Microfluidic electromanipulation with capacitive detection for the mechanical analysis of cells

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The mechanical behavior of cells offers insight into many aspects of their properties. We propose an approach to the mechanical analysis of cells that uses a combination of electromanipulation for stimulus and capacitance for sensing. To demonstrate this approach, polystyrene spheres and yeast cells flowing in a $25\ \mu\text{m} \times 100\ \mu\text{m}$ microfluidic channel were detected by a perpendicular pair of gold thin film electrodes in the channel, spaced $25\ \mu\text{m}$ apart. The presence of cells was detected by capacitance changes between the gold electrodes. The capacitance sensor was a resonant coaxial radio frequency cavity (2.3 GHz) coupled to the electrodes. The presence of yeast cells (*Saccharomyces cerevisiae*) and polystyrene spheres resulted in capacitance changes of approximately 10 and 100 attoFarad (aF), respectively, with an achieved capacitance resolution of less than 2 aF in a 30 Hz bandwidth. The resolution is better than previously reported in the literature, and the capacitance changes are in agreement with values estimated by finite element simulations. Yeast cells were trapped using dielectrophoretic forces by applying a 3 V signal at 1 MHz between the electrodes. After trapping, the cells were displaced using amplitude and frequency modulated voltages to produce modulated dielectrophoretic forces. Repetitive displacement and relaxation of these cells was observed using both capacitance and video microscopy. © 2008 American Institute of Physics. [DOI: 10.1063/1.2992127]

I. INTRODUCTION

New directions of microfluidics research have resulted from the realization that mechanical responses of cells offer insight into many aspects of their behavior.¹ For the analysis of single cells, optical stretchers, micropipette aspiration, magnetic tweezers, and microcantilevers are some of the approaches that have been explored.^{2–5} Other groups have been successful in implementing high sensitivity electrical techniques for cell counting.^{6–8} The present work describes an electrical approach to the mechanical analysis of cells that uses a combination of electromanipulation for stimulus and capacitance for sensing.

Electrical manipulation is possible because the dielectric properties of cells and their surrounding fluid are different.⁹ For many biomedical applications, this dielectric difference in combination with nonuniform electric fields can be used to translate cells (dielectrophoresis), or with uniform time-varying fields to rotate cells (electrorotation).¹⁰ Recently, dielectrophoretic forces have been enhanced with improved control using multi-insulating blocks for manipulating polystyrene microspheres.¹¹ Parikesit and co-workers¹² recently used insulating structures to enhance dielectrophoretic signals for size-dependent sorting of continuously flowing DNA molecules. In

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addition, electric fields can alter the shape of cells through electrostatic pressure.¹³ In our system, changes in both cell position and shape will result in changes in the capacitance between the electrodes that deliver the field.

One of the problems associated with using electric fields for probing biological structures involves the often inherent use of strong electric fields. Biological cells have very thin insulating membranes (~ 6 nm) that surround their cytoplasm, nucleus, and other subcellular components. Therefore, for transmembrane potentials exceeding 1–2 V, these cells are subject to electroporation, in which strong electric fields (exceeding 10^9 – 10^{10} V/m) create nanometer-sized pores in the membranes, which can cause cell lysing (death).¹⁴ However, if the corresponding frequency is high enough (faster than the inverse relaxation time of the cell membrane), the membrane will not have time to charge up to the electroporation potential and the electric field will pass through the membrane to affect the internal cellular structure. For example, the recent usage of short electrical pulses for killing cancer cells in mice has become a subject of great interest.¹⁵

An all-electrical approach offers the possibility of both rapid analysis and very high degrees of integration. Romani and co-workers¹⁶ successfully designed circuits based on complementary metal-oxide semiconductor (CMOS) technology for manipulating and capacitively detecting cells in separate stages, albeit with limited capacitance resolution ($\Delta C_{\min} = 30$ aF). The interfacial capacitance associated with electrical double layers at electrode surfaces often masks the bulk capacitance of solutions at low frequencies. To help overcome this, one group has successfully measured bacterial growth through changes in the bulk capacitance at low frequencies (below 1 MHz) by confining samples within long narrow geometries, which enhance the bulk resistance and hence the sensitivity to bulk capacitance.¹⁷ Furthermore, capacitance-based sensing systems integrated into gyroscopes have achieved 12 zeptoFarad (zF) resolution.¹⁸ If sensors of this sensitivity were combined with microfluidic systems for transporting cells, highly integrated diagnostic systems would be possible.

In this work, high frequencies are used for capacitance detection. We use high frequencies (GHz) for capacitance measurements to avoid interference and variability due to effects such as electrical double layers,^{6,17,19} ionic conduction, and other forms of dielectric variation in materials with frequency, which are dominant at frequencies below 200 MHz.²⁰ The use of high frequencies also opens the door for lower frequencies (MHz) to be used for other purposes such as simultaneous electromanipulation of biological materials.

II. MATERIALS AND METHODS

The experimental apparatus for capacitance measurements is shown in Fig. 1. An automated syringe pump (New Era Pump Systems Inc., NE-1000) delivers fluid and cells through a tube into the inlet connector of the microfluidic channel. Gold electrodes were fabricated across the channel at 90° relative to the channel flow direction. To exploit the use of high frequencies in obtaining capacitance variations due to the presence of cells in the channel, a high- Q quarter wavelength cylindrical cavity resonator made of copper was constructed and brought into contact with the gold electrodes. The resonance frequency of the resonator is approximately 2.3 GHz.

To connect the cavity with the gold electrodes, we extend two short wires from the cavity. The first extends from the tip of the center conductor of the cavity and the second extends from the ground plane. These wires effectively lengthen the cavity by an amount dependent on the new capacitance between the wire and the ground plane. Next, these wires are placed on the gold electrodes by moving the cavity with an x - y - z translator. Care is taken to ensure that both wires are securely placed on the gold electrodes. Since the gold electrodes have a much smaller distance between them than the wires, the capacitance of the cavity-channel combination increases further. Consequently, the cavity has an even longer effective length and therefore a reduced resonance frequency. The signal now travels outside the cavity and will experience significant losses in the channel and glass. As a result, the quality factor decreases, $Q = f_r / \Delta f$,²¹ where Δf is the width of the resonance line shape.

When the resonator contacts the gold electrodes, subsequent variations in the channel capacitance, for example, due to the presence of cells, will vary the effective electrical length of the

FIG. 1. Experimental apparatus. Fluid and cells are delivered through PEEK tubing (a) into inlet connector (b) to the microfluidic channel (c).

cavity resonator and hence its resonance frequency f_r . The transmission spectra of the resonator-channel combination when the channel is filled with air and water are shown in Fig. 2, and can be used to calibrate the sensitivity of the sensor. The capacitance change associated with water replacing air in the channel is calculated to be approximately 45 femtoFarad (fF). Using this value and the measured 65 MHz shift in resonant frequency, the sensitivity of this resonator is estimated to be 1.44 MHz/fF, which is comparable to resonators of similar resonance frequency.²¹

A schematic of the manipulation and detection system is shown in Fig. 3. We measure changes in the resonance frequency of the sensor by square wave modulating the drive frequency of the rf source near the resonant frequency. To optimize the sensitivity to capacitance changes, the modulation depth frequency f_{mod} is chosen to be the frequency separation between the resonance frequency and the frequency where the steepest gain-frequency slope in the transmission spectrum occurs. For a Lorentzian spectrum, this value occurs when the signal is 82% of the maximum signal.

To make up for the signal lost primarily in the glass, the signal is amplified by 27 dB using a low-noise amplifier. After amplification, the output signal is delivered to a lock-in amplifier, which extracts the signal produced as the source switches between $f_{r1} - f_{\text{mod}}$ and $f_{r1} + f_{\text{mod}}$ at the LF frequency, f_{ref} . Assuming a symmetric transmission spectrum (see Fig. 4), the signals at $f_{r1} - f_{\text{mod}}$ and $f_{r1} + f_{\text{mod}}$ are identical when the transmission spectrum centers at the resonance frequency of the channel-resonator combination, f_{r1} . When the resonance frequency shifts to a new resonance frequency, f_{r2} , due to the passing of cells between the channel electrodes, the signals at $f_{r1} - f_{\text{mod}}$ and $f_{r1} + f_{\text{mod}}$ become different. Since the lock-in amplifier output represents the signal difference between $f_{r1} + f_{\text{mod}}$ and $f_{r1} - f_{\text{mod}}$, the output will therefore deviate from zero when the cells pass through the channel.

The signal difference, $V_2 - V_1$, will either become positive or negative depending on whether

FIG. 2. Transmission spectra of the resonator-channel combination for air-filled and water-filled channels are shifted by 65 MHz. This corresponds to a 45 fF capacitance change.

the resonance frequency increases or decreases. Because the channel capacitance varies inversely to changes in resonance frequency, this means that $V_2 - V_1$ becomes positive or negative depending on whether the capacitance decreases or increases. A proportionality factor between voltage and capacitance can be estimated by changing the average frequency of the source by 100 kHz, then measuring the change in the output voltage of the lock-in amplifier, and using the sensitivity measured above to find the proportionality factor relating voltage to capacitance. In general, this conversion factor is sensitive to numerous factors, including the sensitivity of the lock-in amplifier. Conversion factors of 50 aF/V and 522 aF/V were used to calculate the capacitance changes from the voltage signals generated from yeast and polystyrene spheres, respectively.

To simultaneously deliver MHz range or below signals in order to manipulate cells using dielectrophoresis and GHz signals for capacitance detection, a resistance/capacitance (RC) circuit was built onto the resonant cavity. The circuit is designed to act like an open circuit to the GHz signals but allow the low-frequency signals to pass through to the rf ground electrode. Building on previous work,²¹ we achieved 2 aF sensitivity, at 30 Hz bandwidth, in the water-filled microfluidic channels.

III. MICROFLUIDIC CHANNEL FABRICATION

The microfluidic chips with integrated electrodes are fabricated in three steps: lithography and etching of the fluid channels in the top glass plate; lithography and etching of the gold electrodes on the bottom glass plate; and alignment, contact, and bonding (annealing) of the two plates in order to form the completed structure. The glass substrates are first cleaned by Piranha (3:1 ratio of sulfuric acid and hydrogen peroxide) then coated with chromium and gold by sputtering. For the microchannels, the chromium (30 nm) and gold (150 nm) layers form the physical mask for

FIG. 3. Schematic of the manipulation and detection system. A frequency modulated rf signal is delivered to the cavity resonator. The output signal is amplified and sent to the lock-in amplifier. Dielectrophoretic manipulation is achieved using a low-frequency generator, which delivers frequencies below 3 MHz to the fluid channel using a RC isolation circuit.

FIG. 4. When the resonance frequency increases from the voltage difference, $V_2 - V_1$, increases from zero. Through calibration, this voltage difference represents the corresponding capacitance shift.

FIG. 5. Capacitance variations in the channel due to 10 μm diameter polystyrene spheres.

glass etching, and are patterned by photolithography and wet etching to define the channels. After covering the back of the substrate with plastic film, the microchannels are isotropically etched in a hydrofluoric acid solution. The resulting channels have an approximately trapezoidal cross section. For the channels used in the present work, the depth is 25 μm and the average width is approximately 140 μm (160 μm at the top and 120 μm at the bottom). Subsequent to the glass etching, inlet and outlet vias are drilled. The channel substrate is diced and the etch mask completely stripped by acetone and wet etch. The electrode substrate is prepared with a thinner sputtered metallization (15 nm chromium and 75 nm gold), empirically determined not to interfere with the sealing of the microchannels. Photolithography and wet etching is again used to pattern the electrode structures and alignment marks. For the present work, the electrode widths and separation each were 25 μm .

Prior to alignment and bonding, the channel and electrode plates must be thoroughly cleaned. The basic steps are Piranha, followed by soap and water, treatment in a high-pressure washer, and drying with nitrogen. Aggressive cleaning is possible for the channel substrate, whereas the electrode substrate must be treated somewhat more gingerly in order to keep these structures intact. In the latter case, the Piranha is cold, extra care is taken while washing with soap and water, and the length of time in the pressure washer is reduced. The clean plates are aligned and brought into contact using a homemade alignment jig (University of Alberta NanoFab). The adherent interfaces are then fused by annealing to 550 $^{\circ}\text{C}$. For the chromium/gold metallization, it is necessary to perform the anneal in an environment without oxygen (a vacuum furnace is used here), otherwise chromium oxidation (perhaps on account of oxygen diffusion through pores in the sputtered gold, as well as on account of chromium interdiffusion through gold) reduces the adhesion of the electrodes to the substrate.

FIG. 6. Capacitance variations in the channel due to 6 μm diameter yeast cells.

IV. CAPACITANCE DETECTION OF FLOWING POLYSTYRENE SPHERES AND YEAST CELLS

Experimental results from polystyrene spheres and yeast cells are provided in Figs. 5 and 6, respectively. In both cases, we observe a decrease in capacitance because the permittivities of both polystyrene and yeast are less than that of water ($80\epsilon_0$). The larger capacitance change from polystyrene spheres (~ 100 aF) compared with yeast cells (~ 8 aF) occurs because the polystyrene spheres are larger and have a higher dielectric contrast compared with water. Capacitance differences within each figure arise because different particles pass at different heights above the electrode plane and due to particle size variations.

V. SIMULATIONS

Finite element analysis simulations were performed using the COMSOL® electromagnetics module where the complex Laplace equation, $\nabla \cdot (\bar{\epsilon} \nabla V) = 0$, was used to solve for the electric fields in the channel. Polystyrene spheres were modeled as uniform spheres and yeast cells were modeled as double-shelled spheres. To determine the effective permittivity for the double-shell structure, Eqs. (1) and (2) are applied in sequence: once for the cytoplasm/membrane combination and again to incorporate the cell wall,

TABLE I. Relative permittivity and conductivity data.^a

Material	$\epsilon_{\text{cytoplasm}}$	$\epsilon_{\text{membrane}}$	ϵ_{water}	$\sigma_{\text{cytoplasm}}$ (S/m)	σ_{membrane} (S/m)	σ_{wall} (mS/m)
Yeast	60	5	80	0.2	10^{-7}	14
Polystyrene	2.5	N/A	80	2×10^{-4}	N/A	N/A

^aN/A=Not applicable.

$$\bar{\epsilon}_{\text{eff1}} = \bar{\epsilon}_{\text{memb}} \left\{ \frac{a^3 + 2 \left(\frac{\bar{\epsilon}_{\text{cyt}} - \bar{\epsilon}_{\text{memb}}}{\bar{\epsilon}_{\text{cyt}} + 2\bar{\epsilon}_{\text{memb}}} \right)}{a^3 - \left(\frac{\bar{\epsilon}_{\text{cyt}} - \bar{\epsilon}_{\text{memb}}}{\bar{\epsilon}_{\text{cyt}} + 2\bar{\epsilon}_{\text{memb}}} \right)} \right\}, \quad a = \frac{R_{\text{cyt}} + d_{\text{memb}}}{R_{\text{cyt}}}, \quad (1)$$

$$\bar{\epsilon}_{\text{eff2}} = \bar{\epsilon}_{\text{wall}} \left\{ \frac{b^3 + 2 \left(\frac{\bar{\epsilon}_{\text{eff1}} - \bar{\epsilon}_{\text{wall}}}{\bar{\epsilon}_{\text{eff1}} + 2\bar{\epsilon}_{\text{wall}}} \right)}{b^3 - \left(\frac{\bar{\epsilon}_{\text{eff1}} - \bar{\epsilon}_{\text{wall}}}{\bar{\epsilon}_{\text{eff1}} + 2\bar{\epsilon}_{\text{wall}}} \right)} \right\}, \quad b = \frac{R_{\text{cell}}}{R_{\text{cell}} - d_{\text{wall}}}, \quad (2)$$

where $\bar{\epsilon}_{\text{cyt}}$, $\bar{\epsilon}_{\text{memb}}$, and $\bar{\epsilon}_{\text{wall}}$ are the complex cytoplasm, membrane, and wall permittivities, R is the radius, and d is thickness.²² The values of these parameters for polystyrene and yeast^{23–26} are given in Tables I and II.

Figures 7 and 8 show the capacitance change as a function of particle position for yeast cells and polystyrene spheres. Both the channel depth and the electrode spacing are 25 μm . The membrane permittivity was calculated using the parallel plate approximation, $C = \epsilon A / d$, often used in the literature. For a typical membrane thickness of 5 nm and a membrane capacitance per unit area of 0.01 F/m²,²⁷ the relative permittivity is about 5.0.

The simulation results agree reasonably well with the experimental results, suggesting that the particles more or less remain on the same plane as that of maximum velocity. In laminar flow, which occurs almost exclusively in microfluidic systems, the velocity profile is parabolic, having a maximum in the center of the channel and zero at the channel edges. For the polystyrene case, the predicted capacitance change is approximately twice that of the experimental capacitance change. This is likely due to a larger dielectrophoresis force, which arises from the sphere having a larger volume. At high frequencies (2 GHz), this force will be repulsive, making the sphere flow through the channel at a lower vertical position, which would cause a smaller capacitance change. As expected, the simulation also predicts that the capacitance change has a relatively strong dependence on the vertical position of the cell relative to the electrodes.

VI. DIELECTROPHORESIS

The coplanar electrode configuration generates electric fields that bend into the microfluidic channel. The resulting nonuniform electric field distribution within the channel makes cell trans-

TABLE II. Radius (cell) or thickness.^a

Material	Cell (μm)	Membrane (nm)	Wall (μm)
Yeast	3	5	0.2
Polystyrene	5	N/A	N/A

^aN/A=Not applicable.

FIG. 7. Calculated capacitance change of 6 μm yeast cells as a function of position. The electrode width and channel height are 25 μm each.

lation possible using dielectrophoresis (DEP), which uses nonuniform electric fields to polarize cells and move them along the electric field (squared) gradient. The dielectrophoretic force experienced by a spherical particle is given by^{28,22}

$$F_{\text{DEP}} = 2\pi R^3 \epsilon_0 \epsilon_m \text{Re}[f(\omega)] |\nabla |E_{\text{RMS}}|^2|, \quad (3)$$

where R and ϵ_m are the particle radius and the relative fluid permittivity, E_{RMS} is the root-mean-squared electric field, and $\text{Re}[\ ]$ denotes the real part of the Clausius-Mossotti factor, $f(\omega)$, which is given by

$$f(\omega) = \frac{\bar{\epsilon}_p - \bar{\epsilon}_m}{\bar{\epsilon}_p + 2\bar{\epsilon}_m}, \quad (4)$$

$$\text{Re}[f(\omega)] = \frac{(\epsilon_p' - \epsilon_m')(\epsilon_p' + 2\epsilon_m') + (\epsilon_p'' - \epsilon_m'')(\epsilon_p'' + 2\epsilon_m'')}{(\epsilon_p' + 2\epsilon_m')^2 + (\epsilon_p'' + 2\epsilon_m'')^2}, \quad (5)$$

where $\bar{\epsilon}_p$ and $\bar{\epsilon}_m$ are the complex permittivities of the particle and external medium, each having the general form $\bar{\epsilon} = \epsilon' - j\epsilon'' = \epsilon' - j\sigma/\omega$. The field gradient term is given by the expression

$$|\nabla |E_{\text{RMS}}|^2| = \nabla (E_x^2 + E_y^2 + E_z^2) = 2 \left\{ \begin{aligned} &(E_x E_{x,x} + E_y E_{y,x} + E_z E_{z,x})\hat{x} + (E_x E_{x,y} + E_y E_{y,y} + E_z E_{z,y})\hat{y} \\ &+ (E_x E_{x,z} + E_y E_{y,z} + E_z E_{z,z})\hat{z} \end{aligned} \right\}, \quad (6)$$

FIG. 8. Calculated capacitance change of 10 μm polystyrene spheres as a function of position. The electrode width and channel height are 25 μm each.

FIG. 9. Channel geometry used for calculating the dielectrophoretic force exerted on a $6\ \mu\text{m}$ cell placed directly beneath one electrode. The electrode width and channel height are $25\ \mu\text{m}$ each. The channel width is $120\ \mu\text{m}$.

FIG. 10. Magnitude of ∇E_{RMS}^2 from the bottom ($-3\ \mu\text{m}$) to the top ($3\ \mu\text{m}$) of the cell. The horizontal axis refers to the vertical position relative to the center of the cell. The ∇E_{RMS}^2 value at the cell center of $1.2 \times 10^{14}\ \text{V}^2/\text{m}^3$ gives an estimated dielectrophoretic force of $10.4\ \text{pN}$ at $1\ \text{MHz}$.

FIG. 11. Capacitive detection of the dielectrophoretic trapping and release of yeast cells. The trapping signal (3 V @ 1 MHz) was turned on and off every 5 s. Three yeast cells were trapped in sequence from 6–11 s, when the trapping signal was on. Smaller signal dips that occur when the trapping signal is off arise from the flow of yeast cells by the electrodes. These events were also observed using optical microscopy.

where $E_{i,j}$ represents the derivative of the i th component of the RMS electric field with respect to j . Again, all field components were determined from solving the Laplace equation. For MHz frequencies, the DEP force is attractive and will pull cells toward the electrodes.

The applied voltage chosen should be sufficiently high to provide DEP forces that are strong enough to overcome the fluid flow and viscous drag forces in the channel. The viscous drag force is given by $F_{\text{drag}} = 6\pi\eta Rv$, where R and v are the particle radius and velocity, and η is the fluid viscosity. For a fluid viscosity of 0.001 Ns/m^2 , a $3 \mu\text{m}$ radius, and a $250 \mu\text{m/s}$ velocity, the drag force is approximately 14.1 pN. Finite element simulations done using the schematic shown in Fig. 9 reveal that the magnitude of the gradient of the RMS electric field squared (∇E_{RMS}^2) is about $1.2 \times 10^{14} \text{ V}^2/\text{m}^3$ at a 3 V input potential. This corresponds to the average ∇E_{RMS}^2 value calculated throughout the cross section of a cell located vertically in the middle of the channel directly beneath one of the electrodes (Fig. 10). At 1 MHz, Eq. (3) gives a dielectrophoretic force of 10.4 pN, which is comparable to the drag force. For particles to move in fluid environments, Pethig and Markx¹⁹ noted that the DEP force should be at least ten times larger than that due to Brownian motion and gravitational settling forces (which are typically a few fN).

By applying a 3 V, 1 MHz frequency signal, we observe the sequential trapping of yeast cells from the fluid flow onto the electrodes. When the trapping potential is removed, the cells are released back into the fluid flow. Smaller capacitance changes are observed as cells flow past the electrodes with the trapping signal off. Figure 11 illustrates this effect as a first demonstration of simultaneous electromanipulation and capacitive detection of individual cells in microfluidic channels.

Each voltage dip represents an event, whether it is a cell passing by the electrode pair or the trapping of an individual cell. As yeast cells flow through the channel, a 1 MHz trapping signal

FIG. 12. Response of trapped cells to repetitive amplitude manipulation at low frequency (1 Hz).

was turned on and off every 5 s. Giving particular attention to the 6–11 s time frame in Fig. 11, when the trapping signal was on, we observed the sequential trapping of three individual yeast cells. When the trapping signal was turned off at 11 s, the three trapped cells were released. These events were observed both via capacitance and optical detection. During those time frames when the trapping signal was off, the smaller voltage dips corresponded only to the flow of individual yeast cells by the electrode pair.

With a number of 5–10 cells trapped on the electrode, we demonstrate that the cells can be repetitively manipulated by the application of low-frequency (1 Hz) potentials, and that the effects of these manipulations can be observed via capacitance. The response time of these manipulations was recorded and found to be less than 100 ms (Fig. 12). The signal also varies gradually during the on and off times. When the cells are temporarily released, the lift force caused by the laminar parabolic velocity profile in fluid flow will move the particle from regions of low velocity to regions of high velocity (i.e., the center of the channel). Therefore, as the particle moves away from the electrodes, the capacitance slowly decreases.

VII. SUMMARY AND CONCLUSIONS

We have developed a system which uses a combination of electromanipulation for stimulus and capacitance for sensing. The capacitance changes of 8 aF and 100 aF caused by the presence of 6 μm yeast cells and 10 μm polystyrene spheres, respectively, agree reasonably well with simulated values. We have demonstrated that electromanipulation of cells with simultaneous capacitive detection can be achieved in microfluidic channels. Dielectrophoresis calculations show that pN forces are possible in our channel for reasonably chosen voltages. Using fiber-optic dual-beam trapping, Wei *et al.*²⁹ determined the force constants of Chinese hamster ovary cells to be on the order of pN/ μm . Wanichapichart *et al.*³⁰ determined the elastic constant of *Dendrobium* protoplasts by elongating them in ac fields. The elastic constant of their membrane varied nonlinearly with field strength ranging from 40 to 80 pN/ μm .³⁰ Those studies suggest that deformation experiments on these model systems should be feasible with the new system.

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- ¹ S. Suresh, J. Spatz, J. P. Mills, A. Micoulet, M. Dao, C. T. Lim, M. Beil, and T. Seufferlein, *Acta Biomater.* **1**, 15 (2005).
- ² K. J. Van Vliet, G. Bao, and S. Suresh, *Acta Mater.* **51**, 5881 (2003).
- ³ S. Hénon, G. Lenormand, A. Richert, and F. Gallet, *Biophys. J.* **76**, 1145 (1999).
- ⁴ J. Guck, R. Ananthakrishnan, H. Mahmood, T. J. Moon, C. C. Cunningham, and J. Käs, *Biophys. J.* **81**, 767 (2001).
- ⁵ B. Lincoln, H. M. Erickson, S. Schinkinger, F. Wottawah, D. Mitchell, S. Ulvick, C. Bilby, and J. Guck, *Cytometry, Part A* **59A**, 203 (2004).
- ⁶ L. L. Sohn, O. A. Saleh, G. R. Facer, A. J. Beavis, R. S. Allan, and D. A. Notterman, *Proc. Natl. Acad. Sci. U.S.A.* **97**, 10687 (2000).
- ⁷ S. Gawad, L. Schild, and Ph. Renaud, *Lab Chip* **1**, 76 (2001).
- ⁸ D. K. Wood, S.-H. Oh, S.-H. Lee, H. T. Soh, and A. N. Cleland, *Appl. Phys. Lett.* **87**, 184106 (2005).
- ⁹ U. Zimmermann, U. Friedrich, H. Mussauer, P. Gessner, K. Hamel, and V. Sukhorukov, *IEEE Trans. Plasma Sci.* **28**, 72 (2000).
- ¹⁰ X.-B. Wang, Y. Huang, R. Holzel, J. P. H. Burt, and R. Pethig, *J. Phys. D* **26**, 312 (1993).
- ¹¹ N. Lewpiriyawong, C. Yang, and Y.-C. Lam, *Biomicrofluidics* **2**, 034105 (2008).
- ¹² G. O. F. Parikesit, A. P. Markestijn, O. M. Piciu, A. Bossche, J. Westerweel, I. T. Young, and Y. Garini, *Biomicrofluidics* **2**, 024103 (2008).
- ¹³ T. L. Mahaworasilpa, Ph.D. dissertation, The University of New South Wales, Australia, 1992.
- ¹⁴ S. B. Dev, D. P. Rabussay, G. Wiedera, and G. A. Hofmann, *IEEE Trans. Plasma Sci.* **28**, 206 (2000).
- ¹⁵ K. H. Schoenbach, R. Nuccitelli, and S. J. Beebe, *IEEE Spectrum* **43**, 20 (2006).
- ¹⁶ A. Romani, R. Guerrieri, M. Tartagni, N. Manaresi, and G. Medoro, in *Proceedings of the IEEE International Symposium on Circuits and Systems*, Kobe, Japan, 2005 (IEEE, Piscataway, NJ, 2005), Vol. 3, p. 2911.
- ¹⁷ S. Sengupta, D. A. Battigelli, and H.-C. Chang, *Lab Chip* **6**, 682 (2006).
- ¹⁸ J. A. Geen, S. J. Sherman, J. F. Chang, and S. R. Lewis, *IEEE J. Solid-State Circuits* **37**, 1860 (2002).
- ¹⁹ R. Pethig and G. H. Markx, *Trends Biotechnol.* **15**, 426 (1997).
- ²⁰ P. R. C. Gascoyne and J. V. Vykoukal, *Proc. IEEE* **92**, 22 (2004).
- ²¹ T. Tran, D. R. Oliver, D. J. Thomson, and G. E. Bridges, *Rev. Sci. Instrum.* **72**, 2618 (2001).
- ²² T. B. Jones, *Electromechanics of Particles* (Cambridge University Press, New York, 1995).
- ²³ K. Asami, T. Hanai, and N. Koizumi, *J. Membr. Biol.* **28**, 169 (1976).
- ²⁴ Y. Huang, R. Hölzel, R. Pethig, and X.-B. Wang, *Phys. Med. Biol.* **37**, 1499 (1992).
- ²⁵ K. Asami and T. Yonezawa, *Biophys. J.* **71**, 2192 (1996).
- ²⁶ J. Voldman, R. A. Braff, M. Toner, M. L. Gray, and M. A. Schmidt, *Biophys. J.* **80**, 531 (2001).
- ²⁷ J. Gimsa, T. Müller, T. Schnelle, and G. Fuhr, *Biophys. J.* **71**, 495 (1996).
- ²⁸ H. A. Pohl, *Dielectrophoresis* (Cambridge University Press, London, 1978).
- ²⁹ M.-T. Wei, K.-T. Yang, A. Karmenyan, and A. Chiou, *Opt. Express* **14**, 3056 (2006).
- ³⁰ P. Wanichapichart, K. Maswiwat, and K. Kanchanapoom, *Songklanakarin J. Sci. Technol.* **24**, 799 (2002).