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Optics-Free, Non-Contact Measurements of Fluids, Bubbles and Particles in Microchannels using Metallic Nanoislands on Graphene

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Abstract

Despite the apparent convenience of microfluidic technologies for applications in healthcare, relatively few devices are in commercial development because they often rely on capital-intensive optics and other peripheral equipment that limits throughput. Here, we evaluated fluids, gases and particles as they flowed through a microfluidic channel without the use of a camera or laser, which we call “optics-free” microfluidics. We did this by monitoring the deformation caused by the analyte on the channel side walls. This minute deformation was transduced into a simple resistance measurement by using an ultra-sensitive piezoresistive film comprising metallic nanoislands on graphene. We were able to relate changes in the resistance of the sensor to the theoretical deformation of the channel at varying flow rates. Then, we used air bubbles to induce a perturbation on the elastomeric channel walls and measured the viscoelastic relaxation of the side channel. We obtained a viscoelastic time constant of $11.3 \pm 3.5 \text{ s}^{-1}$ for polydimethylsiloxane, which is consistent with other techniques. Finally, we flowed silica particles and human mesenchymal stem cells and measured the deformation profile on the channel. These experiments represent a convenient, continuous, non-contact measurement of either rigid or deformable particles, without the use of a laser or camera.

TOC Figure:

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Author Contributions. C.D. and D.J.L. conceived the project. C.D., S.J.E. designed and performed experiments. J.R. and L.V.K. assisted with specialized experiments and fabrication. F.C. and J.V.J. designed and assisted cell measurements. C.D. wrote the manuscript. All authors discussed and commented on the manuscript.

Additional Information. D.J.L. is an inventor on a patent related to the use of metallic nanoislands on graphene as a means of mechanical sensing, and is a shareholder in GrollTex, Inc., which supplied the graphene used in this study.

Keywords

Strain sensor; graphene; viscous fluids; elastohydrodynamics; particles; bubbles

Microfluidic devices have long been touted as a powerful analytical tool to characterize a wide range of analytes, including particles, cells, and fluids.— These devices, however, have not seen wide-scale adoption outside of the lab because using microfluidic devices requires significant capital. An individual microfluidic device might not be expensive, but the vast majority of microfluidic devices operate on optics-based systems which typically include high-speed or sensitive cameras, sophisticated confocal microscopes, vibration isolation tables and laser excitation systems, which often require fluorescent probes.— We describe a novel technique that does not rely on optical-based characterization of fluid flow and analytes.

We embedded thin-film strain sensors made from palladium nanoislands deposited on single-layer graphene in the bulk of the elastomer in close proximity to a channel wall. The composite film measures changes in the electrical resistance caused by deformation of the wall (Figure 1a). This deformation can be related to the fluid flow, or to the properties of a flowing particle.— The couplings that occur between fluid flow and elastic structures are known as elastohydrodynamic phenomena., — In addition to measuring analytes, the platform we describe could be used to validate elastohydrodynamic theories, which can be difficult with current experimental techniques.— In contrast to other methods of measuring and sorting objects in microfluidic channels, this method does not place an obstacle in the pathway of an analyte. Some current techniques of mechanical sensing flow analytes over cantilevers— or around mechanical features,— such as spirals. Cantilever measurements, however, still require lasers to capture small deflections of the tip and must be rigorously isolated from vibration. Differentiating analytes based on mechanical features, either through biasing flow around features (e.g. deformability-based cell margination),— or through collisions into obstacles (e.g. deterministic lateral displacement) can be limited in throughput by the speed of the camera used for sorting and damage caused to the structures or to the analyte.

To transduce the deformation of the walls that occurs on the micron scale (Figure 1b), we found it advantageous to use sensors that did not need to be placed in the fluid environment.

We fabricated a composite metal-on-graphene piezoresistive sensor, previously developed in our laboratory, by evaporating palladium onto single-layer graphene (Figure 1d). These sensors can measure strains as low as 0.001%, . The sensitivity at low strains is attributed to a combination of phenomena, including strain-induced scattering between nanoislands initially in contact and modulation of the tunneling current between metallic nanoislands once separated, along with the intrinsic piezoresistance of graphene. While there are other strain sensors with high gauge factors,– we required high sensitivity at low strains, minimal fabrication steps, low physical profiles and ultralow stiffness so as to have a negligible effect on the mechanical response of the sidewalls of the channels. We fabricated simple microfluidic devices out of poly(dimethylsiloxane) (PDMS) containing a single, straight channel, with the strain sensor embedded near the channel (Figure 1c–e). Devices differed in their cross-sectional dimensions (width × height), as well as by the Young’s modulus of the PDMS (achieved by varying the base-to-crosslinker ratio). Full details of fabrication can be found in the SI.

We connected the microfluidic devices to a commercial PID-controlled, isocratic fluid pump (1260 Infinity II GPC/SEC, Agilent) and measured the changes in resistance of the sensor at different flow rates of water for different devices. The raw data can be seen in Figure 2a and b, which were taken with the device directly on a bench—without isolation from vibration. Most ultra-sensitive sensors suffer from unwanted detection of ambient vibration. Embedding the sensor in the viscoelastic elastomer dampened these ambient vibrations, which enabled the sensor to measure the submicron deformations in the channel with a signal well above the background mechanical noise.

A change of 0.1% in resistance during flow rate measurements corresponds to increments of absolute resistance on the order of 10 Ω . Given a flow rate, we can relate the imposed channel deformation by a fluid using the relationships developed by Gervais et al. (used here) or Christov et al.. The channel deformation is (and shown in Figure 2c):

$$Q = \frac{h_o^4 E}{48 \alpha \mu (L - z_{\text{sensor}})} \left(\left(1 + \frac{\alpha p(z) W}{E h_o} \right)^4 - 1 \right) \quad (1)$$

$$\frac{\Delta h}{h_o} = 2^4 \sqrt{\frac{3 Q \mu (L - z_{\text{sensor}})}{h_o^4 E} + 1} - 1 \quad (2)$$

Where Q is the flow rate, h_o is the initial channel height, E is the elastic modulus of the channel walls in the device, L is the length of the channel, z is the axial position along the device, μ is the fluid viscosity, W is the width of the channel, $p(z)$ is the pressure distribution along the channel and α is a proportionality constant with a range from 0.5 to 15 (see Ref. 31 and 30, and SI for more details). For high pressures, such as in the device with a relatively small $50 \times 50 \mu\text{m}$ cross-sectional area, the relationship between deformation and flow rate became noticeably non-linear. Thus, in Figure 2d, the relationship between

changes in resistance and deformation are linear for the three devices with a larger cross-sectional area, but not the $50 \times 50 \mu\text{m}$ device (red diamonds). We obtained a normalized change in resistance, which normalizes the sensitivity of the nanoislands on graphene sensor and the distance of the sensor from the fluid channel, by multiplying the change the resistance by its slope, m , compared to a reference slope, m_0 , of the device at 750×200 , $E=2 \text{ MPa}$. This value, m/m_0 , is denoted as the “gain” in Figure 2e. On the y -axis, we have plotted the normalized change in resistance of the palladium nanoisland strain sensor, which is proportional to the strain. On the x -axis, we have plotted our experimental conditions in the form of h/h_0 , which relates the strain in the channel assuming elastohydrodynamic deformation, given by Eq. 2. We observed a collapse of the data in the linear regime onto a single master plot with a slope of 0.78, which is in close agreement to a theoretical value of one. This demonstrates that the sensor is sensing deformation due to elastohydrodynamic phenomenon. The deviation from one could be due to differences between the devices and theory: the devices here do not have a limiting dimension, and for the purposes of demonstrating trends in strain with flow rate, we have simply taken the fitting parameter, α , to be one. In addition, the distance between the sensor to the channel can vary between devices ($\sim 1\text{--}3 \mu\text{m}$), which decreases the strain as the sensor is further in the bulk (the strain on the sensor, however, remains proportional to the deformation on the sidewalls). Christov et al. solved for α without requiring simulations, but this approach required a thin, deformable layer on top of the channel, whereas the devices here have a semi-infinite layer on top.

We measured the transient changes in channel deformation due to air bubbles ($\sim 30\text{--}50 \mu\text{L}$) in a device with cross-sectional dimensions of $300 \times 300 \mu\text{m}$, made with PDMS with a modulus of 1 MPa . In contrast to previous studies which used optical methods,— we were able to monitor dynamic events in the channel ($\sim 10 \text{ kHz}$ sampling rates) at far higher rates that accessible to most cameras ($\sim 20\text{--}100 \text{ Hz}$), and without optical limits (micron-or-less wall deformation). Figure 3a shows the relatively large changes in resistance as a bubble flowed past the sensor, with variations due to velocity and size of bubbles. The large change in resistance is surprising because the pressure drop across a $30\text{--}50 \mu\text{L}$ bubble is small: approximately $\sim 5\text{--}50 \text{ Pa}$ for flow velocities of 1 mm/s to 10 mm/s . To investigate the origin of these large changes in resistance, we measured the resistance while taking high-speed video (Basler Ace, 820 FPS) for the case of an “infinitely-long” bubble, where a channel of fluid is cleared by air. Figure 3b shows the calculated deformation due to a transiting ‘infinitely long’ bubble. We show the sensor resistance and deformation (μm) on the other y -axis, as calculated from the fluid flow rate, by dividing the percent relative change in resistance ($R_0 = 5.35 \text{ k}\Omega$) by $5.9 \times 10^{-2} \text{ m}$ (Figure 2d). By doing so, we are assuming that the deformation profile over the strain sensor is the same between a pure fluid and an air bubble; though they presumably deform the walls with a different profile, but the magnitude of deformation on the sensor is similar.

In region 0, the channel was flowing only water; we applied a small increase in flow rate, indicated by the green arrow, to serve as a calibration. This pulse highlights the magnitude of the signals produced by air bubbles, compared to those produced by changes in flow rate. In region I, we observed that the resistance began to increase rapidly; from the image in Figure 3c, this increase corresponds to the entire air-water interface transiting across the sensor. In

region II, the image from Figure 3d shows that the fluid interface has passed the sensor, which corresponds to the lengthy plateau in the normalized resistance in Figure 3b. This plateau, which has a modest negative linear slope, corresponds to clearing the channel of fluid with air, since the sensor is located in the middle of the channel. We have observed that clearing the channel with air at higher velocities results in a shorter plateau and vice versa. This process is mechanically noisy as the channel sputters water, which is reflected in the deformation trace.

We took advantage of this phenomenon to measure the viscoelasticity of the PDMS. Figure 3e shows the channel relaxing in the absence of any fluid. Using a Kelvin-Voigt model of viscoelastic materials, the transient change in resistance (normalized by maximum resistance) was treated as a spring-dashpot (dashed lines, Figure 3f). This spring-dashpot responded to the changes in fluid within the channel, represented as a square wave with a width that spans region I to region II. We obtained a viscoelastic relaxation time constant, τ , of $11.3 \pm 3.5 \text{ s}^{-1}$ and viscosity (of the solid) of $0.20 \pm 0.08 \text{ MPa}\cdot\text{s}$, which compares reasonably well to 7.2 s^{-1} and $0.15 \text{ MPa}\cdot\text{s}$, in the literature (hexane-extracted 10:1 PDMS measured with an elastic modulus of 1.08 MPa). The maximum frequency of bubbles we achieved was at 33 Hz (see Figure S4 of SI) due to our capabilities to generate bubbles rapidly. This could potentially be higher because the maximum frequency was limited by our ability to generate bubbles rapidly, but not due to the mechanical response of the material.

We have confirmed that large changes in resistance occurs when the air-water interface moves across the channel. The strain profile caused by a moving air-water interface is unusual: most strain sensors experience gradual change in deflection across the majority of the sensor, e.g., a strain sensor bent like a cantilever. We hypothesize that the large changes in resistance of the sensor, through the PDMS side walls, occur due to relatively high compression (i.e., strain) in a narrow portion, around the air-water interface, as opposed to a gradual bend across the length of the entire sensor.

We then examined the deformation of rigid particles (silica microspheres) and deformable objects (human mesenchymal stem cells) as they transited through the channel. As a particle transits through a channel, it will cause the fluid to flow around the particle, deforming the walls of the channel. The silica spheres (Megabead, PolySciences, Inc., Calibration grade, C.V. $<3\%$) were $80 \text{ }\mu\text{m}$ in diameter and flowed through a device with cross-sectional dimensions of $300 \times 300 \text{ }\mu\text{m}$, made with PDMS ($E = 1 \text{ MPa}$). Figure 4a shows the change in resistance and the calculated change in deformation as the silica sphere flowed past the sensor. Again, this assumes that the deformation caused by the particle and a pure fluid is the same, which is not necessarily true, but gives a magnitude of channel deformation. A sequence of images showing the silica sphere past the sensor can be seen in Figure 4b.

We see that the change in resistance (Figure 4a) of the sphere follows a linear increase as the particle transits across the sensor, reaches a maximum after approximately 30 ms . At this moment (Figure 4b), the particle was approximately $2/3$ through the sensor (at length = 2.8 mm). It is not immediately clear why the maximum resistance was a sharp peak, but the presence of a peak suggests that the particle deforms the walls in front and behind the actual particle.

Human-derived mesenchymal stem cells (hMSCs, Lonza, PT-2501) were trypsinized and then flown into the device to demonstrate a proof-of-principle in measuring the deformability of particles in a continuous manner. This could be advantageous in high-throughput screening of cells that differ in mechanical properties only, such as label-free detection of circulating tumor cells. Cells were approximately 25–40 μm in diameter, and the resistance and deformation on the sensor caused by a cell flowing in the $300 \times 300 \mu\text{m}$ device it is shown in Figure 4c. The cell is both smaller and softer than the silica particle, and we see a smaller signal from the sensor. A composite image of the cell motion in a channel is shown in Figure 4d. The velocity of the moving particle, whether cell or silica sphere, affects the amount of deformation on the wall and particles moving too slowly will not be detectable. Future development of the theoretical elastohydrodynamic deformation profile may make it simpler to distinguish between air bubbles, rigid particles and cells from the characteristic time-dependent resistance recorded by the sensor during transit of the object.

We demonstrated that the deformation of the sidewalls in microfluidic channel could be used to measure a variety of phenomenon, such as the fluid flow rates, the viscoelastic relaxation of the channel side walls in the presence of air bubbles, and channel deformation caused by particles and cells. This technique may enable new avenues of investigation in physics and biology. These devices can be used to experimentally verify novel elastohydrodynamic phenomenon, such as the passage of deformable particles in the presence of deformable walls, or the flow around a deformable junction in the channel. Within cellular biology, this device is complementary to many existing optical techniques because it only requires that one of the channel walls is deformable. For example, this device could provide a continuous method to measure the mechanical properties of cells, instead of tedious atomic force microscopy on single cells.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(a) Fluid flowing against a soft wall, such as poly(dimethylsiloxane) (PDMS), deforms the channel in relation to the fluid flow rate (v) and viscosity. Air bubbles and solid particles also cause characteristic deformations along the channel wall. (b) Piezoresistive thin films comprising palladium nanoislands on graphene placed near the channel can transduce minute elastohydrodynamic deformation into voltage changes. (c) Schematic diagram of the device showing placement of the sensor near the channel. (d) Scanning electron microscope (SEM) images of palladium nanoislands on graphene, (e), Bright-field image of device, with the edge of the sensor and fluid channel visible.

Figure 2.

(a) Recording resistance changes in the device due to changes in flow rate (right y-axis) into the device. (b) Changes in resistance quickly followed changes in the flow rate. (c) Theoretical relationship between fluid flow rate and channel deformation for devices tested here, calculated according to Ref.1, 6, 11 Note the 1/10 factor on the 50 $\times$ 50 μm device (red dashed line). (d) Percent change in resistance at different flow rates, plotted against the theoretical deformation at the wall for several devices in varying geometries and elastic modulus. Gain and linearity given by slope and r^2 values, respectively. (e) Master curve relating channel deformation to changes in resistance for all devices. Naming convention are the channel's width (W) by the channel's height (H) in microns, followed by the elastic modulus of the device. Error of slope calculated on confidence intervals of 95%.

Figure 3. Detecting air bubbles and measuring viscoelasticity of the channel.

(a) Flowing 30–50 μL air bubbles in water causes large changes in resistance in the device made of $E = 1 \text{ MPa}$ PDMS with channel dimensions $300 \times 300 \mu\text{m}$. Air bubbles indicated with red arrows. (b) Clearing the channel with air creates several identifiable regions, from 0-III. Green arrow to a calibration peak. Baselined with zero corresponding to the deformation of the open channel. (c) Region I where air bubble begins to transits under the sensor. Micrograph from video (top, 820 FPS), schematic drawing of fluid (middle), and deformation of the wall (bottom). (d) Region II where air bubble displaces water completely from channel under the sensor. (e) Region III where channel is void of fluid but the wall deformation occurs over some finite domain due to viscoelastic relaxation. Deformation calculated from fluid calibration. (f) Kelvin-Voigt model of viscoelastic relaxation of several trials in channel walls (dashed lines) as compared to data (solid lines). Scale bar = 1 mm in the micrographs P1-P3.

Figure 4. Deformation profiles of silica particles and human mesenchymal stem cells. (a) 80 μm silica particles were flown through a $300 \times 300 \mu\text{m}$, $E = 1 \text{ MPa}$ channel, causing resistance changes. These resistance changes were converted to channel deformation, per calibration from Figure 2. In (b), portions of images taken as particle passed through fluidic channel and over the sensor, delineated in orange. (c) Human mesenchymal stem cells (25–40 μm diameter) were flown in the same channel geometry and the channel deformation was monitored. In (d) Portions of image as cells passed through fluidic channel. Background image was subtracted to highlight cell motion with the cyan line to guide the eye. Metal nanoisland-on-graphene sensor interface shown with orange dashed line.