Simulation-Aided Design of Microfluidic Devices

Computer simulations help microfluidic device designers get from concept to prototype quickly and efficiently.

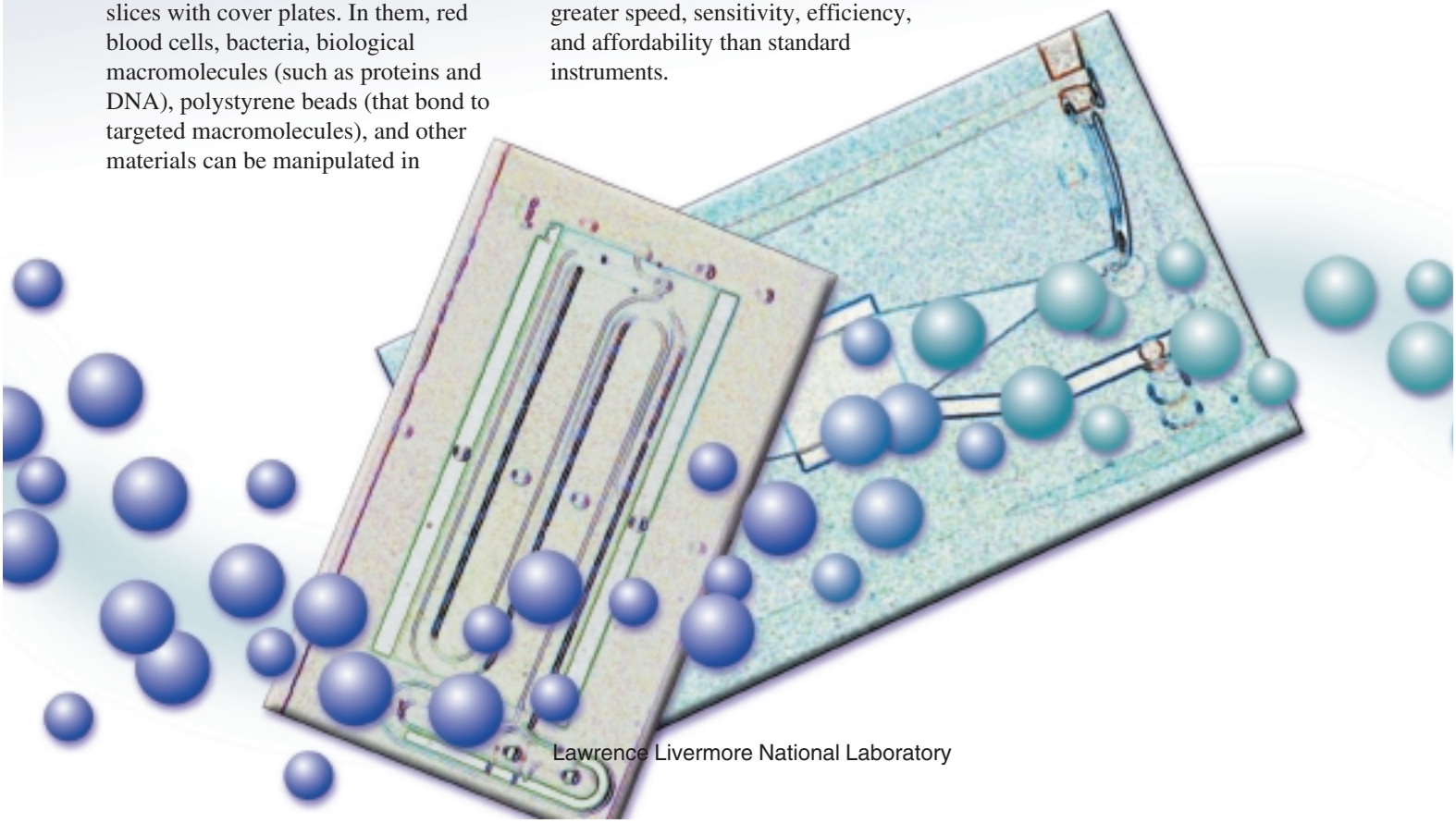
THE microchip revolution made possible today's miniaturized electronics industry. In like manner, the microchip is changing laboratory instruments that analyze fluids. Large and costly instruments are being replaced by microchip-based systems known as microfluidic devices. These miniature systems move fluids through a maze of microscopic channels and chambers that have been fabricated with the same lithographic techniques used for microelectronics.

Microfluidic devices are fashioned from silicon, glass, plastics, and ceramics into 2- or 3-square-centimeter slices with cover plates. In them, red blood cells, bacteria, biological macromolecules (such as proteins and DNA), polystyrene beads (that bond to targeted macromolecules), and other materials can be manipulated in channels with characteristic length scales on the order of 100 micrometers. The devices integrate sensors, actuators, and other electromechanical components to dispense with myriad moving parts and the people required to operate and service them.

Microscale instruments and processing are the future of medical research and the chemical and pharmaceutical industries. Microfluidic devices hold the promise of a small analytical laboratory on a chip to identify, separate, and purify cells, biomolecules, toxins, and other materials. They would perform these tasks with greater speed, sensitivity, efficiency, and affordability than standard instruments.

They might also be used in the future for detecting chemical and biological warfare agents, delivering precise amounts of prescription drugs, keeping tabs on blood parameters for hospital patients, and monitoring air and water quality.

For more than a decade, Lawrence Livermore researchers have been working on several aspects of microfluidic devices. The Laboratory's Center for Microtechnology has more than 30 experts in electronics, biology, optics, and engineering who are developing microfluidic components



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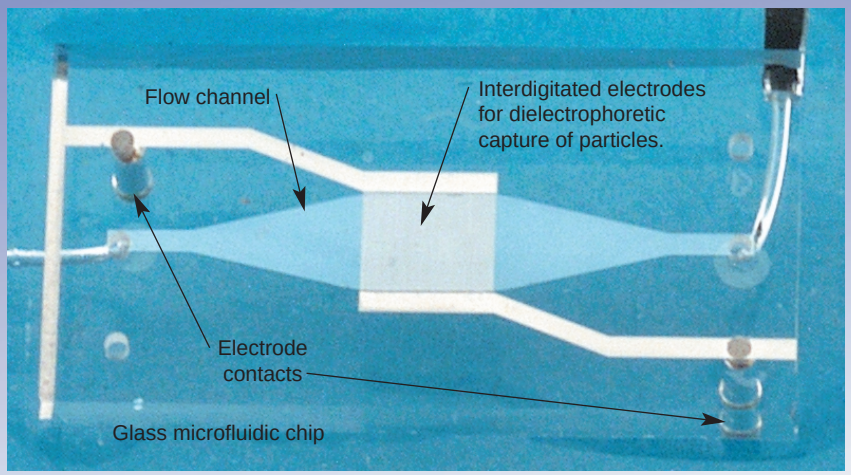
for transporting, sensing, separating, mixing, and storing fluids and their constituents. (See *S&TR*, July/August 1997, pp. 11–17.) Current Livermore projects include the design and prototyping of devices for the human genome program, chemical and biological warfare agent detection, and medical analysis.



In actual size, this microfluidic device designed by Livermore engineer Peter Krulevitch is barely larger than a postage stamp.

First Complete Model Designed

To help guide the design of microfluidic devices at the Center for Microtechnology and elsewhere, a team of Livermore researchers is developing a complex, three-dimensional simulation tool. The team consists of chemical engineers David Clague and Elizabeth Wheeler, postdoctoral mechanical engineer Todd Weisgraber, and University of California (UC) at Berkeley student Gary Hon. In this work, they collaborate with other Livermore researchers from several disciplines as well as colleagues at universities. The team has been funded for the past three years by the Laboratory Directed Research and Development (LDRD) Program through Livermore's Center for Computational Engineering and, more recently, by the Defense Advanced Research Projects Agency (DARPA) of the Department of Defense.

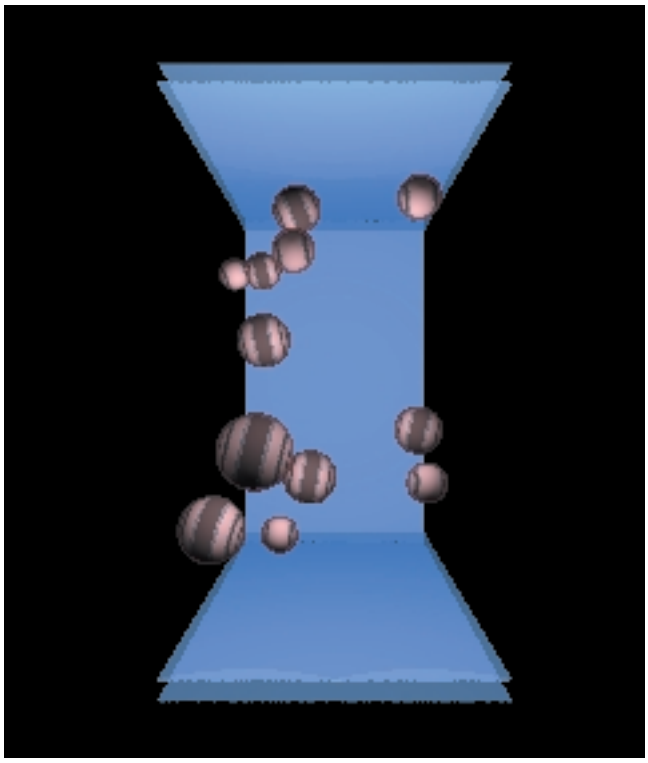
The team's computer code has drawn increasing interest because it provides an accurate representation of the behavior of suspended particles, especially polystyrene beads and biological macromolecules, as they travel inside a microfluidic device. The simulation capability incorporates into a single numerical code complex channel geometries and such parameters as fluid flow rates, particle interactions, and external forces. "We want to predict the complex interplay of the forces involved in microfluids to give designers a way to accurately predict how beads, cells, and macromolecules will behave," says team leader Clague.

Clague notes that suspended particles traveling within microscopic channels are subject to a number of physical forces that influence their transport and separation from each other and the channel walls. The forces, such as subtle electrical attractions and repulsions, can be used to achieve the movement and manipulation of suspended particles in ways that would not work in traditional bench-scale laboratory instruments.

The Livermore simulation capability provides a new tool to assist microfluidic device designers who want to engineer systems that will reliably move, separate, concentrate, and identify suspended particles of interest. With effective simulation, the designers can see the effects of design decisions before they build a prototype. For example, a designer may want to position selected biological macromolecules in the central region of a microchannel for capture by an electric field and therefore must determine what field strength will be required. Or a designer may want to see how restricting a channel with a tiny post might affect the fluid flow rate and the mixing behavior of particles as they are forced to "slalom" around it.

The program uses a form of the Boltzmann transport equation called the lattice Boltzmann equation (LBE) to represent the behavior of fluids and suspended particles within microfluidic devices. (Ludwig Boltzmann was an Austrian physicist whose greatest achievement was the development of statistical mechanics, which explains how the microscopic constituents of matter—atoms and their properties—determine macroscopic properties such as thermal conductivity or viscosity.) In recent years, the LBE method has gained popularity and usefulness in simulating the flow of complex gases and liquids. It is based on a statistical description of the fluid on a cubic lattice in which each lattice site represents up to several thousand individual fluid molecules.

In the team's numerical model, spheres represent polystyrene beads and biological macromolecules within the lattice. The spheres can be assigned different sizes, densities, and electrical properties. Because of their size, the spheres can occupy several lattice sites. The code tracks the spheres as they move on the lattice and calculates the extent to which the spheres interact with each other, the channel walls, the fluid, and external forces that may be applied to manipulate them. The simulation tracks the time evolution of both the fluid and suspended spheres. The algorithms (mathematical routines) used by the program tend to be readily applied, allowing calculations in a straightforward manner and making it easy to incorporate new forces.



Simulations can accurately reflect a host of physical forces that act on suspended particles flowing in a microfluidic device that typically measures 100 micrometers long, wide, and high. These forces, such as subtle electrical attractions and repulsions, are typically of much less importance in traditional bench-scale laboratory instruments.

A Natural for Parallel Computing

Because the LBE method is naturally suited for parallel computing, the simulation capability is designed for large computers, preferably supercomputers that use tens to hundreds of microprocessors together. Simulations representing time scales on the order of tens of seconds of continuous suspension require a few days of computer time. The team uses several Livermore machines for their simulations, including the Compass Cluster and two massively parallel supercomputers: Blue, the 740-gigaops unclassified portion of Blue Pacific, one of the Department of Energy's Accelerated Strategic Computing Initiative supercomputers, and the 680-gigaops TeraCluster2000. (See *S&TR*, October 2001, pp. 4–10.) The TeraCluster2000 is the preferred computing platform; simulations on it use up to 50 microprocessors working simultaneously.

One important advantage of the code is its flexibility. The simulated suspended particles can be assigned different physical and electrical attributes, including electrostatic forces that cause fluids containing biological macromolecules to act far less predictably than ideal species, which would consist of hard, inert spheres.

External forces such as gravity, alternating current, or direct current can be simulated. These forces can be turned on and off to isolate their specific effects on particle behavior. Livermore engineer Peter Krulevitch, a microfluidic device project leader, says that until now, no program was capable of simulating all the forces acting on fluids containing particles. "The problem has just been too complex," he says.

The LBE method contrasts with traditional fluid modeling based on finite-element analysis and boundary-element methods, which typically deal with pure fluids. Results from the Livermore code, however, can be handed off to larger-scale computer-aided design simulation tools that use standard finite-element analysis.

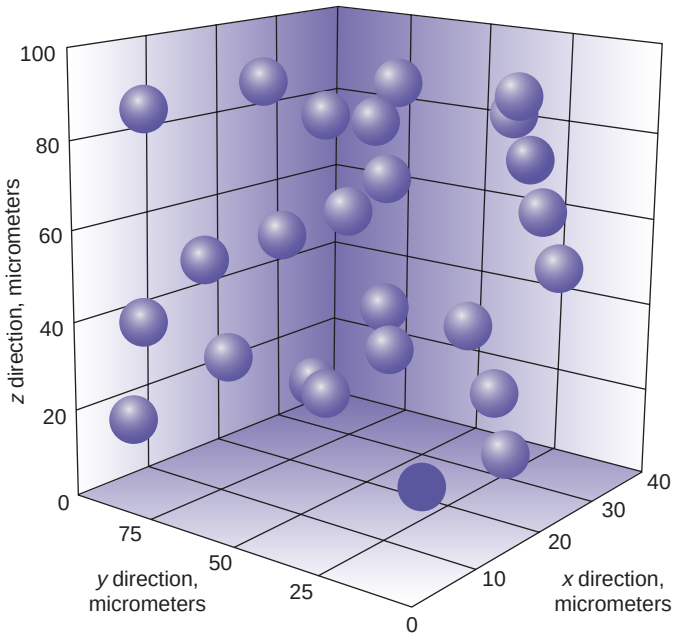
Mike Pocha, a Center for Microtechnology section leader, notes that device designers can build prototype devices—a long and painstaking process—and determine their capabilities or, preferably, simulate them first and then build a prototype guided by the simulation results. Going from concept to manufacturing a prototype is increasingly more time-consuming and expensive as microfluidic devices get more complex, says Clague. "With a more comprehensive simulation tool, researchers will be better able to predict what will happen to the suspended species in these complex microenvironments. Ultimately, such a capability will speed the design effort and reduce costs."

The physics involved with the operation of microfluidic devices is complex and varies, depending on the fluid, the molecules suspended in the fluid, and the extent, if any, of external fields. In building the code, the team has steadily added capabilities that more completely represent the physical forces at work in microfluidic devices. After every addition of a new feature, the team makes sure the results are in excellent agreement with existing theory and, where possible, with published alternative numerical methods.

LDRD Laid the Groundwork

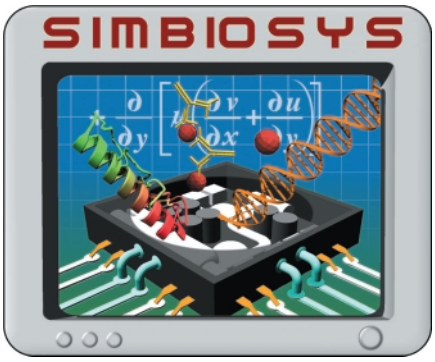
One of the team's first accomplishments under LDRD funding was simulating hydrodynamic forces acting on a stationary sphere. These forces are dependent on the velocity of the suspending fluid and the proximity of the suspended particles to channel walls. The LBE method naturally takes into account the entire spectrum of fluid and particle behavior, including inertial effects and hydrodynamic interactions between suspended particles. In other words, the simulations account for the minute disturbances propagated within a fluid by the particles that "feel" each other's presence and, as a result, change their trajectories and the properties of the fluid.

The hydrodynamic forces, including inertial effects, are particularly well captured. The first is the drag force, which is a result of the fluid exerting a force on a suspended particle because of differences in fluid and particle velocities. The second force is a lift force, which is caused by small inertial effects and gradients in fluid velocity. The lift force is exerted perpendicular to the flow, causing the species to migrate to the center of the channel. Also coming into play is a particle's density, which affects its buoyancy within a fluid and the extent to which it can be lifted.



Simulations using the lattice Boltzmann equation method are based on a cubic lattice, here with dimensions of 40 by 100 by 100 micrometers. Spheres (in this example, measuring 5 micrometers in diameter) represent polystyrene beads and biological macromolecules within the lattice. The simulations track the spheres as they move on the lattice and calculate the extent to which they interact with each other, the channel walls, the fluid, and the external forces that are used to manipulate them.

Fluids normally flow through microfluidic channels without turbulence so that suspended particles typically mix only by diffusion. One of the key parameters used to characterize fluid flow is the Reynolds number, which defines flow conditions and measures the relative importance of inertial effects to viscous effects. Most fluid flow in small channels occurs at a low (but finite) Reynolds number. However, even at small Reynolds numbers, researchers have found that there are small lift effects. The Livermore simulation capability takes into account these inertial effects for predicting the extent of lift as a function of Reynolds numbers.



The Livermore simulation work is part of the Simbiosys (Simulation of Biomolecular Microsystems) program administered by the Defense Advanced Research Projects Agency. The program funds the development of advanced computational tools for the BioFluidic Chips design effort.

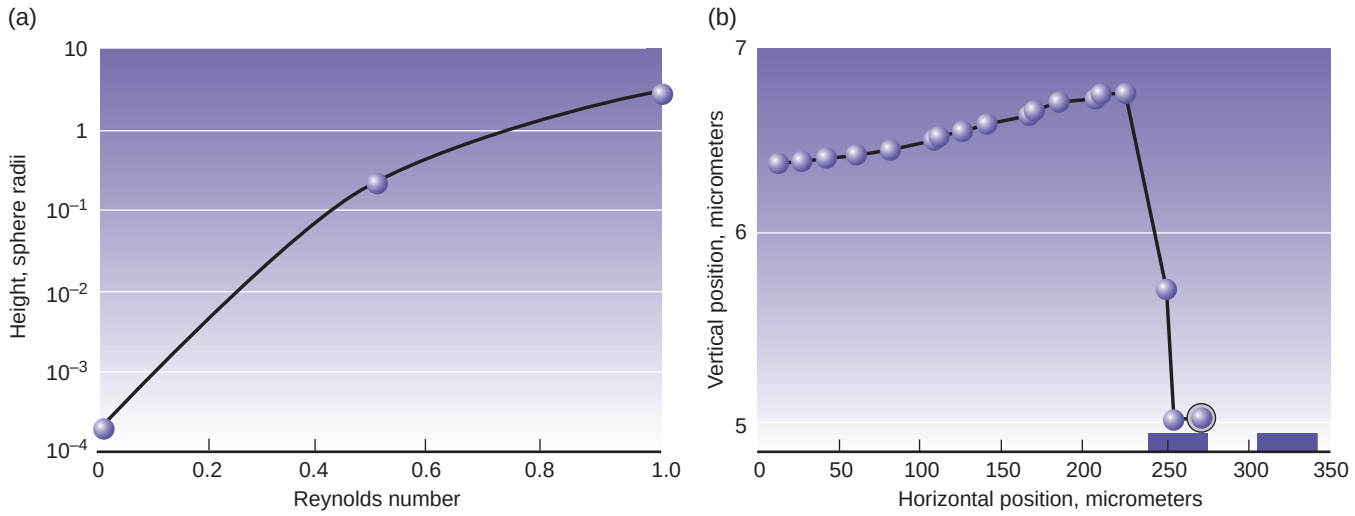
The code also simulates the effects on particles that are near channel walls. Much like the effect of a boat's wake, the motions of molecules cause disturbances in the fluid that bounce off the channel walls and reflect back on the particles. Close to the walls, particles experience forces retarding their motion, and even closer to the walls, they experience large resistive forces known as lubricating forces.

Adding Real Effects

If the simulation is to be accurate, it must also account for non-Newtonian characteristics that are exhibited by biofluids containing human cells, bacteria, and biological macromolecules such as proteins and DNA. These materials do not behave like electrically neutral and perfectly round spheres. Instead, they have widely varying shapes, densities, and often electrical charges that are asymmetrically distributed.

More importantly, these materials tend to have elastic character, which gives rise to unexpected effects. Strands of DNA, for example, can be long and gangly with a preferred, three-dimensional shape that orients itself in a particular manner to its neighbors. If forced to travel through a narrow channel, the strands deform but then exert a small force in an attempt to recover their favored configuration, much like a compressed spring reverts to its normal shape. If there is a sufficient concentration of such strands, this restoring force can have a profound effect on fluid behavior.

Depending on their concentration, particles interact with each other and



(a) The simulation capability can be used to predict the extent of inertial lift as a function of the fluid's Reynolds number. The lift force acts to push suspended particles up or down toward the center of the channel. (b) Dielectrophoresis (DEP) is an efficient method for capturing selected particles in microfluidic devices. DEP electrodes (rectangles) generate nonuniform alternating current electric fields that induce electrical polarization in biological macromolecules. The DEP forces overcome inertial lift forces to cause a selected particle to move toward the electrodes and to remain there.

with the channel walls. Under certain conditions, they can coagulate with each other or stick to walls because of van der Waals and electrostatic forces (electrical attraction and repulsion forces between species). The simulation team is incorporating these and other forces associated with biological macromolecules into the models, including hydrophobic (water hating) and hydrophilic (water loving) interactions. Clague explains that some proteins have hydrophobic regions that cause the proteins to aggregate when they are in close proximity to other proteins; therefore, these unique forces must be taken into account.

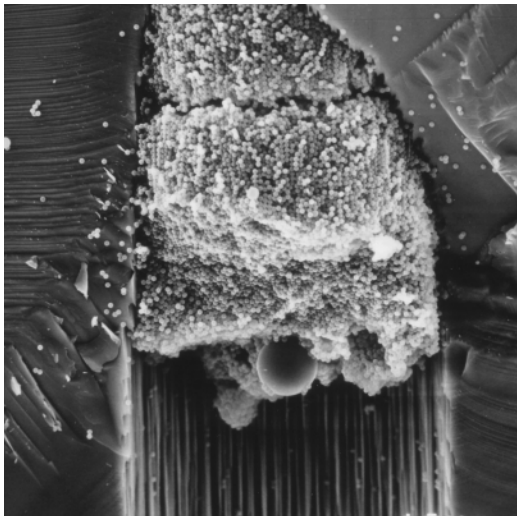
Last August, the team began work for DARPA, the advanced research arm of the Department of Defense and a major backer of microfluidic technology. One of DARPA's goals is to develop devices called BioFluidic Chips (BioFlips) that will identify biological macromolecules and microbes based on certain electrical or chemical properties. Soldiers would use BioFlips devices both to detect chemical and biological agents and to monitor their own general health. (See the box on p. 10.) As part of the microfluidic development effort, a program called Simulation of Biomolecular Microsystems (Simbiosys) is funding the development of advanced computational tools for the BioFlips design effort. The Livermore team's simulation work is part of the Simbiosys program.

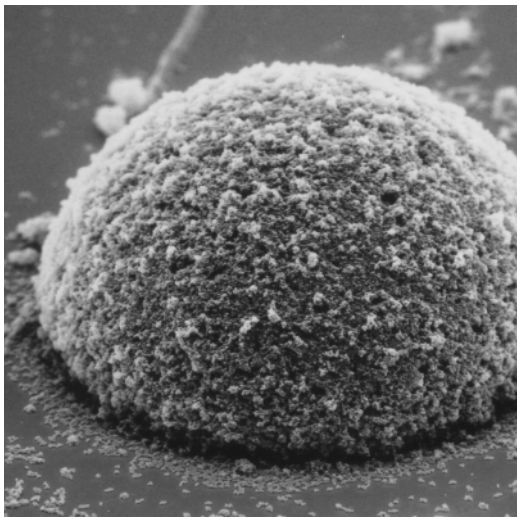
Focus on Dielectrophoresis

The team's work for DARPA builds upon LDRD research, particularly with regard to simulating the coupling of hydrodynamic and dielectrophoretic forces. Dielectrophoresis (DEP) is an efficient and increasingly popular method for separating molecules in microflows. DEP electrodes generate nonuniform, alternating current electric fields that induce electrical polarization in target species. On an absolute scale, the force is quite small, but in microfluids, the force can be quite effective in manipulating and positioning biological macromolecules with electrodes using less than 10 volts. The degree of induced polarization is dependent on the electrical properties of the molecule, the surrounding fluid, and the magnitude and frequency of the applied electric field.

"Different species typically have their own unique dielectric response fingerprint that can be exploited by DEP," says Clague. As a result, DEP can be used to select from among a number of different particles suspended in the same fluid. The selected particle will either be drawn toward or repelled from the region of high field intensity (toward or away from the DEP electrode located within a channel wall). The first instance is referred to as positive DEP, and the second is referred to as negative DEP.

DEP forces can be switched on and off to selectively capture cells, bacteria, spores, polystyrene beads, DNA, proteins, and other matter. Once captured, the molecules can be held in place or, with the removal of the force, sent on their way to a different location for analysis.





The Laboratory team is collaborating with University of California researchers at Berkeley and Davis to simulate the transport of suspended particles in microneedles. These simulations are helping to obtain a better understanding of why particles can stick together and plug microneedles, as shown. (Photos courtesy of Professor Dorian Liepmann of the University of California at Berkeley.)

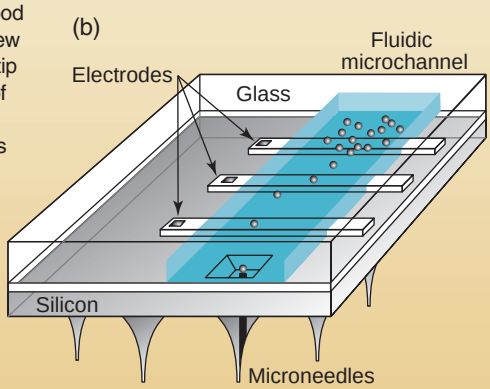
For example, DEP can be used to selectively capture a suspected pathogen. The pathogen would then be shuttled to a different area where its DNA would be extracted and analyzed.

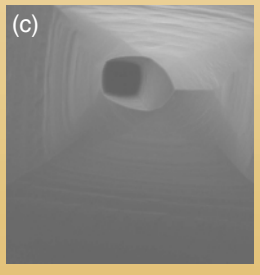
The DEP simulation work involves close collaboration with pathologist Peter Gascoyne at the University of Texas M.D. Anderson Cancer Center in Houston, Texas. Gascoyne and his colleagues, in a project sponsored by DARPA, are developing an instrument that uses DEP to separate cells and identify them based on their dielectric properties. A prototype has been used on whole blood samples to separate malignant cells from normal cells.

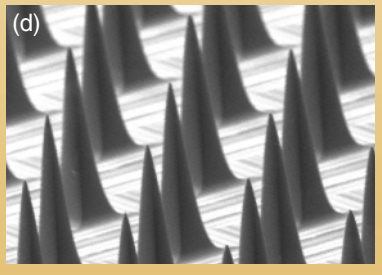
An important group of simulations is focused on examining the interplay of suspended particle concentration, flow rates (and inertial lift effects), and DEP forces with the effects from different kinds of suspended particles. Preliminary simulations show that the hydrodynamic interactions between particles can screen and thwart DEP forces; therefore, concentration effects become very important. The suspended particles that are not screened encounter a positive DEP force and are pulled to the electrode surface, where they are held motionless.

The team is continuing to enhance the numerical model to investigate the forces influencing DEP manipulation of molecules suspended in flowing fluids.

Monitoring the Health of Soldiers







(a) The Defense Advanced Research Projects Agency is developing BioFluidic Chips (BioFlips) that are small enough to be worn on an earlobe and can identify biological macromolecules based on certain electrical or chemical properties. (b) A BioFlip uses an array of microneedles for continuous blood monitoring. (c) View of a microneedle tip and (d) an array of microneedles. (Photo and figures courtesy of Professor Rosemary Smith of the University of California at Davis.)

The BioFluidic Chips (BioFlips) program of the Defense Advanced Research Projects Agency (DARPA) is developing a clinical lab on a chip. BioFlips would offer all the advantages of microfluidic devices: miniaturized channels and reservoirs for increased speed of reaction, increased sensitivity, reduced cost of reagents, and reduced power consumption. The devices would be capable of rapid detection of infections and chemical and biological warfare agents, making possible potentially rapid treatment. BioFlips would be worn directly on the skin, perhaps on the earlobe for continuous blood monitoring through microneedles.

BioFlips would provide real-time, unobtrusive monitoring to directly assess the health of defense personnel. A commander could continuously monitor the status of troops—whether they are fatigued or have been exposed to biological threats, including bacteria, viruses, and toxins. The devices could monitor such entities as white blood cells, antibodies, blood pH, and blood glucose.

BioFlips promise fast health assessment, from seconds to minutes, in contrast to laboratory blood cultures using traditional methods that take hours or even days to process. If successful, the technology could perhaps be extended to improve national health care by unobtrusive and continuous monitoring of high-risk patients.

BioFlips designers need powerful computational tools to guide and speed their efforts. Hence, DARPA is sponsoring an allied DARPA program called Simulation of Biomolecular Microsystems (Simbiosys). The Simbiosys program recognizes that engineers have limited understanding of biological molecules and biochemical reactions and, furthermore, that biologists do not generally have knowledge about key biochemical reaction rates and little knowledge about the behavior of biological molecules in microscopic channels. The goal is the creation of what DARPA managers are terming the "first interface between biology and engineering." Effective simulation models will enable greater understanding of the transport of biological materials at the micrometer scale to enable better control and efficiency of the devices.

One research avenue they are taking is to give biological macromolecules more realistic characteristics. For example, the team has explored replacing the simulated spheres with more accurate bead-and-spring representations of long-chain polymers such as DNA fragments. Also under development are representations of cell properties unique to organelles and membranes, that can significantly influence the response. Finally, the team is working on the inclusion of electrostatic and van der Waals forces as well as hydrophobic and hydrophilic interactions.

The team has collaborated with UC Berkeley researchers on developing arrays of 50-micrometer-diameter needles. The goal is to deliver drugs more efficiently, but interactions between particles cause the microneedles to become clogged. The Livermore team's simulation work is targeted at obtaining a better understanding of the problem. This work complements a DARPA-funded project at UC Davis, where researchers are developing microneedle arrays for drawing body fluids painlessly to monitor soldiers' health on the battlefield.

Clague expects the simulation program to become increasingly useful as applications for microfluidic devices expand. By providing a tool that allows microfluidic device designers to turn the variety of physical forces at play on and off, the team hopes to make possible the discovery of new ways to manipulate suspended particles. Such detailed and accurate simulations speed the design and development of novel microfluidic devices. As a result, the simulation effort may well have an important role in saving soldiers' lives and in developing new medical devices that could help drive down national health care costs.

—Arnie Heller

Key Words: BioFluidic Chips (BioFlips), Center for Microtechnology, Defense Advanced Research Projects Agency (DARPA), dielectrophoresis (DEP), lattice Boltzmann equation (LBE), microfluidic devices, Reynolds number, Simulation of Biomolecular Microsystems (Simbiosys).

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