# Design Tools for BioMEMS

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## ABSTRACT

Microsystems used for chemical analyses and biological assays are termed BioMEMS or labs-on-a-chip. These systems often require some of the traditional electromechanical capabilities of MEMS, and in addition require the manipulation of fluids in either continuous flow or droplet form. The distinction between continuous flow and droplets defines two broad categories of BioMEMS. Different applications call for one or the other of these approaches, but in either case, software for design and simulation can make a significant contribution to design optimization and reduction in time to market. A computer aided design and analysis approach is presented in which system-level analysis is favored over detailed analysis, although it is shown that this is not always possible, nor preferred. Examples of the use of design and analysis software in BioMEMS development are presented including: electrostatic actuation, a lab-on-a-chip for separation, on-chip optics, a digital fluidic processor, electro-spray ionization, and a two-stage chemical reaction.

## Categories and Subject Descriptors

J.6 [**Computer-Aided Engineering**]: [Computer-Aided Design]

## General Terms

Algorithms, Design, Verification.

## Keywords

MEMS, BioMEMS, lab-on-a-chip, μTAS, CAD, system-level modeling, BEM, FEM

## 1. INTRODUCTION

While commercial microelectromechanical systems (MEMS) are now appearing in a variety of applications, mostly as sensors or actuators, some of the most exciting applications are in BioMEMS. These systems will be widely used in medicine, homeland security, and on the battlefield, because of low-cost, disposability, low weight, and low power consumption. However the path to deployment of these devices is more difficult than for most sensors or actuators because they incorporate multiple physical phenomena, which complicate design, and in some cases the devices require FDA approval. The term MEMS emphasizes the original vision that was centered on electrostatic actuation of silicon and metal parts. MEMS have progressed beyond this to include many different physical effects. BioMEMS nearly always include fluid flow and may include electrohydrodynamics; optics; and electromagnetic actuation in some form, such as electrostatic, magnetic, or piezoelectric.

There are many different forms of devices called BioMEMS. Usually what is meant by the term is a device for the manipulation of chemicals in amounts at least as small as a micro-liter, proteins, or cells, for the purposes of DNA separation, disease screening, contaminant detection, drug discovery, drug delivery, or patient monitoring. (Micro-surgical instruments or MEMS attached to normal-sized surgical instruments may also be called BioMEMS, but usually the term does not include such devices and that restriction is honored here.) Other device names included under the term BioMEMS are *micro-total-analysis system*, which emphasizes the idea of a system that performs all of the tasks from sample input to result detection; *lab-on-a-chip*, which emphasizes the replacement of familiar laboratory processes and quantities with operations at chip scale, and *array processor*, which takes its name from its parallel approach to conducting assays. Another term that appears in connection with BioMEMS, but does not exclusively belong to it, is the self-defining *microfluidics*.

In this paper, the focus is on the two leading paradigms for lab-on-a-chip fluidics. The so-called *first-generation* chips use pressure-driven channel flow and are specifically designed for certain analyses or assays. More recently, a *second-generation* paradigm has emerged that is often termed *digital microfluidics.* These chips are not purpose-built, but rather are designed as general microfluidic processors. Here the operands are droplets, rather than continuous flow, and the range of possible analyses or assays is not limited by the design *a priori*, it is only limited once a chip is deployed, by the reagents loaded on the chip and the droplet manipulations programmed into the chip logic.

In the subsequent sections a CAD-for-MEMS philosophy is presented, followed by example BioMEMS and the simulations that are useful for guiding the design process and optimizing the design.

## 2. MODELING PHILOSOPHY

Any useful CAD tool for MEMS or BioMEMS would include the following: a graphical front end in which devices could be constructed, possibly under the constraint of available process descriptions; a series of physics simulation modules, including mechanics, electrostatics, fluidics, optics, *etc.*; and a graphical back end in which the simulation results could be visualized.


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It is the simulation modules that are of primary interest here. There are two markedly different approaches that can be taken to simulation [1]. One is system-level modeling, where analytical or semi-analytical models of device components are placed and connected in a schematic of the device and the whole device is simulated. This approach allows the straightforward coupling of many different physical domains, including control circuitry, but is limited by the availability and/or accuracy of component models. The second is detailed modeling, where numerical solutions of partial differential or integral equations are found by methods such as finite element or boundary element. Here as well, different physical domains may be coupled, but the computational cost becomes high with multiple domains and complicated devices.

Ideally, device designers should be working at the system level, at least at the outset of a new design cycle. At this level the behavior of the entire device can be understood, and very large design spaces can be constrained. Once promising design candidates have been identified, detailed modeling should be used to confirm system-level results and further optimize design parameters. (See Figure 1.) The success of the system-level approach depends critically on two aspects of the modeling tool: (1) a rich library of parameterized component models, and (2) an extraction capability for building *reduced-order* component models from detailed simulation for components not covered by the library. For some components neither 1 nor 2 is available and the only recourse is detailed simulation from the outset.

In the following sections system-level and detailed models of example design problems are presented. The models are built and simulations are conducted in the CAD-for-MEMS tool CoventorWare™ [2]. These simulations demonstrate: (1) the success and limitations of beginning with system-level modeling; and (2) the use of detailed modeling for investigation of physics, and verification of system-level results. (The automatic extraction of a reduced-order model from detailed simulation is too large a topic to cover here.)

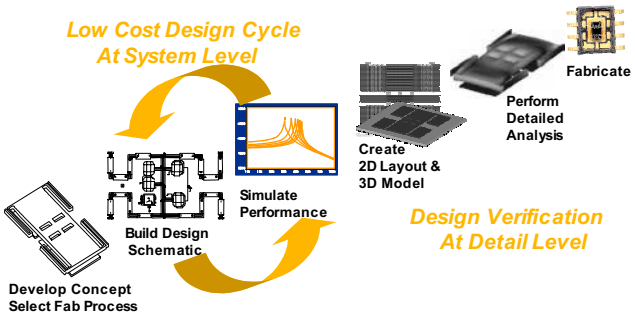


**Figure 1. Philosophy of the design procedure from concept to fabrication. The process moves from left to right, with modeling at the system level to explore the design space, automatic creation of layout and solid model, and modeling at the detailed level for validation, extraction, and further optimization.**

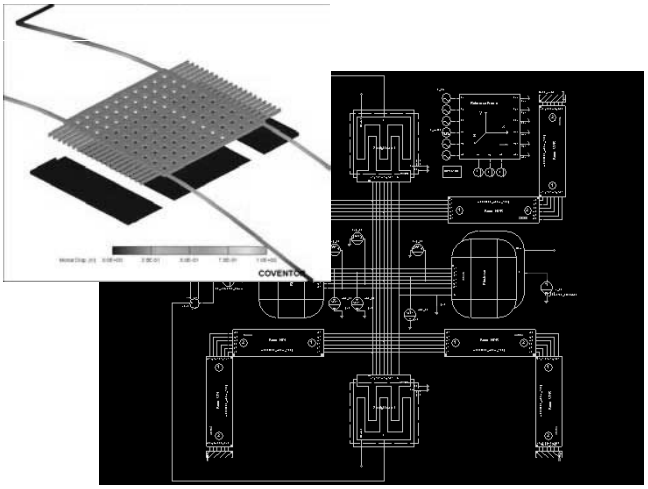

**Figure 2. Detailed and system-level simulation. At the upper left is the result of an FEM computation of the vertical mode shape (x100) for a tethered plate above electrodes. At the lower right is the schematic for the system-level simulation of the same device.**

## 3. EXAMPLE: ELECTROMECHANICS

BioMEMS may use electrostatic, piezoelectric, or magnetic actuation of mechanical parts for manipulating valves, pumping fluid, creating droplets, or manipulating optical components as will be shown below. These actuation mechanisms are ubiquitous in MEMS, so they should be well represented in system-level component libraries and detailed simulation modules should be present for their analysis.

For example, the system-level modeling tool CoventorWare ARCHITECT™ contains linear and nonlinear mechanical beams

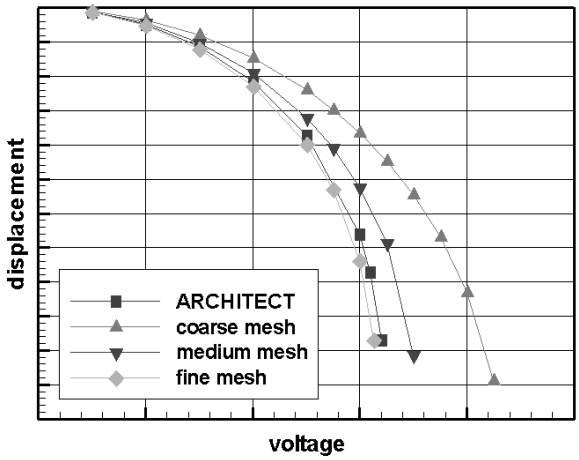


**Figure 3. Comparison of system-level and detailed level results for electromechanical displacement as a function of applied voltage bias. "ARCHITECT" denotes the system-level results; "mesh" denotes the FEM/BEM results.**

and plates with which to build structures, and electrostatic combs (rectilinear and circular) and plate electrodes with which to actuate the structures. These component models can include perforations and other geometric details popular in MEMS design.

Figure 2 shows results from CoventorWare MemMech™ for the vertical mode shape of a tethered plate and the schematic for ARCHITECT that can be used to compute this and other results using library component models at system level. Figure 3 shows how the detailed and system-level approaches compare. For these results, at both detailed and system levels, a sequence of voltage biases is applied between the tethered plate and its electrode. A series of meshes is used for the detailed modeling approach, CoventorWare CoSolve™, so that the ARCHITECT result can be evaluated in context of the convergence of the detailed result. CoSolve is a coupled electromechanical solver using the finite element method (FEM) for the mechanical analysis and the boundary element method (BEM) for the electrostatic analysis. This result is typical in that the ARCHITECT result is close to the result from FEM/BEM for a fine mesh, and the detailed result shows greater displacement for a given voltage due to the component models tending to be slightly stiffer than FEM predicts and tending to generate slightly lower electrostatic force than BEM predicts.

## 4. EXAMPLE: 2D SEPARATION

First-generation labs-on-a-chip use continuous flow (usually electrokinetically driven flow in channels) and commonly are fabricated in plastic and glass. These chips were first designed for DNA separation, and were useful for SNP scoring, pathogen detection, drug discovery and DNA fingerprinting [3]. The capabilities of first-generation chips have since been broadened by the addition of more separation techniques and on-chip chemistry; they can now be used for protein analysis, pathogen detection, immunoassays and point-of-care diagnostics. The fluidic processes required for these analyses are: pre-concentration, pumping, mixing, separation, and detection of results. A useful library of fluidic and optical components should be able to address most of the needs of the first-generation lab-on-a-chip designer.

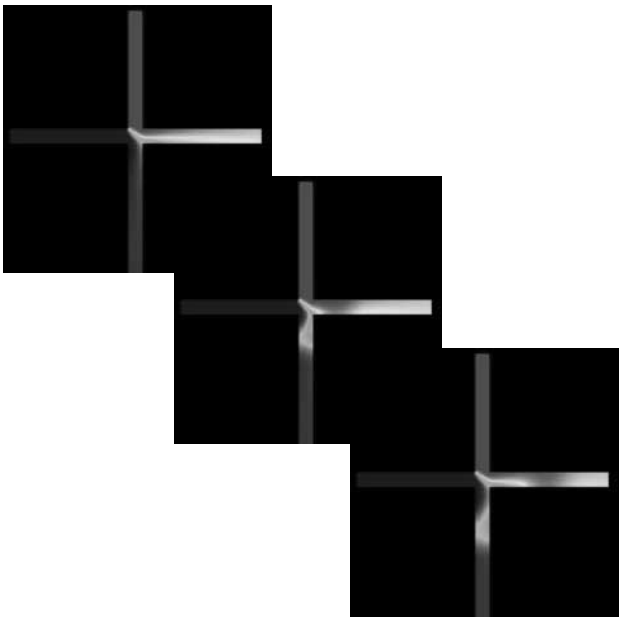

**Figure 4. Sample injection. Sample (red) and buffer (blue) mix only weakly by diffusion at the cross. Upon switching of the electric field, a controlled portion of sample is allowed to proceed for further analysis.**

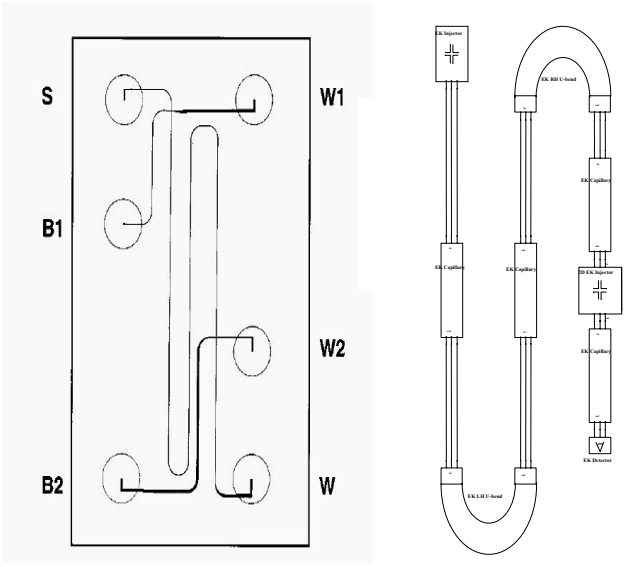


**Figure 5. A lab-on-a-chip for two-dimensional separation [6]. On the left is an image of the chip reservoirs and capillaries. On the right is the schematic for system modeling. The sample reservoir is "S", buffers are in "B1" and "B2", while "W" denotes waste.**

A simple lab-on-a-chip for performing two-dimensional separations provides an example for system-level modeling of microfluidics. The term *separation* denotes the processing of a mixture containing several analytes so that spatially separated accumulations of like analytes are formed with sufficient concentration for detection. Peak capacity is a convenient way to measure the efficiency of separation systems, and is defined as the theoretical maximum number of peaks that can be separated in a given separation time. Two-dimensional separation is an effective approach because when the second separation dimension

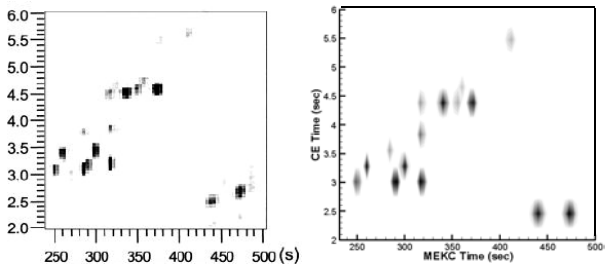


**Figure 6. Validation of the two-dimensional separation lab-on-a-chip system-level model. On the left are experimental results from a separation. On the right are the simulation results.**

is orthogonal to the first, the total peak capacity is the product of the peak capacities in each dimension. The miniaturization of separation can provide high efficiency and the convenience and low cost of working with small sample volumes [4]. A key technology for these labs-on-a-chip is the injection of controlled amounts of sample into the analysis stream. There is a wide variety of valve designs for this purpose. A popular approach is to control flow with electric fields rather than moving mechanical parts; examples of this technique include the classic pinched injection [4] and the double-T injector. Figure 4 is a detailed

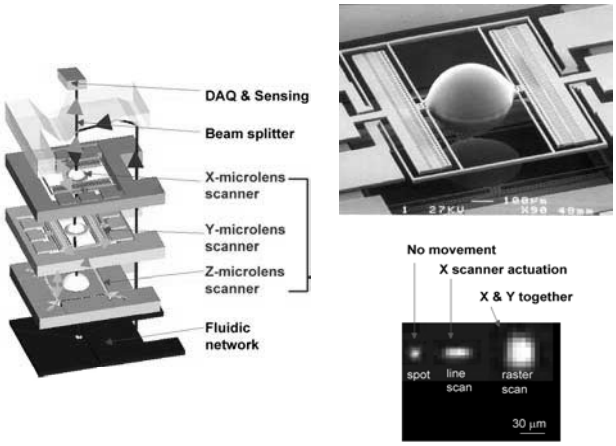


**Figure 7. Scanning confocal microscope for on-chip optics. At the left is a sketch of the design. At the upper right is a micrograph showing the polymer lens and its comb-driven carriage. At the lower right are achievable scanning patterns.**

simulation from CoventorWare SwitchSim™ of an electrokinetically driven valve that is designed to allow the injection of variable amounts of sample. A continuous stream of sample enters at the top of the cross and leaves at the right, while a continuous stream of buffer arrives from the left and leaves at the bottom. This electrokinetic flow is maintained by an electric field, and the irrotational properties of the flow maintain a sharp interface between sample and buffer (note the small amount of diffusion at the two-fluid interface). When desired, the field is switched and a controlled amount of sample proceeds towards the bottom and is available for analysis.

Figure 5 shows a lab-on-a-chip designed for two-dimensional separations, where the first separation dimension is provided by micellar electrokinetic chromatography (MEKC), and the second by capillary electrophoresis (CE) [6]. The system is designed to analyze complex protein and peptide mixtures; MEKC and CE separate based on different physical properties, so the techniques are orthogonal and are good candidates for a two-dimensional system. The valve technique described above is used to inject separated analyte peaks from the MEKC column into the CE column. The capillaries, including the bends, the valve, and the separation techniques can be modeled at system-level, and the

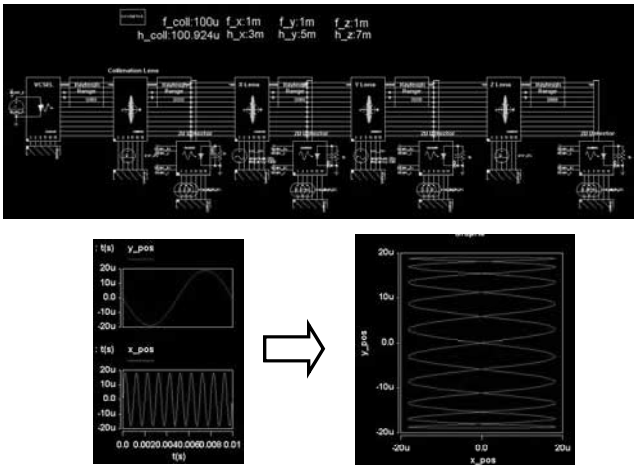


**Figure 8. System-level simulation results for the scanning confocal microscope of Figure 7. At the top is the ARCHITECT schematic. Below are the *x*- and *y*-direction scanning patterns that together give the desired raster pattern.**

schematic for the chip is also shown. Simulation with this schematic produced the separation results that are shown along side experimental results in Figure 6, where it can be seen that the agreement is quite good.

In keeping with the vision of micro-*total* analysis for these chips, the optical detection systems should be on chip along with the fluidic network and any controlling electronics. This goal has not been realized in most cases, but there has been progress in the integration of micro optics [7]. Figure 7 shows a sketch of a scanning confocal microscope designed for on-chip detection. Both the scanning motion (*x*-*y* plane) and the focusing motion (+/-*z*) are provided by electromechanical comb drives. This

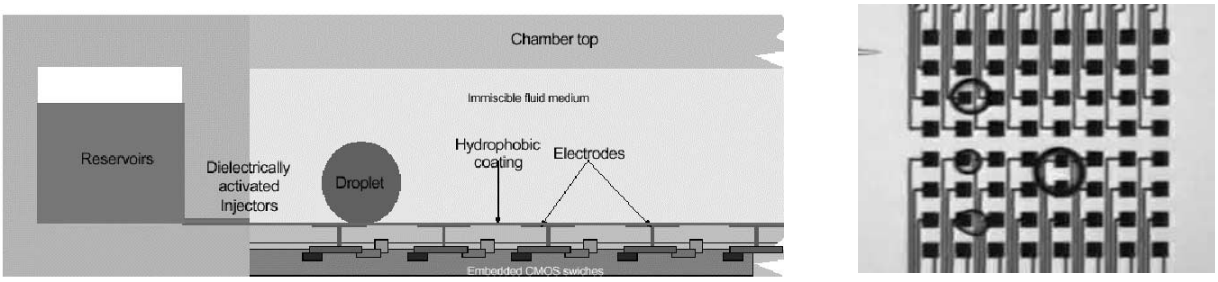


**Figure 9. The Programmable Fluid Processor (PFP) [8]. At the left is an elevation view of the device. At the right is an experimental image of the reaction chamber with multiple droplets sitting on the top of electrodes in the array. (Images are courtesy of Professor P. R. C. Gascoyne of M. D. Anderson Cancer Center.)**

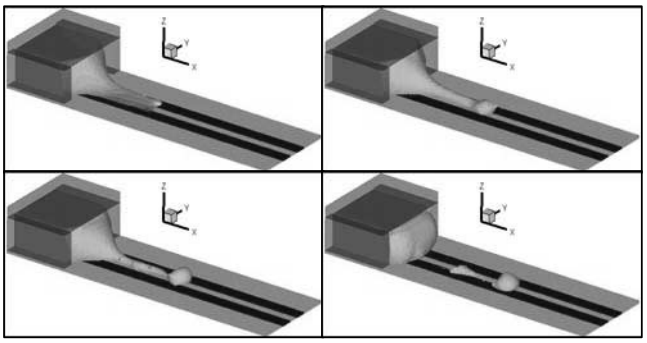

**Figure 10. Droplet generation on a DEP-driven lab-on-a-chip: formation of a single droplet (simulation). In addition to the conditions specified in figure 16, the voltage difference between the two electrodes is reset to zero at time t=50μsec. The images are in sequence corresponding to time starting at t=50μsec with a 20μsec interval. The simulation shows that a single droplet is released from the DEP finger. The satellite droplets (in image 4) originating from the formation of the tail (in image 3) can be minimized through further tuning of the operating parameters.**

electromechanical, multi-lens, optical system has been modeled at system level and the scanning behavior is shown in Figure 8. Careful tuning of the resonant behavior of the *x*-direction comb drive versus the *y*-direction comb drive produces the raster scanning. Since the system-level components are parameterized, this modeling provides guidance on the dimensions of the comb tethers to achieve the desired frequencies.

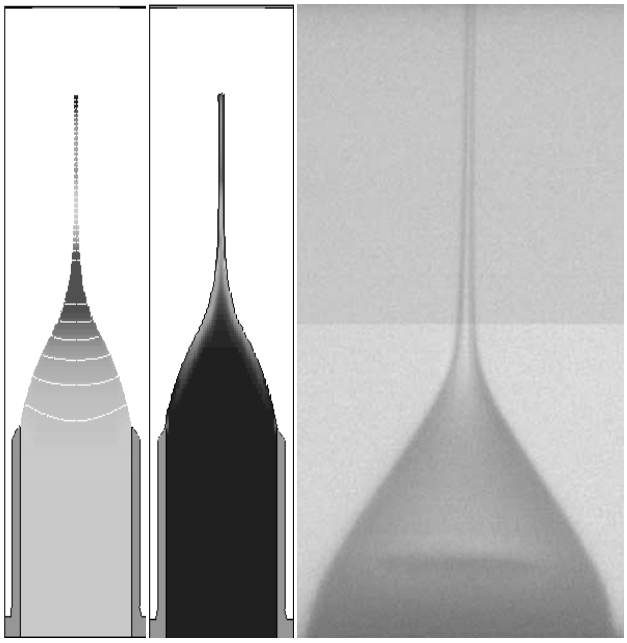

**Figure 11. CEW driven droplet generation: a fully developed Taylor cone. At the left are two images obtained from simulation. The color in the first image indicates the electric potential; the color in the second image indicates the interfacial density of free charge. At the right is a micrograph from experiment (courtesy of Dr D. Sobek of Agilent Technologies, Inc).**

## 5. EXAMPLE: DIGITAL MICROFLUIDICS

Second generation labs-on-a-chip use droplets as the operands rather than continuous flow. Consider the Programmable Fluid Processor (PFP) shown in Figure 9 [8]. This is a lab-on-a-chip under development at M. D. Anderson Cancer Center that will have applications in disease screening and military and civilian contaminant detection. In the PFP, samples and reagents are drawn from reservoirs as aqueous droplets and suspended in an insulating liquid. The droplets are moved by electrohydrodynamic (EHD) force [9], so that they mix and their contents react in the pre-programmed sequences of an analysis. The droplet manipulations required for such analyses are: generation, translocation, fusion, and fission. At present, invention or

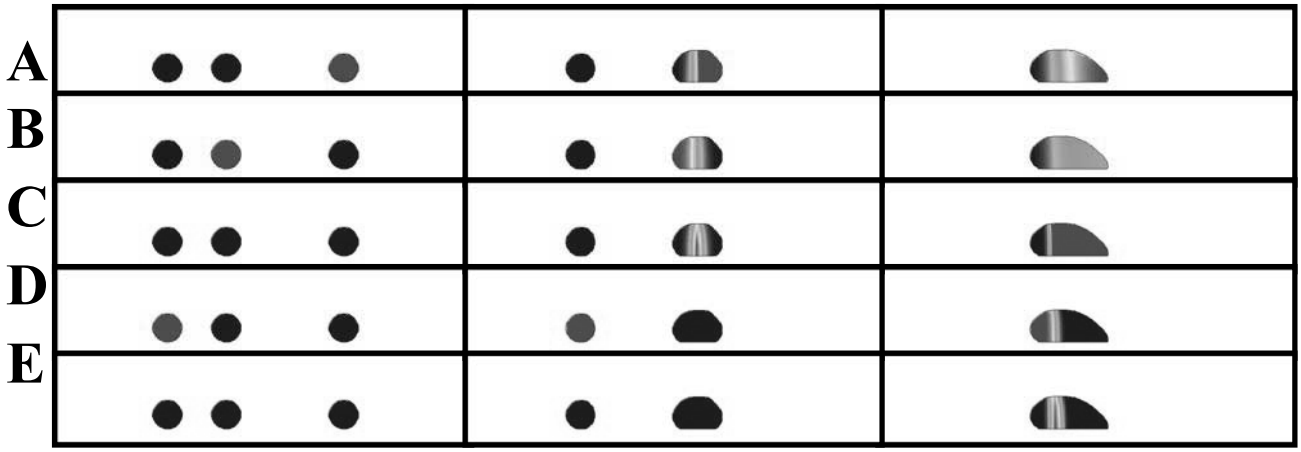


**Figure 12. Simulation of a two-stage chemical reaction on a droplet-based DEP-driven lab-on-a-chip. The columns show the chemical concentration, due to diffusion and reaction, for chemicals A-E at three successive times from left to right. Initially, there are 3 droplets containing chemicals D, B, and A from left to right in the top row of the leftmost column. The 2 droplets on the right are merged so that chemicals A and B react to produce chemical C. The merged droplet, on the right in the second column is then merged with the third original droplet, which contains chemical D. The subsequent reaction produces chemical E. Each row in the figure tracks the concentration of the chemical indicated by letter to the left, with red indicating maximal concentration.**

extraction of reduced-order models of these processes is a topic of research, and consequently detailed simulations must be carried out to support the design of this type of lab-on-a-chip. The simulations in this section were performed using CoventorWare DropSim™.

Figure 10 shows a simulation of droplet generation using the EHD forcing known as *dielectrophoresis* (DEP) [10]. DEP is the force of electric origin that arises from the presence of dipole moments in the medium. In this simulation, the design and the operating procedure is such that a droplet is formed successfully. The performance of such injectors is sensitive to the geometry of the electrodes and the timing of the field excitation, so detailed simulation provides critical insight to designers.

Another complicated droplet phenomenon not yet covered by reduced-order modeling is electro-spray ionization (ESI) [11]. In this case the EHD forcing generating droplets is called *continuous electrowetting* (CEW) [9]. ESI is the process of turning the liquid solution output of a lab-on-a-chip into gas-phase ions representative of the analytes. These gas-phase ions are suitable for input to mass spectrometry. Other droplet generation techniques, such as the DEP-driven process described above cannot possibly produce droplets small enough to achieve gas phase. In Figure 11, simulation results show that CEW-drawn fluid from a nozzle creates a jet, a *Taylor cone*, which is an order of magnitude smaller in diameter than the nozzle itself. Rayleigh instability breaks this jet into droplets that explode due to Coulombic forcing, creating the gas-phase ions. Figure 11 also shows the excellent qualitative agreement between the simulation and experiment for the formation of the Taylor cone.

The point of all of this droplet manipulation is so that assays may be carried out, of course. So droplet-based chemical reactions may be simulated as well, using concentration-based chemical reaction models. In Figure 12 the results of a simulation of a two-stage chemical reaction are presented. The reaction simulation is carried out in conjunction with the dielectrophoretic translocation of the droplets carrying the chemicals.

## 6. CONCLUSIONS

The design of complex BioMEMS, like the design of MEMS in general, can benefit greatly from the guidance provided by simulation tools. While system-level simulation is preferred due to its low cost, detailed simulation is almost always needed, at least to confirm conclusions drawn from work at the system level.

A useful design tool for BioMEMS should have a broad array of simulation capabilities at both system and detailed level so that all of the important aspects of physics and component interactions can be characterized. Moreover, a useful tool should have a friendly, graphical, front end in which to create designs, preferably one that is tied to the available processes for fabrication, and also a friendly, graphical, back end in which to display and explore results so that their full meaning can be appreciated.

## 7. ACKNOWLEDGMENTS

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