary between fluids. Chein and Tsai (2004) dem-

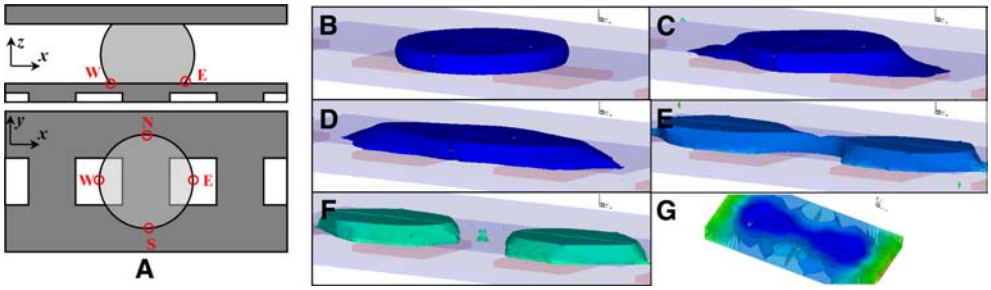

Fig. 3 Droplet fission on an Electrowetting On Dielectric (EWOD) driven lab-on-a-chip from Zeng and Korsmeyer (2004). (**a**) illustrates the device configuration. All four electrodes embedded in the insulating material are ON electrodes. The square electrodes are 100 mm wide and 100 mm apart. The thickness of the insulating coating is 5 mm. Initially (without the presence of the electric field), this droplet of 1 mL is of a "pancake" shape maintaining a contact angle of 117°. (**b**)–(**f**) show the transient process of droplet fission (simulation), corresponding to times 0, 75, 150, 450 and 600 ms. Upon application of 70 V to all four electrodes, the reduction of the contact angle elongates the droplet in the *x*-direction, shrinking the *yz*-plane cross-section at the center of the droplet, which eventually breaks the droplet into two parts. Satellite droplets can also be observed in (**f**). (**g**) shows the electric potential distribution (simulation) at time 450 ms (corresponding to (**e**)). The color indicates the electric potential, also drawn are the iso-potential surfaces. Reproduced by permission of The Royal Society of Chemistry from Zeng and Korsmeyer (2004)

onstrated the use of the VOF technique to model the side-by-side flow behavior of two liquids with differing viscosities (specifically water and glycerine). They then used the model to develop a series of intricate flow-switching techniques. Kuban et al. (2003) examined the flow of two immiscible fluids atop one another (viewed perpendicular to the plane on which the channel is inscribed) in a shallow microfluidic channel with the goal of determining the conditions that impart stability to these vertically stratified flows. Stiles and Fletcher (2004) also examined the hydrodynamic control of the interface between two immiscible liquids using numerical simulations.

3.5 Magnetic, magneto-rheological and electro-rheological phenomena

To date, the majority of the interest in exploiting magnetic phenomena on the microscale has been in the use of biologically functionalized magnetic micro- or nanobeads to help downscale conventional analysis techniques such as immunoassays or DNA hybridization. Recently, however, there has been some interest in using ferrofluids (magnetic fluids created by suspending ferromagnetic particles in a carrier fluid) as fluidic actuation elements (e.g., novel pumping (Ahn et al. 2004)) or valveing techniques (Hartshorne et al. 2004). An example of the use of numerical techniques to design such systems is that by He et al. (2003) who used an FEM approach to model applied magnetic field gradients and resulting flow rates for ferrofluids in a microfluidic system (Hatch et al. 2001b). Even though less exploited in microfluidic systems, more advanced functionalities could potentially be afforded by the so-called smart-fluids (e.g., magneto-rheological or electro-rheological fluids), which have the unique functionality in that by subjecting them to a suitable stimulus (in the case of the aforementioned, a strong magnetic or electric field) one can create self-assembled structures that serve to, for example, locally increase the viscosity field (Stanway 2004). One of the difficulties in creating magneto-rheological defined structures in microfluidic systems is the localization of the magnetic field gradients to the strength required to locally trap the particles on scales demanded by microfluidic systems. To help accomplish this, Rida and Gijs (2004) used FEMLAB-based FE simulations to design and simulate magnetic field strengths and size generated from the integrated magnetic components of their device. In their work, a self-assembled magneto-rheological plug is used to induce highly efficient mixing (the use of an AC field induces rotation of the magnetic dipoles further increasing the mixing efficiency.). Such systems hold great promise for next generation microfluidic systems (Doyle et al. 2002).

Magnetohydrodynamic actuation (Lemoff and Lee 2000) has not been widely exploited to date as a transport technique in microfluidic systems, likely due to the more complex microfabrication required over traditional electroosmotic pumps. It does however show great promise for a variety of situations such as continuous recirculation of discrete samples (e.g., West et al. 2002) or within fluidic networks (Bau et al. 2003). Gleeson et al. (2004) provide an excellent overview of analytical and numerical modeling of magnetohydrodynamic flows in microsystems, applying their technique to analyze the mixing of two fluids in an annular channel. Numerical analysis of magnetohydrodynamic flow generated by inlaid platinum microdisk electrodes was conducted using a FE-based technique by Mehta and White (2003). Readers are also refereed to a series of excellent analytical and experimental works by the Bau group (Xiang et al. 2003 ; Yi et al. 2002).

3.6 Acoustic phenomena

As discussed by Marmottant and Hilgenfeldt (2004), in general, acoustic techniques do not naturally lend themselves to microfluidics-based applications as even high-frequency ultrasonics exhibit wavelengths on the order of a millimeter. Recently, however, there has been

some interest in exploiting acoustic phenomena for such applications as mixing (Yaralioglu et al. 2004), particle separation (Pettersson et al. 2004) and acoustic streaming using microbubbles (Marmottant and Hilgenfeldt 2004) and as such there has been some attempts to numerically model and design such devices. Lutz et al. (2003) simulated the flow and mass transport around a cylindrical electrode subject to a low-intensity acoustic oscillation. The resulting flow pattern created spatially defined microscale chemical environments around the electrode separated from the bulk field by a stable streamline and acting as a microchemical trap. Details of the model are available in a previous work (Bowman and Schwartz 1998). Also of interest is the work of Townsend et al. (2004) who modeled particle agglomeration at the nodal planes of a standing wave applied perpendicular to the flow direction, numerically demonstrating how the technique can be used to suspend or focus particles. The approach they used is based on computing the hydrodynamic forces using a CFD code, and then incorporating them into a MATLAB-based model and is similar to many of the discrete particle techniques discussed in the proceeding section.

3.7 Unique numerical approaches

In addition to providing an overview of some of the systems to which numerical methods have been applied, a goal of this review is to illustrate the novelty of some numerical approaches themselves. Lee et al. (2003) used an interesting combined CFD/experimental approach to model the dynamics of a hydrogel-based pH regulator. By combining the fluid dynamics simulation of the microflow system with experimental results of hydrogel swelling and volume flow through a star shaped orifice into a SIMULINK control system model, they were able to accurately predict the pH level of the outlet stream. Dutta et al. (2002) demonstrated the use of the spectral FE method to model the local flow structure in a variety of different microfluidic geometries. The use of spectral elements and the structured/unstructured mesh enabled the double-layer profile to be captured much more accurately than would otherwise have been possible. Le Mâitre et al. (2001) illustrate the advantages of their stochastic Navier–Stokes solver (the novel solver combines a spectral stochastic uncertainty representation scheme with a FD-projection method for flow simulation) by examining flow, transport and mixing in a microchannel geometry.

3.8 Simulation of microfluidic networks

Most of the simulations described above and presented in the remainder of this work tend to be very localized in nature, examining in great detail a particular region of a microfluidic system. In general, this is done in order to concentrate computational resources on the problem of interest rather than wasting them in capturing the flow field for the entire chip. Developing techniques for global modeling of microfluidic networks, is an important step, if not the most important, toward the goal of performing *whole-chip* numerical prototyping. One of the more impressive techniques for performing such analysis was presented by Kirby et al. (2001) who developed an integrated circuit and microfluidic simulator that allows for the coupled simulation of flow, structure, thermal and electrical domains using the SPICE3f5 for circuit simulation and their Nektar microfluidics code (Kirby et al. 1999). The technique is demonstrated by modeling a microscale liquid-dosing system and promises as a technique for more complex MEMS devices. Qiao and Aluru (2002) also demonstrated an electrical circuit based technique for rapidly capturing the essential features of complex electroosmotic or pressure-driven flow networks. Also of interest from this group is the development of meshless analysis of steady-state electroosmotic transport using the finite cloud method (2000). Xuan and Li (2004a) describe an interesting model for pressure-driven or electroosmotic flow in microfluidic networks using phenomenological coefficients from nonequilibrium thermodynamics to describe the effects of channel size and surface properties. The model is used here to describe the flow from a one-to-multi-branch microchannel system but could be extended to more general systems. Chien and Bousse (2002) presented a general technique for calculating the node pressure at a junction in a microfluidic network. Their technique was deemed particularly useful in systems where nonuniform surface or solution properties are present and could be extended beyond the simple T geometry used here.

4 Cellular/particulate/macromolecular transport

One of the great strengths of microfluidic systems is that they have given researchers an unprecedented ability to manipulate, sort, store and analyze individual microscale particles and macromolecules enabling single cell analysis via such techniques as capillary electrophoresis (Stuart and Sweedler 2003), sorting and cytometry (Fu et al. 2002) and dielectrophoresis (Cui et al. 2001), for such applications as drug development (Weigl et al. 2003), tissue engineering (Saltzman and Olbricht 2002) and biosensors (Pancrazio et al. 1999). As such there has been renewed interested in the simulation of small, large and many particle transport in confined microfluidic systems to aid in the design and optimization of such systems.

The study of particle hydrodynamics dates back well over 100 years and thus the sheer amount of work that has been published on the subject makes a comprehensive review of it beyond the breadth of this article. In general, however, suffice it to say that much (but by no means all) of the current theory behind particle transport was developed in the context of study of colloidal

dispersions and related electrokinetic phenomena (see Russel et al. 1989; Lyklema (1991, 1995) and the papers by Keh and Anderson (1985) and Saville (1977)) or in the context of the study of particle migration in shear flows (such as the Sergé and Silberberg effect) [see Ho and Leal (1974) and Leal (1980)]. Numerically, many of the same techniques available for coupled flow and particle transport simulation vary strongly in the details (implementation is often done using the same basic techniques described above for free-surface flows). In general, the most comprehensive and globally applicable models rely on some combination of solving for the flow field using a FE or similar technique, computing the various hydrodynamic and other important forces (e.g., buoyancy, electrostatic, magnetic) acting on the particle and then updating its position using Newton's law, then remeshing and projecting the previous timesteps velocity onto the new mesh (see the work of Hu et al. (1992) for a description of direct simulation of particle motions).

As mentioned above the interest in particulate flows in lab-on-chip devices generally stems from the interest in creating microfluidic cell handling devices (though particle flows are of importance in a number of other applications as well, for example, microscale flow visualization). Chen et al. (2004) presented a very comprehensive numerical prototyping study and experimental verification, for a microfluidic cell sorter for Drosophillia cells using the CFD-ACE+ software and a volume of fluid technique for particle tracking. This work is an excellent example of how numerical techniques can be used to optimize the design of particular microfluidic components as flow fields for different channel layouts are simulated and study the effect of control pressure, chamber length and entrance length on switching time to find geometries and conditions for optimized embryo movement. Figure 4 shows an illustrative example of the numerically simulated cell sorting within the device. Yang et al. (2004) examined cell docking and alignment in a variety of microfluidic dam structures (parallel and perpendicular to the main flow route) through hydrodynamic simulation. Through their FLUENT-based simulations, they were able to propose techniques to attenuate the hydrodynamic forces on trapped cells and propose an improved design, which combined the advantages of both classes of design. Ma et al. (2002) also used FLUENT to examine the local hydrodynamic

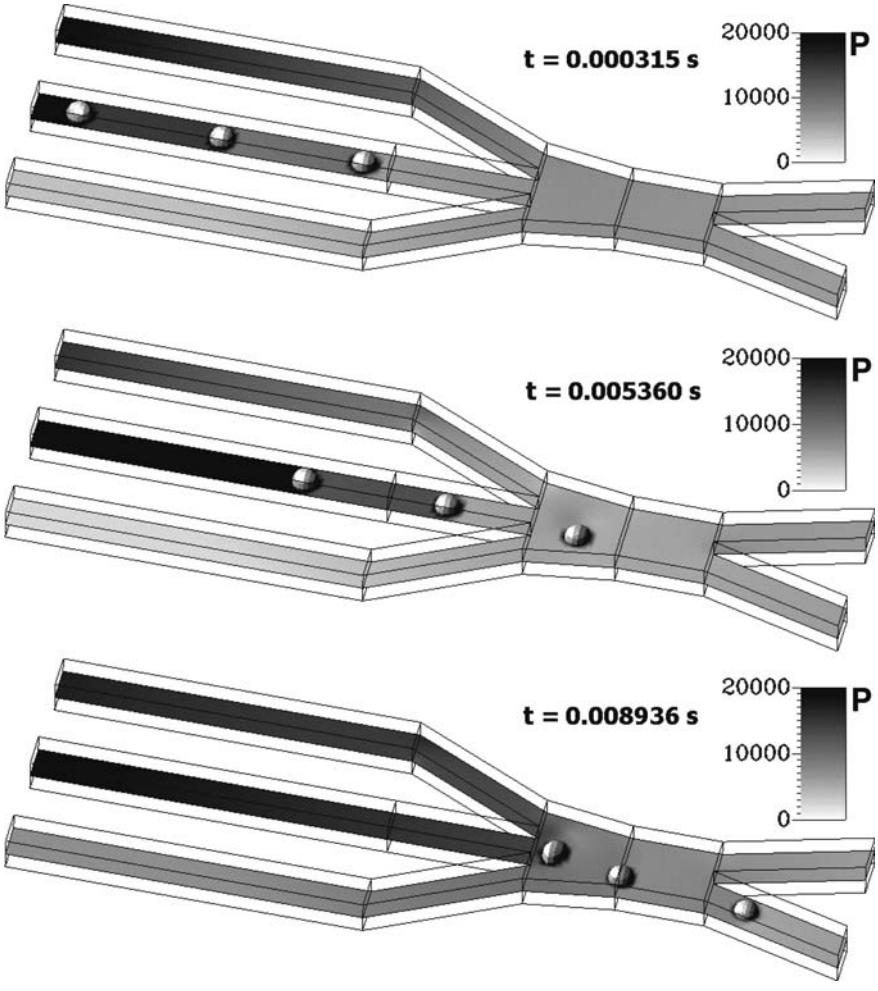

Fig. 4 Three dimensional simulation of cell motion in a flow through switching device. Reprinted with permission from Elsevier Science from Chen et al. (2004)

forces and energy dissipation rates in their constriction-based microfluidic device and related the results back to the observed robustness of a series of different cell lines. Though not involving any particle tracking, the work by Gaver and Kute (1998) is also of particular interest as they applied the boundary element method to the examination of the stresses, forces and torques on an adhered cell in a microchannel. Also of interest is the work of Jendrejack et al. (2003) numerically examined the dynamics of ~1–100 μm-long DNA in confining microchannels determining that the diffusivity of highly confined chains does not following classical scaling relations.

Other works of more general interest include in particular that by Liu et al. (2002) who presented a fast method for particulate microflows based on the combination of the force-coupling method (Maxey et al. 1997) with the spectral/hp element method for solving the Navier–Stokes equations. In that work, numerical simulations of interacting fluid–particle motions in 3-D geometries are presented. Also of interest are the works of: Markarian et al. (2003), using a FE technique to model the motion and segregation of positively polarized particles flowing through dielectrophoretic microfluidics; Li and Bashir (2004) who presented FE-based simulations of the dynamics of particle stopping using a dielectrophoresis technique; and Nieuwenhuis and Vellekoop (2004) who used Coventorware- based simulations to examine the effectiveness of a series of different dielectrophoretic particle sorters.

5 On-chip chemical reactivity

Though fluid mechanics and species transport are extremely important (as demonstrated by the large number of quality studies described above), if one considers what is actually required to engineer a true lab-on-chip, they comprise of single part only. Equally important, but less well-exploited areas, are those such as reactivity and specificity or on-chip thermal analysis. It is the goal of the following two sections to provide some illustrative examples of how these areas have been exploited in on-chip numerical modeling.

5.1 Heterogeneous reactions

Heterogeneous reactions comprise those reactions that occur in the presence of a surface or interface. Such reactions are exploited widely in lab-on-chip devices through either surface or bead-based nucleic acid (e.g., DNA microarrays) and antigen–antibody (e.g., enzyme linked immunosorbent assays) binding reactions, to name a few. Erickson et al. (2003) presented a theoretical and computational model for heterogeneous DNA hybridization kinetics on thermally resolved biochips, which combined a two-mechanism hybridization approach (Axelrod and Wang 1994; Chan et al. 1995) (i.e., a target could become hybridized either directly from the bulk phase or through an initial nonspecific adsorption and surface diffusion step), with nearest neighbor thermodynamics (Allawi and SantaLucia 1997, 1998a, b, c; SantaLucia et al. 1996; Peyret et al. 1999) and a pressure-driven flow transport formulation. The model was shown to compare well with hybridization experiments conducted on optical fibers (Zeng et al. 2002) and was used to demonstrate the ability of thermally resolved biochips to detect single base pair mismatches. Figure 5 is an illustrative example of the results of these simulations for the case of a uniform concentration of oligonucleotides convected in from the left side through pressure-driven flow that hybridize with the fully complementary probes on a surface with a 20 °C temperature gradient. In their work on the development of plastic biochannel hybridization devices, Lenigk et al. (2002) presented computer simulations of the hybridization kinetics of their device, done using the CFD-ACE+ multiphysics solver, demonstrating the advantages of oscillating target transport on the overall reaction rate. Also of note is the work of Baras et al. (2003) who used a series of numerical tools (Serenade^{TM} and Momentum^{TM}) to model and design resonator geometries for label-free THz detection of surface phase DNA hybridization (Nagel et al. 2002).

5.2 Homogeneous reactions

Homogeneous reactions occur within the bulk phase and are exploited for a variety of on-chip functions in which precise control of the reagent delivery and dwell time is required (e.g., chemical synthesis or nanoscale self-assembly). Debusschere et al. (2003) presented a highly coupled 2-D model for combined flow species transport and reactivity, accounting for such effects as buffer electrochemistry and variable surface ζ-potential. The model is demonstrated through the modeling of a protein labeling reaction. Also of interest here is the implementation of a stochastic uncertainty propagation method (Ghanem and Spanos 1991) to quantify the uncertainty in the model predictions. Baroud et al. (2003) presented a numerical solution to the binding of Ca^{2+} with Ca-Green marker in a T channel, which compared favorably with experimental results. In their work, Yarmush et al. (1996) presented numerical solutions to a convection-diffusion-reaction formulation for surface phase gel-immobilized ligands in a microscale flow chamber. The analysis allowed them to characterize the device in terms of a series of operational regimes based on flow velocity. Henley et al. (2003) used a FE-based technique to perform a coupled flow/mass transport voltammetric analysis of a microelectrochemical reactor. MacInnes (2002) simulated the electrokinetic and pressure-driven flow at a T-junction and applied their results to model the reactivity between the two inlet streams. The flow model used in that work is elaborated on in a later article by MacInnes et al. (2003). Hatch

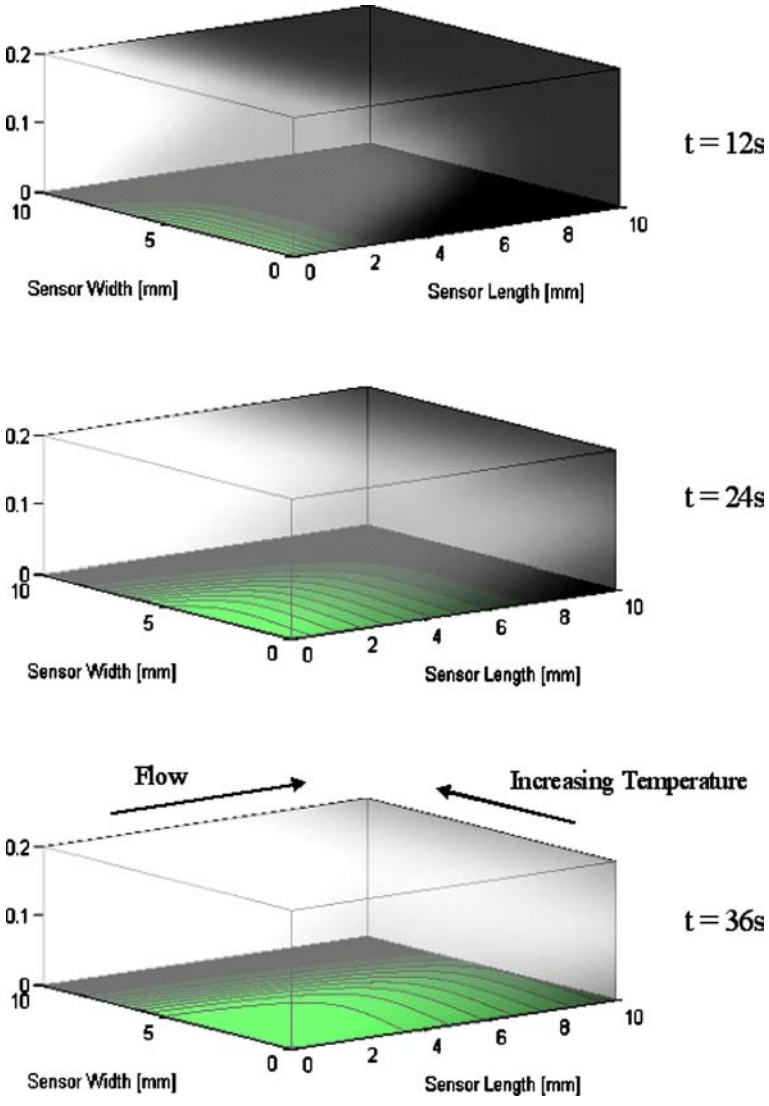

Fig. 5 Simulated dynamic hybridization in a microfluidics based biosensor from Erickson et al. (2003). In this case, bulk oligonucleotides are convected in via pressure-driven flow from the left side of the sensor (transparent white contours) and hybridize with surface immobilized probes (green contours). A 20 °C temperature gradient ($T_{min} = 40$ °C, $T_{max} = 60$ °C) is applied across the surface, which spans the melting temperature of the oligonucleotides used here, resulting in a unique finger print hybridization pattern. Reprinted with permission from Elsevier Science from Erickson et al. (2003)

et al. (2001a) used a numerical model as a technique to predict assay performance for their diffusion-based immunoassay in a T-sensor (a similar model was used in a previous work by Kamholz et al. (2001)).

6 On-chip thermal analysis

Unlike the transport and reactivity problems discussed above, which are confined to the fluidic domain, thermal modeling in microfluidics presents some unique challenges. Different from a macroscale system, where the fluidic domain is most often of comparable size to the solid regions, a microchannel system typically encompasses only a very small fraction of the substrate and thus heat transfer is typically governed by a large timescale thermal diffusion process through the solid region (particularly in the case of polymeric substrates). As such the equations in all regions are coupled and must be solved simultaneously. Erickson et al. (2003d) presented a combined numerical and experimental (using a microscale thermometry technique based on the work of Ross et al. (2001)) approach to examine Joule heating and heat transfer at a microchannel intersection in poly(dimethylsiloxane) (PDMS), and hybrid PDMS/Glass microfluidic systems. The numerical model accounted for the rapid changes in solution conductivity on the potential field and viscosity on the flow field as well as thermal diffusion into the polymeric substrate and the mechanisms of ultimate heat rejection. The detailed numerical analysis revealed that the vast majority of steady-state heat rejection is through lower substrate of the chip, which was significantly impeded by the lower thermal conductivity PDMS substrate. Figure 6 is an illustrative example of this, showing the temperature contours within the solid substrates and the fluidic region, after a 2.05-kV potential has been applied for 30 s, for (a) PDMS/PDMS and (b) PDMS/Glass systems. As can be seen for the PDMS/PDMS system, the temperature profile in the substrate is centered on the fluid

region and then spreads radially outward. Lim et al. (2004) used 3-D numerical simulations to investigate the effects of channel topography on the ability to reject joule heat and reduce axial dispersions in electrophoretic separations. Xuan et al. (2004b) simulated the effects of joule heating on flow in a capillary and presented some experimental verification using a similar Rhodamine B based thermometry technique as that described above. Tang et al. (2004a, b) studied coupled electrokinetic flow and species transport in a capillary subject to joule heating. Their approach is unique in that they also considered the heating effects on the double-layer field. Also of interest is the work of Chung et al. (2003) who examined the heat transfer characteristics of their infrared thermal velocimetry system used to measure flow rates in silicon based MEMS devices.

To date, likely the most important lab-on-chip application involving controlled thermal delivery has been in the development of microscale thermal cycling reactors (in particular those used for performing the polymerase chain reaction (PCR) on chip). The PCR reactors present an interesting opportunity for material and geometric optimization through numerical simulation as the desired properties during the heating phase (high resistance to heat rejection to decrease heating time and power load) often conflict with those during the cooling phase (low overall resistance in order to increase the rate of heat rejection). As part of the characterization of their microscale thermal cycling reactors, Lao et al. (2000) used 3-D numerical simulations to map the spatial temperature distribution of the device. Using such simulations to examine the fundamental heat transfer characteristics of the device allows for more rapid and power efficient thermal cyclers. El-Ali et al. (2004) performed 3-D numerical simulations of their PCR reactor (using the CFD-ACE package as well as ANSYS) to demonstrate that their particular heater arrangement provides a uniform temperature profile within the heater system (± 2 °C) and to predict the system power load. Sadler et al. (2003) performed an excellently detailed study on the thermal management of BioMEMS (looking specifically at a PCR reactor and a DNA hybridization chip) with the CFD-ACE package. Optimization of such parameters as heater power input, fluid flow rate, sensor placement and air-gap geometry were considered.

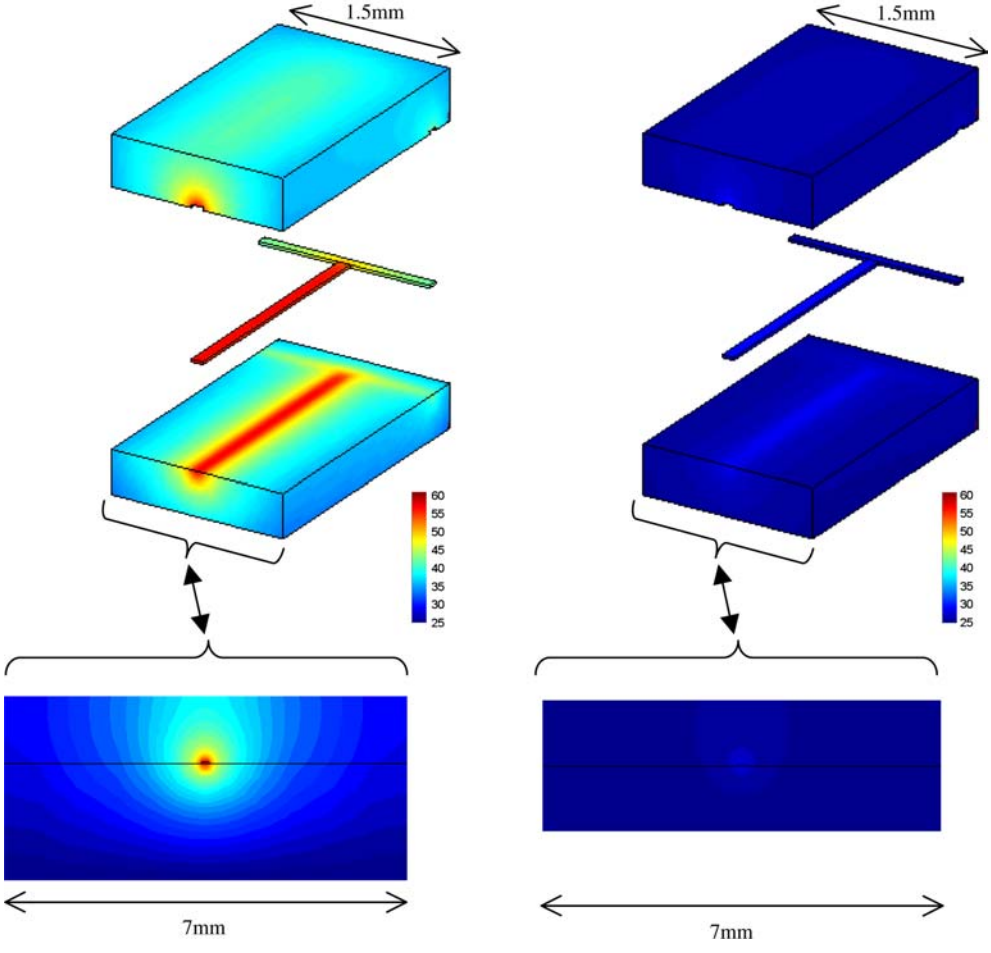

Fig. 6 Simulated temperature contours for (**a**) PDMS/PDMS and (**b**) PDMS/Glass composite systems 30 s after a 2050 kV voltage was applied from Erickson et al. (2003d). Upper image shows the 3-D temperature contours in the substrates in the region very near the fluidic region while lower figure details the 2-D temperature profile in the channel cross-section 2.5 mm downstream of the intersection. Simulation details are provided in the text or in the aforementioned reference. *Note*: entire computational domain not shown. Reproduced by permission of The Royal Society of Chemistry from Erickson et al. (2003d)

7 Summary and outlook

In this review, we have provided an overview of some of the different ways in which numerical simulations have been applied to the development of microfluidic processes and devices. While the majority of studies to date have focused on microscale fluid mechanics and species transport, we have attempted here to illustrate some of the other equally important aspects of microscale transport analysis such as thermal analysis and chemical reactivity. In general, it is felt that there are two broad areas where the use of numerical methods could exhibit significant growth.

At present, numerical simulations are typically used as tools to investigate or explain previously observed experimental phenomena. As microfluidic devices become increasingly complex, optimizing fluidic and transport design becomes more and more difficult to do experimentally. As such it is believed that future demand in the field will be for highly integrated simulation tools that allow users without a significant CFD background to "numerical prototype" entire microfluidic devices. It is conceived that a properly designed simulation program could reduce the time from concept to prototype and provide immediate estimates of potential chip performance (e.g., the time required for complete surface hybridization or the speed of thermal cycling for PCR) enabling the researcher to take a fruitful path from the beginning.

As advancements in microfabrication techniques allow for dramatic increases in the packing density of microfluidic channels, heaters, optics and other sensors coupled with the popularization of lower thermal conductivity polymeric substrates, the exploitation of computational simulation and development of experimental methods for on-chip thermal analysis is likely to become more and more important. The trend toward increased channel density in electrokinetic systems for example, is analogous to the increase in transistor density in integrated computer chips and thus as packing density increases some of the same thermal management problems are likely to be encountered. The problem is significantly more interesting in microfluidic devices, however, as the goal in many cases is not just to reject heat but to harnessed it to drive or enhance chemical processes.

References

Ahn J, Oh J, Choi B (2004) A novel type of a microfluidic system using ferrofluids for an application of u-TAS. Microsystem Technol 10:622–627

Ajdari A (1995) Electro-osmosis on inhomogeneously charged surfaces. Phys Rev Lett 75:755–758

Ajdari A (1996) Generation of transverse fluid currents and forces by an electric field: Electro-osmosis on charge-modulated and undulated surfaces. Phys Rev E 53:4996–5005

Ajdari A (2001) Transverse electrokinetic and microfluidic effects in micropatterned channels:Lubrication analysis for slab geometries. Phys Rev E 65:016301

Allawi HT, SantaLucia J (1997) Thermodynamics and NMR of internal G–T mismatches in DNA. Biochemistry 36:10581–10594

Allawi HT, SantaLucia J (1998a) Nearest-neighbor thermodynamics of internal A–C mismatches in DNA: sequence dependence and ph effects. Biochem 37:9435–9444

Allawi HT, SantaLucia J (1998b) Thermodynamics of internal C–T mismatches in DNA. Nucleic Acids Res 26:2694–2701

Allawi HT, SantaLucia J (1998c) Nearest neighbor thermodynamic parameters for internal G–A mismatches in DNA. Biochem 37:2170–2179

Anderson JL (1985) Effect of nonuniform ζ-potential on particle movement in electric fields. J Colloid Interface Sci 105:45–54

Axelrod D, Wang M (1994) Reduction-of-dimensionality kinetics at reaction-limited cell surface receptors. Biophys J 66:588–600

Baras T, Kleine-Ostmann T, Koch M (2003) On-chip THz detection of biomaterials: a numerical study. J Biol Phys 29:187–194

Baroud C, Okkels F, Menetrier, P Tabeling (2003) Reaction-diffusion dynamics: confrontation between theory and experiment in a microfluidic reactor. Phys Rev E 67:060104

Bau H, Zhu J, Qian S, Xiang Y (2003) A magneto-hydrodynamically controlled fluidic network. Sens Actuators B 88:207–218

Bharadwaj R, Santiago J, Mohammadi B (2002) Design and optimization of on-chip capillary electrophoresis. Electrophoresis 23:2729–2744

Bianchi F, Ferrigno R, Girault H (2000) Finite element simulation of an electroosmotic-driven flow division at a t-junction of microscale dimension. Anal Chem 72:1987–1993

Biddiss E, Erickson D, Li D (2004) Heterogeneous surface charge enhanced micromixing for electrokinetic flows. Anal Chem 76:3208–3213

Bowman JA, Schwartz DT (1998) High Peclet number mass transfer in the acoustic streaming flow between two concentric cylinders. Int J Heat Mass Trans 41:1065–1075

Chan V, Graves D, McKenzie S (1995) The biophysics of DNA hybridization with immobilized oligonucleotide probes. Biophys J 69:2243–2255

Chen C, Zappe S, Sahin o, Zhang X, Fish M, Scott M, Solgaard O (2004) Design and operation of a microfluidic sorter for Drosophila embryos. Sensors Actuators B 102:59–66

Chien R, Bousse L (2002) Electroosmotic pumping in microchips with nonhomogeneous distribution of electrolytes. Electrophoresis 23:1862–1869

Chien R, Tsai S (2004) Microfluid switching design using volume of fluid model. Biomed Microdevices 6:81–90

Chmela E, Blom M, Gardeniers J, van den Berg A, Tijssen R (2002) A pressure driven injection system for an ultra-flat chromatographic microchannel. Lab Chip 2:232–241

Chung TJ (2002) Computational fluid dynamics. Cambridge University Press, Cambridge UK

Chung J, Grigoropoulos C, Greif R (2003) Infrared thermal velocimetry in MEMS-based fluidic devices. J MEMS 12:365–372

Chung Y, Hsu Y, Jen C, Lu M, Lin Y (2004) Design of passive mixers utilizing microfluidic self-circulation in the mixing chamber. Lab Chip 4:70–77

Cox R (1986) The dynamics of the spreading of liquids on a solid-surface .1. viscous-flow. J Fluid Mech 168:169–194

Cui L, Holmes D, Morgan H (2001) The dielectrophoretic levitation and separation of latex beads in microchips. Electrophoresis 22:3893–3901

Culbertson C, Jacobson S, Ramsey J (1998) Dispersion sources for compact geometries on microchips. Anal Chem 70:3781–3789

Darhuber A, Davis J, Troian S, Reisner W (2003) Thermocapillary actuation of liquid flow on chemically patterned surfaces. Phys Fluids 15:1295–1304

Darhuber A, Chen J, Davis J, Troian S (2004) A study of mixing in thermocapillary flows on micropatterned surfaces. Phil Trans R Soc Lond A 362:1037–1058

Debusschere B, Najm H, Matta A, Knio O, Ghanem R, Le Maitre O (2003) Protein labeling reactions in electrochemical microchannel flow: numerical simulation and uncertainty propagation. Phys Fluids 15:2238–2250

de Mello A (2002) Plastic fantastic? Lab Chip 2:31N–36N

Dettmer W, Saksono P, Peric D (2003) On a finite element formulation for incompressible Newtonian fluid flows on moving domains in the presence of surface tension . Comm Num Meth Eng 19:659–668

Dick E (1996a) Introduction to finite element techniques. In: Wendt JF (ed) Computational fluid dynamics, an introduction. Springer-Verlag, Berlin

Dick E (1996b) Introduction to finite volume techniques. In: Wendt JF (ed) Computational fluid dynamics, an introduction. Springer-Verlag, Berlin

Donea J, Huerta A, Ponthot J, Rodrıguez-Ferran A (2004) Arbitrary Lagrangian–Eulerian methods In: Stein R, de Borst R, Hughes T (eds) Encyclopedia of computational mechanics. J Wiley

Doyle P, Bibette J, Bancaud A, Viovy J (2002) Self-assembled magnetic matrices for DNA separation chips. Science 295:2237

Duffy D, McDonald J, Schueller O, Whitesides G (1998) Rapid prototyping of microfluidic systems in poly(dimethylsiloxane). Anal Chem 70:4974–4984

Duffy D, Gillis H, Lin J, Sheppard N, Kellogg G, (1999) Microfabricated centrifugal microfluidic systems: characterization and multiple enzymatic assays. Anal Chem 71:4669–4678

Dutta P, Beskok A (2001) Analytical solution of time periodic electroosmotic flows: analogies to Stokes' second problem. Anal Chem 73:5097–5102

Dutta P, Beskok A, Warburton TC (2002) Electroosmotic flow control in complex microgeometries. J MEMS 11:36–44

El-Ali J, Perch-Nielsen IR, Poulsen CR, Bang DD, Telleman P, Wolff A (2004) Simulation and experimental validation of a SU-8 based PCR thermocycler chip with integrated heaters and temperature sensor. Sens Actuators A 110:3–10

Erickson D, Li D (2002a) Microchannel flow with patchwise and periodic surface heterogeneity. Langmuir 18:8949–8959

Erickson D, Li D (2002b) Influence of surface heterogeneity on electrokinetically driven microfluidic mixing. Langmuir 18:1883–1892

Erickson D, Li D, Park C (2002c) Numerical simulations of capillary-driven flows in nonuniform cross-sectional capillaries. J Colloid Interface Sci 250:422–430

Erickson D, Li D (2003a) Analysis of alternating current electroosmotic flows in a rectangular microchannel. Langmuir 19:5421–5430

Erickson D, Li D (2003b) Three-dimensional structure of electroosmotic flow over heterogeneous surfaces. J Phys Chem B 107:12212–12220

Erickson D, Li D, Krull UJ (2003) Modeling of DNA hybridization kinetics for spatially resolved biochips. Anal Biochem 317:186–200

Erickson D, Sinton D, Li D (2003d) Joule heating and heat transfer in poly(dimethylsiloxane) microfluidic systems. Lab Chip 3:141–149

Erickson D, Li D (2004a) Integrated microfluidic devices. Anal Chim Acta 507:11–26

Erickson D, Li D (2004b) Microscale flow and transport simulation for electrokinetic and lab-on-chip applications, In: Bashir R, Wereley S (eds) Biomems and Biomedical nanotechnology, volume IV: biomolecular sensing, processing and analysis, Kluwer Academic Publishing (in press)

Ermakov S, Jacobson S, Ramsey J (1998) Computer simulations of electrokinetic transport in microfabricated channel structures. Anal Chem 70:4490–4504

Ermakov S, Jacobson S, Ramsey J (2000) Computer simulations of electrokinetic injection techniques in microfluidic devices. Anal Chem 72:3512–3517

Ferziger J, Perić M (2002) Computational methods for fluid dynamics. Springer-Verlag, Berlin

Fiechtner G, Cummings E (2003) Faceted design of channels for low-dispersion electrokinetic flows in microfluidic systems. Anal Chem 75:4747–4755

Fiechtner G, Cummings E (2004) Low-dispersion electrokinetic flows for expanded separation channels in microfluidic systems: multiple faceted interfaces. J Chromatogr A 1027:245–257

Fu A, Chou H, Spence S, Arnold F, Quake S (2002) An integrated microfabricated cell sorter. Anal Chem 74:2451–2457

Fu L, Yang R, Lee G, Liu H (2002a) Electrokinetic injection techniques in microfluidic chips. Anal Chem 74:5084–5091

Fu L, Yang R, Lee G (2002b) Variable-volume-injection methods using electrokinetic focusing on microfluidic chips. J Sep Sci 25:996–1010

Fu L, Yang R, Lee G (2002c) Analysis of geometry effects on band spreading of microchip electrophoresis. Electrophoresis 23:602–612

Fu L, Yang R, Lee G (2003) Electrokinetic focusing injection methods on microfluidic devices. Anal Chem 75:1905–1910

Garg V (1998) In: Garg V (ed) Applied computational fluid dynamics. Marcel Dekker, New York

Gascoyne P, Vykoukal J (2002) Particle separation by dielectrophoresis. Electrophoresis 23:1973–1983

Gaver D, Kute S (1998) A theoretical model study of the influence of fluid stresses on a cell adhering to a microchannel wall. Biophys J 75:721–733

Ghanem R, Spanos P (1991) Stochastic finite elements: a spectral approach. Springer, New York

Ghosal S (2002a) Lubrication theory for electro-osmotic flow in a microfluidic channel of slowly varying cross-section and wall charge. J Fluid Mech 459:103–128

Ghosal S (2002b) Effect of analyte adsorption on the electroosmotic flow in microfluidic channels. Anal Chem 74:771–775

Gleeson JP, Roche OM, West J, Gelb A (2004) Modelling annular micromixers. SIAM J Appl Math 64:1294–1310

González A, Ramos A, Green NG, Castellanos A, Morgan H (2000) Fluid flow induced by nonuniform ac electric fields in electrolytes on microelectrodes. II. A linear double-layer analysis. Phys Rev E 61:4019–4028

Green NG, Ramos A, González A, Morgan H, Castellanos A (2000) Fluid flow induced by nonuniform ac electric fields in electrolytes on microelectrodes. I. Experimental measurements. Phys Rev E 61:4011–4018

Green NG, Ramos A, González A, Castellanos A, Morgan H (2001) Electrothermally induced fluid flow on microelectrodes. J Electrostat 53:71–87

Green NG, Ramos A, Morgan H (2002) Numerical solution of the dielectrophoretic and travelling wave forces for interdigitated electrode arrays using the finite element method. J Electrostat 56:235–254

Gresho PM, Sani RL (1997) incompressible flow and the finite element method: advection-diffusion and isothermal laminar flow. John Wiley and Sons, New York

Griffiths SK, Nilson RH (2000) Band spreading in two-dimensional microchannel turns for electrokinetic species transport. Anal Chem 72:5473–5482

Gupta OP (1999) Finite and boundary element methods in engineering. Ashgate Publishing Company

Harrison D, Manz A, Fan Z, Ludi H, Widmer HM (1992) Capillary electrophoresis and sample injection systems integrated on a planar glass chip. Anal Chem 64:1926–1932

Harrison D, Fluri K, Seiler K, Fan Z, Effenhauser C, Manz A (1993) Micromachining a miniaturized capillary electrophoresis-based chemical analysis system on a chip. Science 261:895–897

Hartshorne H, Backhouse C, Lee W (2004) Ferrofluid-based microchip pump and valve. Sens Actuators B 99:592–600

Hatch A, Kamholz AE, Hawkins KR, Munson MS, Schilling EA, Weigl BH, Yager P (2001a) A rapid diffusion immunoassay in a T-sensor. Nature Biotech 19:461–465

Hatch A, Kamholz A, Holman G, Yager P, Böhringer K (2001b) A ferrofluidic magnetic micropump. J MEMS 10:215–221

He W, Lee S, Jiles D, Schmidt D, Porter M, Shinar R (2003) Design of high-magnetic field gradient sources for controlling magnetically induced flow of ferrofluids in microfluidic systems. J App Phys 93:7459–7461
Heinrich JC, Pepper DW (1999) Intermediate finite element method: fluid flow and heat transfer applications. Taylor & Francis, Philadelphia Pa
Henley IE, Yunus K, Fisher AC (2003) Voltammetry under microfluidic control: computer-aided design development and application of novel microelectrochemical reactors. J Phys Chem B 107:3878–3884
Hirt C, Nichols B (1981) Volume of fluid (VOF) method for the dynamics of free boundaries. J Comput Phys 39:201–225
Ho B, Leal L (1974) Inertial migration of rigid spheres in 2-dimentional unidirectional flows. J Fluid Mech 65:365–400
Holden M, Kumar S, Castellana E, Beskok A, Cremer P (2003) Generating fixed concentration arrays in a microfluidic device. Sens Actuators B 92:199–207
Hong CC, Choi JW, Ahn CH (2004) A novel in-plane passive microfluidic mixer with modified Tesla structures. Lab Chip 4:109–113
Hu H, Joseph D, Crochet M (1992) Direct simulation of fluid particle motions. Theo Comp Fluid Dyn 3:285
Hu Y, Werner C, Li D (2003) Electrokinetic transport through rough microchannels. Anal Chem 75:5747–5758
Hu Y, Werner C, Li D (2003) Influence of three-dimensional roughness on pressure-driven flow through microchannels. J Fluids Eng 125:871–879
Hunter R (1981) Zeta potential in colloid science: principles and applications. Academic Press, London
Jen C, Wu C, Lin Y, Wu C (2003) Design and simulation of the micromixer with chaotic advection in twisted microchannels. Lab Chip 3:77–81
Jendrejack R, Schwartz D, Graham M, de Pablo J (2003) Effect of confinement on DNA dynamics in microfluidic devices. J Chem Phys 119:1165–1173
Jin Y, Luo G (2003) Numerical calculation of the electroosmotic flow at the cross region in microfluidic chips. Electrophoresis 24:1242–1252
Johnson T, Locascio L (2002) Characterization and optimization of slanted well designs for microfluidic mixing under electroosmotic flow. Lab Chip 2:135–140
Johnson T, Ross D, Locascio L (2002) Rapid microfluidic mixing. Anal Chem 74:45–51
Kamholz A, Schilling E, Yager P (2001) Optical measurements of transverse molecular diffusion in a microchannel. Biophys J 80:1967–1972
Karniadakis GE, Beskok A (2002) Micro flows: fundamentals and simulation. Springer, New York
Keh H, Anderson J (1985) Boundary effects on electrophoretic motion of colloidal spheres. J Fluid Mech 153:417–439
Kirby R, Warburton T, Sherwin S, Beskok A, Karniadakis GE (1999) The Nektar code: dynamic simulations without remeshing, In: Proceedings of 2nd International Conference on Computational Technologies for Fluid/Thermal/Chemical Systems with Industrial Applications
Kirby R, Karniadakis G, Mikulchenko O, Mayaram K (2001) An integrated simulator for coupled domain problems in MEMS. J MEMS 10:379–391
Knox J, McCormack K (1994a) Temperature effects in capilliary electrophoresis.1. Internal capillary temperature and effect upon performance. Chromatographia 38:207–214
Knox J, McCormack K, (1994b) Temperature effects in capilliary electrophoresis. 2. Some theoretical calculations and predictions .Chromatographia 38:215–221
Kuban P, Berg J, Dasgupta P (2003) Vertically stratified flows in microchannels. Computational simulations and applications to solvent extraction and ion exchange. Anal Chem 75:3549–3556
Lao A, Lee T, Hsing I, Ip N (2000) Precise temperature control of microfluidic chamber for gas and liquid phase reactions. Sens Actuators A 84:11–17
Le Mâitre O, Knio O, Najm H, Ghanem R (2001) A stochastic projection method for fluid flow I. Basic formulation. J Comp Phys 173:481–511
Leal L (1980) Particle motions in a viscous-fluid. Ann Rev Fluid Mech 12:435–476
Lee S, Eddington D, Kim Y, Kim W, Beebe D (2003) Control mechanism of an organic self-regulating microfluidic system. J MEMS 12:848–854
Lemoff A, Lee A (2000) An AC magnetohydrodynamic micropump. Sens Actuators B 63:178–185
Lenigk R, Liu R, Athavale M,Chen Z, Ganser D, Yang J, Rauch C, Liu Y, Chan B, Yu H, Ray M, Marrero R, Grodzinskia P (2002) Plastic biochannel hybridization devices: a new concept for microfluidic DNA arrays. Anal Biochem 311:40–49
Li H, Bashir R (2004) On the design and optimization of microfluidic dielectrophoretic devices: a dynamic simulation study. Biomed Microdevices 6:289–295
Li Y, Kaler K (2004) Dielectrophoretic fluidic cell fractionation system. Anal Chim Acta 507:151–161
Lim D, Kuo JS, Chiu DT (2004) Parametric investigation on the effect of channel topologies on electrophoretic separations. J Chromatogr A 1027:237–244
Lin J, Fu L, Yang R (2002) Numerical simulation of electrokinetic focusing in microfluidic chips. J Micromech Microeng 12:955–961
Lin S, Tseng F, Chieng C (2003) Numerical simulation of the stamping process through microchannels. J Colloid Interface Sci 258:179–185
Lin Y, Wu W, Fan C (2004a) Design and simulation of sample pinching utilizing microelectrodes in capillary electrophoresis microchips. Lab Chip 4:60–64
Lin H, Storey B, Oddy M, Chen C-H, Santiago J (2004b) Instability of electrokinetic microchannel flows with conductivity gradients. Phys Fluids 16:1922–1935
Lippmann G (1875) Relation entre les phenomenes electriques et capillaires. Ann Chim Phys 5:494–549
Liu D, Maxey M, Karniadakis G (2002) A fast method for particulate microflows. J MEMS 11:691–702
Long D, Stone HA, Ajdari A (1999) Electroosmotic flows created by surface defects in capillary electrophoresis 212:338–349
Lu L, Ryu K, Liu CA (2002) Magnetic microstirrer and array for microfluidic mixing. J MEMS 11:462–469
Lu H, Gaudet S, Schmidt M, Jensen K (2004) A microfabricated device for subcellular sorting. Anal Chem 76:5705–5712
Lutz BR, Chen J, Schwartz DT (2003) Microfluidics without microfabrication. PNAS USA 100:4395–4398
Lyklema J (1991) Fundamentals of interface and colloid science, volume 1: fundamentals. Academic Press, London
Lyklema J (1995) Fundamentals of interface and colloid science, volume 2: solid–liquid interfaces. Academic Press, London
Ma N, Koelling K, Chalmers J (2002) Fabrication and use of a transietn contractional flow device to qantify the sensitivity of mammalian and insect cells to hydrodynamic forces. Biotechnol Bioeng 80:428–437
MacInnes J (2002) Computation of reacting electrokinetic flow in microchannel geometries. Chem Eng Sci 57:4539–4558
MacInnes J, Du X, Allen R (2003) Prediction of electrokinetic and pressure flow in a microchannel T-junction. Phys Fluids 15:1992–2005
Markarian N, Yeksel M, Khusid B, Farmer K, Acrivos A (2003) Particle motions and segregation in dielectrophoretic microfluidics. J Appl Phys 94:4160–4169
Marmottant P, Hilgenfeldt S (2004) A bubble-driven microfluidic transport element for bioengineering. PNAS 101:9523–9527
Maxey M, Patel B, Chang E, Wang L (1997) Simulations of dispersed turbulent multiphase flow. Fluid Dyn Res 20:143–156
Mehta D, White H (2003) Finite-element analysis of magnetic field driven transport at inlaid platinum microdisk electrodes. Chem Phys Chem 4:212–214
Meinhart C, Wang D, Turner K (2003) Measurement of AC electrokinetic flows. Biomed Microdevices 5:139–145

Molho J, Herr A, Mosier B, Santiago J, Kenny T, Brennen R, Gordon G, Mohammadi B (2001) Optimization of turn geometries for microchip electrophoresis. Anal Chem 73:1350–1360

Nagel M, Haring Bolivar P, Brucherseifer M, Kurz H, Bosserhoff A, Buttner R (2002) Integrated THz technology for label-free genetic diagnostics. Appl Phys Lett 80:154–156

Neil C, Tyree Z, Finlayson B, Folch A (2004) Combinatorial mixing of microfluidic streams. Lab Chip 4:342–350

Ng J, Gitlin I, Stroock A, Whitesides G (2002) Components for integrated poly(dimethylsiloxane) microfluidic systems. Electrophoresis 23:3461–3473

Nieuwenhuis J, Vellekoop M (2004) Simulation study of dielectrophoretic particle sorters. Sensors Actuators B 103:331–338

Oddy M, Santiago J, Mikkelsen J (2001) Electrokinetic instability micromixing. Anal Chem 73:5822–5832

Paegel B, Blazej R, Mathies R (2003) Microfluidic devices for DNA sequencing: sample preparation and electrophoretic analysis. Curr Opin Biotech 14:42–50

Pancrazio J, Whelan J, Borkholder D, Ma W, Stenger D (1999) Development and application of cell-based biosensors. Ann Biomed Eng 27:697–711

Patankar N, Hu H (1998) Numerical simulation of electroosmotic flow. Anal Chem 70:1870–1881

Petersson F, Nilsson A, Holm C, Jonsson H, Laurell T (2004) Separation of lipids from blood utilizing ultrasonic standing waves in microfluidic channels. Analyst 129:938–943

Peyret N, Seneviratne PA, Allawi HT, SantaLucia J (1999) Nearest-neighbor thermodynamics and NMR of DNA sequences with internal A–A, C–C, G–G, and T–T mismatches. Biochemistry 38:3468–3477

Qiao R, Aluru N (2002) A compact model for electroosmotic flows in microfluidic devices. J Micromech Microeng 12:625–635

Quilliet C, Berge B (2001) Electrowetting: a recent outbreak. Curr Opinion Colloid Int Sci 6:34–39

Reddy J, Gartling D (2001) The finite element method in heat transfer and fluid dynamics. CRC Press, Boca Raton Fl

Ren L, Li D (2002) Theoretical studies of microfluidic dispensing processes. J Colloid Int Sci 254:384–395

Ren C, Li D (2004) Effects of spatial gradients of electrical conductivity on chip-based sample injection processes. Anal Chim Acta 518:59–68

Ren L, Sinton D, Li D (2003) Numerical simulation of microfluidic injection processes in crossing microchannels. J Micromech Microeng 13:739–747

Rida A, Gijs M (2004) Manipulation of self-assembled structures of magnetic beads for microfluidic mixing and assaying. Anal Chem 76:6239–6246

Ross D, Gaitan M, Locascio LE (2001) Temperature measurement in microfluidic systems using a temperature-dependent fluorescent dye. Anal Chem 73:4117–4123

Russel W, Saville D, Schowalter W (1989) Colloidal dispersions. Cambridge University Press

Sadler D, Changrani R, Roberts P, Chou C, Zenhausern F (2003) Thermal management of BioMEMS: temperature control for ceramic-based PCR and DNA detection devices. IEEE Trans Comp Pack Tech 26:309–316

Saltzman W, Olbricht W (2002) Building drug delivery into tissue engineering. Nat Rev Drug Discov 1:177

Sammarco T, Burns M (1999) Thermocapillary pumping of discrete drops in microfabricated analysis devices. AIChE J 45:350–366

SantaLucia J, Allawi HT, Seneviratne PA (1996) Improved nearest-neighbor parameters for predicting DNA duplex stability. Biochemistry 35:3555–3562

Saville D (1977) Electrokinetic Effects with Small Particles. Ann Rev Fluid Mech 9:321–337

Schönfeld F, Hessel V, Hofmann C (2004) An optimised split-and-recombine micro-mixer with uniform 'chaotic' mixing. Lab Chip 4:65–69

Schwartz J, Vykoukal J, Gascoyne P (2004) Droplet-based chemistry on a Programmable micro-chip. Lab Chip 4:11–17

Söderman O, Jönsson B (1996) Electro-osmosis: velocity profiles in different geometries with both temporal and spatial resolution. J Chem Phys 105:10300–10311

Sounart T, Baygents J (2001) Electrically-driven fluid motion in channels with streamwise gradients of the electrical conductivity. Colloids Surf A 195:59–75

Srinivasan V, Pamula V, Fair R (2004) An integrated digital microfluidic lab-on-a-chip for clinical diagnostics on human physiological fluids. Lab Chip 4:310–315

Stanway R (2004) Smart fluids: current and future developments. Mat Sci Tech 20:931–939

Stiles P, Fletcher D (2004) Hydrodynamic control of the interface between two liquids flowing through a horizontal or vertical microchannel. Lab Chip 4:121–124

Stroock A, Weck M, Chiu D, Huck W, Kenis P, Ismagilov R, Whitesides G (2000) Patterning electro-osmotic flow with patterned surface charge. Phys Rev Lett 84:3314–3317

Stroock A, Weck M, Chiu D, Huck W, Kenis P, Ismagilov R, Whitesides G (2001) Erratum: patterning electro-osmotic flow with patterned surface charge. Phys Rev Lett 86:6050

Stroock A, Dertinger S, Ajdari A, Mezic I, Stone H, Whitesides G (2002) Chaotic mixer for microchannels. Science 295:647–651

Stuart J, Sweedler J (2003) Single-cell analysis by capillary electrophoresis. Anal Bioanal Chem 375:28–29

Sundararajan N, Pio MS, Lee LP, Berlin A (2004) Three-dimensional hydrodynamic focusing in polydimethylsiloxane (PDMS) microchannels. J MEMS 13:559–567

Tang Z, Hong S, Djukic D, Modi V, West A, Yardley J, Osgood R (2002) Electrokinetic flow control for composition modulation in a microchannel. J Micromech Microeng 12:870–877

Tang G, Yang C, Chai C, Gong H (2004a) Numerical analysis of the thermal effect on electroosmotic flow and electrokinetic mass transport in microchannels. Anal Chim Acta 507:27–37

Tang G, Yang C, Chai C, Gong H (2004b) Joule heating effect on electroosmotic flow and mass species transport in a microcapillary. Int J Heat Mass Trans 47:215–227

Tay A, Huang Z, Wu J (1997) IEEE/CPMT Electronic Packaging Technol. Conf, 263

Townsend R, Hill M, Harris N, White N (2004) Modeling of particle paths passing through an ultrasonic standing wave. Ultrasonics 42:319–324

Tseng F, Yang I, Lin K, Ma K, Lu M, Tseng Y, Chieng C (2002) Fluid filling into micro-fabricated reservoirs. Sens Actuators A 97:131–138

Vilkner T, Janasek D, Manz A (2004) Micro total analysis systems. Recent developments. Anal Chem 76:3373–3385

Wang H, Iovenitti P, Harvey E, Masood S (2003) Numerical investigation of mixing in microchannels with patterned grooves. J Micromech Microeng 13:801–808

Weigl B, Bardell R, Cabrera C (2003) Lab-on-a-chip for drug development. Adv Drug Deliver Rev 55:349–377

Welsh J, Harlow F, Shannon J, Daly B (1966) Los Alamos Scientific Laboratory Report LA-3425

West J, Karamata B, Lillis B, Gleeson JP, Alderman J, Collins J, Lane W, Mathewson A, Berney H (2002) Application of magnetohydrodynamic actuation to continuous flow chemistry. Lab Chip 2:224–230

Wolff A, Perch-Nielsen IR, Larsen UD, Friis P, Goranovic G, Poulsen CR, Kutter JP, Telleman P (2003) Integrating advanced functionality in a microfabricated high-throughput fluorescent-activated cell sorter. Lab Chip 3:22–27

Xiang Y, Bau H (2003) Complex magnetohydrodynamic low-Reynolds-number flows. Phys Rev E 68:016312

Xuan X, Li D (2004) Analysis of electrokinetic flow in microfluidic networks. J Micromech Microeng 14:290–298

Xuan X, Xu B, Sinton D, Li D (2004b) Electroosmotic flow with Joule heating effects. Lab Chip 4:87–90

Yang J, Li C, Yang M (2004) Hydrodynamic simulation of cell docking in microfluidic channels with different dam structures. Lab Chip 4:53–59

Yaralioglu G, Wygant I, Marentis T, Khuri-Yakub B (2004) Ultrasonic mixing in microfluidic channels using integrated transducers. Anal Chem 76:3694–3698

Yarmush M, Patankar D, Yarmush D (1996) An analysis of transport resistances in the operation of BIAcore; implications for kinetic studies of biospecific interactions. Mol Immun 33:1203–1214

Yi M, Qian S, Bau H (2002) A magnetohydrodynamic chaotic stirrer. J Fluid Mech 468:153–177

Zeng J, Korsmeyer T (2004) Principles of droplet electrohydrodynamics for lab-on-a-chip. Lab Chip 4:265–277

Zeng J, Almadidy A, Watterson J, Krull UJ (2002) Interfacial hybridization kinetics of oligonucleotides immobilized onto fused silica surfaces. Sens Actuators B 90:68–75