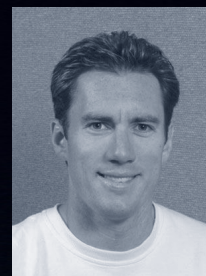


MEMS-based biosensor brings the hope of disposable DNA detector

Wouldn't it be a great service to diagnosing and treating genetic diseases if physicians had a disposable instrument for detecting DNA that worked as simply and quickly as today's home-pregnancy tests? Or if we could have other inexpensive biosensors that could look for specific blood proteins or other biological substances? This isn't such a farfetched proposition thanks to advances in microfluidic-based Lab-on-a-Chip concepts. Professor Carl Meinhart at University of California, Santa Barbara (UCSB) is leading a research team that is examining how to design microfluidic devices for enhanced performance of biosensors that can quickly detect biological molecules.



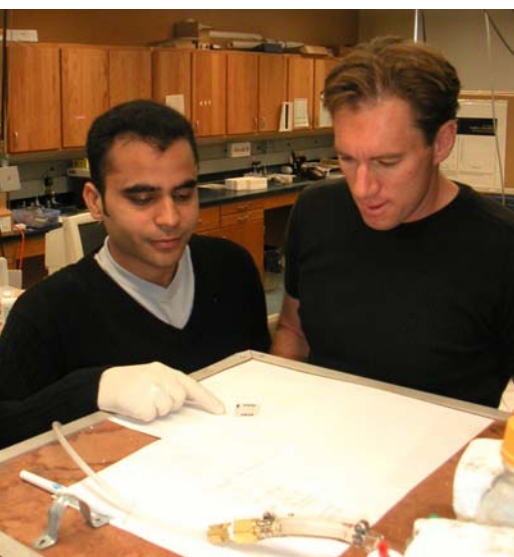
Dr. Carl D. Meinhart is an Associate Professor in the Department of Mechanical and Environmental Engineering at the University of California, Santa Barbara. He is also Director of the UCSB Microfluidics Laboratory, which conducts research in two primary areas: the investigation of fluid mechanics at the microscale, and its application to optimize MEMS-based biosensors.

Dr. Meinhart labels himself as being primarily an experimentalist, but he's equally well known as an expert numerical modeler. He uses COMSOL Multiphysics to develop and verify theories that explain what he observes, to pinpoint which theories agree with observed experimental results. In this way, he feels he'll be better prepared to expand his findings to a large number of application areas that involve the stirring, pumping, and mixing of small (nanoliter) volumes of fluids.

Dr. Meinhart began his work on microfluidic devices thinking it might be applicable to biosensors, an area with great commercial potential. When a sample has a low concentration of the analyte (the species to be analyzed), today's tests can require tens of hours. In contrast, he's developed some microchannel devices that can potentially reduce this time by a factor of 10—by micro-stirring the fluid through the action of applying an appropriate voltage to electrodes.

Find the perfect match

Before looking at the modeling process, first consider the physics of hybridization (to form base pairs between complementary regions). Many DNA tests use this technique to detect the concentration or presence of specific-sequence oligo-nucleotides (the basic building blocks of DNA). One detection technique functionalizes a microchannel surface with a known single-stranded DNA. The flow in the microchannel delivers unknown single-stranded DNA molecules to the functionalized surface. If a complementary match exists, the DNA hybridizes to the functionalized surface, producing either an electrical or optical signal related to analyte concentration. Theory would have it that the diffusion of DNA to the surface limits the rate of hybridization, so the detection system will enhance the reaction by micro-stirring the fluid. Although Dr. Meinhart hasn't yet experimentally confirmed this idea with DNA, he believes it holds promise, and his team is working on bringing this technology to industrially relevant sensors.



Research assistant Gaurav Soni (left) and Prof. Carl Meinhart (right) examine a microchannel device in their laboratory.

To implement his novel approach, Dr Meinhart is designing a microchannel device (Figure 1) with a diameter of $40\ \mu\text{m}$ and a length of $250\ \mu\text{m}$. Without adding any electrical excitation, the transport of the analyte to the reaction surface can be slow because the laminar flow in the channels is parallel to this surface and zero at the surface itself. Thus the main transport perpendicular to the flow and to the surface is through the process of diffusion. If the reaction is limited by diffusion, the detection process can take as long as roughly 10 hours.

Dr Meinhart and his team have developed a method for improving flow near the reaction surface to increase the transport of analyte using ac electrokinetic flow. Here they place two electrodes on the channel wall opposite the binding surface. When they apply a voltage, the AC electrokinetic forces generate a swirling pattern in the fluid that transports a higher concentration of the analyte towards the binding surface, increasing the reaction rate. Explains Meinhart, “By adding carefully designed electrodes and the optimal driving voltage, we can potentially reduce the detection time by a factor of ten, from ten hours to just one.” For a laboratory that needs to perform a large number of tests, this reduction in time is significant.

Six physics involved

The method by which electrical forces stir the fluid is relatively complex, involving a number of physics. In particular, three major phenomena are involved. First is a dielectrophoresis (DEP) force, whereby a molecule acting as an electric dipole reacts to an applied voltage.

Second is an electrothermal force on the fluid.

The electrodes create an AC electric field that non-uniformly Joule heats the fluid. Electrical conductivity

and permittivity are functions of temperature, so gradients in these parameters due to the heating give rise to Coulomb and dielectric forces, which act as an electrothermal force that changes the fluid’s motion (see reference).

A third force arises due to electroosmosis. The fluid is a conductor, so a voltage applied to the electrode triggers ions in the fluid to counterbalance the

potential. The result is a very thin layer of ions at the electrode surfaces only a few nanometers thick. The electric field leaves at a direction normal to the electrode surface, but if the layer is only tens of nanometers thick the field has a slight tangential component, and this electroosmotic force contributes to fluid motion.

Dr. Meinhart’s team has conducted experiments to investigate these forces and their results. They then combine experimental results with numerical simulations to examine the validity of various theories. Creating such a numerical model is quite complex because the problem has a large number of physics, including the behavior of electrical potential, electric field, temperature, electrical conductivity and permittivity, fluid velocity, analyte concentration, and a first-order heterogeneous reaction. The model simultaneously couples six equations:

- Solve the base electrostatics problem using Laplace’s equation.
- Solve the thermal-energy equation with Joule heating from the electric field as a source term.
- Calculate the nonlinear electrothermal force using results from electrostatics and temperature simulations.
- Solve the fluid-velocity field in the channel using the Navier-Stokes equations with the electrothermal force added as a source term. From the electrothermal force equation, the Coulomb force dominates at low frequencies and the dielectric force dominates at high frequencies.
- Use the time-dependent diffusion-convection scalar equation to predict the analyte’s suspended concentration within the microchannel.
- Solve the 1D heterogeneous reaction equation and couple the 1D binding surface to the 2D microchannel.

To assist in creating an accurate mathematical model that would incorporate all these factors in the biosensor, Dr. Meinhart’s team first started using COMSOL Multiphysics in 2000. “Before that time,” he notes, “there were no commercial packages that could solve all of these physics. I’m aware of a researcher who developed his own code to examine flow in a microchannel, but he spent years doing it. With COMSOL Multiphysics, a knowledgeable user can code it up in a week. Meanwhile, some other commercial packages have come around with multiphysics capabilities, but you can only hope that

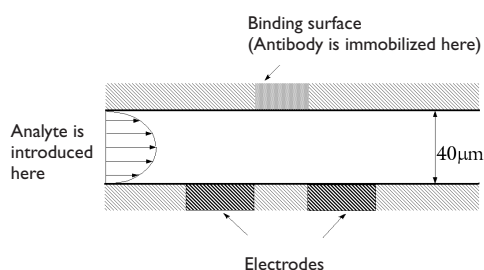


Figure 1—Fluid flows through a microchannel from left to right, and an optimized AC voltage applied at the electrodes on the bottom improves the rate of absorption at the binding surface.

the one you pick includes the needed combination of physics, which it might not depending on the physics you're studying, especially if it's a narrow field. In fact, with such narrow disciplines there's rarely a commercial code. Even if you get lucky and find one, it can be very difficult to link the physics together in such environments. COMSOL Multiphysics, in contrast, is very advanced and flexible. If you're not certain of the governing equations, you can try any number of equations or terms or even build your own until you find the set that does the job."

When built-in equations aren't enough

Dr. Meinhart points to the odd couplings that this problem involves, especially the electrothermal stirring that must account for the electric field, the heating of the fluid, and the nonuniform binding forces. When examining some effects, he found that no package had the necessary equations prewritten. For instance, in calculating the DEP forces he had to take a first and a second derivative of the potential field on a boundary. In that case he was able to type the equations into COMSOL Multiphysics's free-form direct-entry equation fields straight from the keyboard.

The most challenging aspect of creating the model, though, was dealing with the chemical reaction. His team coupled a 1D geometry for the binding surface to a 2D geometry that represents the microchannel. "At first we were stumped as to how to couple physics on these two geometries," comments Dr. Meinhart. "We ended up learning how to do it in a COMSOL Multiphysics course where they had an example similar to our case. We quickly discovered that these hands-on classes are absolutely invaluable when working with sophisticated models."

In his model, developed with the assistance of team members Gaurav Soni, Marin Sigurdson and Dahzi Wang, the incoming flow has a small concentration of the biological analyte, which flows from left to right. Without any voltage applied to the two electrodes on the bottom, the flow profile is characteristic for fully-developed laminar flow, that is, parabolic velocity profile with zero velocity at the channel walls. The analyte is transported with the fluid and is absorbed by the reaction surface on the upper boundary, and any remaining concentration exits the channel on the right side with the fluid. The model solves the steady-state flow interacting with the given electric field and the resulting electrothermal force. Then, for comparison, the team ran a transient simulation of the material balance assuming that the

initial concentration is zero and a given concentration is injected at the inlet.

The image in Figure 2 shows that when an AC voltage is applied to the electrodes, the velocity profile is no longer parabolic and is displaced towards the binding surface. This implies that the analyte concentration is transported towards the binding surface much faster in the presence of an electric field.

A study revealed that 14 V rms applied to strategically placed electrodes can increase the binding rate in the first few minutes by a factor of almost five. Optimization of the electrode geometry and placement through the aid of simulations with COMSOL Multiphysics can render this technique useful for a large variety of microfluidic immuno-sensors.

The team also wanted to quantify the enhancement of the binding reaction, so they compared the binding rates in two cases: with and without the electric field (Figure 3). Applying 10 V rms to the electrodes enhances the bound concentration by a factor of 1.5 within the first five seconds, and this factor keeps on increasing with time. In addition, the binding rate, as seen in the slope of the curves, is almost 1.5 times higher in the case of electrokinetic flow.

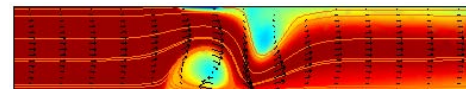


Figure 2—The flow 5 sec after applying a specific voltage to the electrodes stirs the fluid flow so that it focuses the analyte on a narrow path near the reaction surface. The color plot shows the analyte concentration and the arrows show the velocity field.

Quickly investigate new combinations

With the knowledge the team is gaining through modeling with COMSOL Multiphysics, they can quickly and efficiently examine the effects of various geometries for the microchannel as well as placement of the binding surface and the electrodes; they can also investigate what happens with various excitation voltages. In this way, they can quickly optimize the basic principles for particular biosensor applications that examine a wide range of analytes injected into various fluids. These models, in turn, should enable the biosensor industry to create innovative products based on this breakthrough technology and get them to market even faster. In addition, Dr. Meinhart works as an independent consultant in the bio-MEMS field, and COMSOL Multiphysics has made it possible for him as an experimentalist to get involved with the underlying theories and numerics. "FEMLAB has a flexibility far beyond anything else on the market, and that makes it a valuable tool for me because I never know exactly what physics I will need to solve." ■

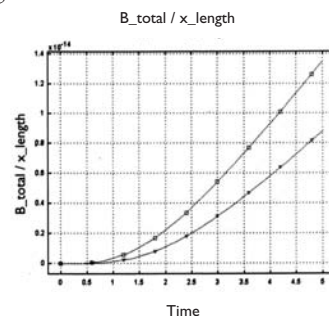


Figure 3—A COMSOL Multiphysics plot of average concentration (mol/liter) vs. time (seconds) illustrates that applying a 10V rms signal to the electrodes enhances the bound concentration by a factor of 1.5 within the first 5 sec; this factor continues to increase with time. The curves' slope gives the binding rate, which is also almost 1.5 times higher in the case of the electrokinetic flow.