A Piezoresistive Sensor for Quantifying Cell-induced Cantilever Deflection

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Abstract **-** We present here a novel piezoresistive-based sensor designed to electronically measure cell-induced cantilever deflection. Presently, there is an unmet need for increased throughput in studying cellular mechanics, which is often performed with optical microscopy and requires elaborate instrumentation. Because our approach is electronic, it offers the potential of very high throughput without the need for microscopic examination or tedious image analysis. Our sensor is comprised of a SiO_2-based cantilever with piezoresistors made from lightly doped polysilicon for the circuitry. The device is designed to be biocompatible for use in cell culture, with the ultimate goal of quantifying forces exerted by single cell onto its surrounding environment. In particular, the platform will be aiming at measuring contractility of cardiomyocytes as the first application. Preliminary experiments, coupled with computational simulations, have demonstrated that the design is sensitive enough to detect HL-1 cells strains on the cantilever. The beams are capable of detecting surface tractions in 500 N/m^2 increments, starting from 0 N/m^2.

Background – The study of cellular mechanics has been an important topic in recent research. In particular, the mechanical forces associated with cells have been proven to be indicative of their relative health. For instance, a red blood cell (RBC) infected with *P. falciparum* parasite becomes 10 times stiffer. Cancer cells, too, exhibit similarly significant changes in their mechanical properties [1]. As such, studying cellular mechanotransduction is an important field of research for understanding the pathological changes that occur in a broad variety of cells. Many biologists traditionally use microscopy paired with specialized substrates to study cell mechanics [2]. However, these techniques are dependent on extensive equipment and require a trained technician to observe and interpret data taken from photos. This severely limits the speed and accuracy of which cell mechanics may be measured, considering the time and labor required to set-up and run each array of experiments. Incidentally, a lengthy procedure would also restrict the amount of cells that can be observed due to their limited experimental viability.

Using MEMS fabrication techniques, a new platform for measuring cellular mechanics is being developed using a piezoresistive-based sensor. This sensor will take electronic measurements, with greater accuracy and precision than traditional optical techniques. Measurements of cellular contraction can also be sampled more rapidly than before, bypassing much of the analysis and time spent to process optical images in conventional approaches. Here we will discuss the current progress in this endeavor, including preliminary results using SiO_2 as a substrate, as well as the simulation and fabrication results.

Current Results – The first-generation devices were based on metal strain gauge capable of measuring strains from point loads on a cantilever. The cantilever was fabricated with MEMS techniques from SiO_2. Stem-cell-derived cardiomyocyte (HL-1) cells have been cultured on a range of SiO_2 beams coated with fibronectin (Figure 1) and have been shown to not only proliferate, but also illicit bending deformation on the cantilevers. This demonstrated an important feasibility test to determine whether SiO_2 could be used in future designs with its mechanical robustness and sensitivity. Given this success and the well-characterized MEMS processes of SiO_2, current second-generation design is under investigation (Figure 2). Using experimental data, and a bimorph-based model suggested in an existing publication [3], a new model was devised using our novel design. This piezoresistive-based approach should perform significantly better than metal strain gauges given th achievable high piezoresistivity with lightly-doped polysilicon. This is especially important to allow for a mechanically robust design that yields low-level deflections during tests. Using these material inputs together with a Wheatstone bridge set up in a quarter configuration, and implementing the bimorph model using Comsol Multiphysics software, we observed signal changes between the voltage dividers on the order of 30 μV per 500 N/m^2 of cell tractions. These promising results served as the bases for device design and fabrication.

Fabrication – Figure 3 is a brief illustration of the fabrication steps, which begin with growing SiO_2 on an undoped silicon wafer (3.1) with wet oxidation (3.2). Lightly-doped p-type polysilicon is sputtered to form the piezoresistors (3.3) with RIE (3.4). The SiO_2 cantilever beams are then etched the same way (3.5). Lift-off technique is then used to deposit and pattern a very thin layer of evaporated SiO_2 to cover exposed circuitry (3.6). The backside is then patterned for backside RIE to remove SiO_2 (3.7). Afterward, we use DRIE to remove silicon almost completely through (3.8), finishing with a gentle XeF_2 etch to finally release the cantilever (3.9). A small well is affixed to the top of the chip (Figure 4), with a glass cover slip attached below to create a cell culture environment separated from the probing area, and to prevent fluid leakage. The sensor has an accessible probing area outside of this well (Figure 5).

Experimental studies are underway using HL-1 cell lines to characterize these sensors. We will use microscopy to calibrate the cell-induced strain to a specific measured signal by measuring the radius of curvature and calculating traction, a method described in [4]. With these continued efforts, we hope to introduce one of the first in a new generation of electrical, optics-free sensors for measuring cell contractility. In later iterations, we foresee an implementation into microfluidic platforms and then lab-on-chip to facilitate broad-scope studies in cell mechanics.

REFERENCES

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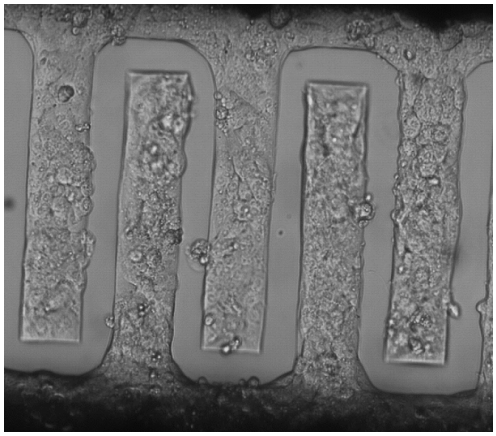


Fig. 1. HL-1 cells growing on SiO_2 cantilevers

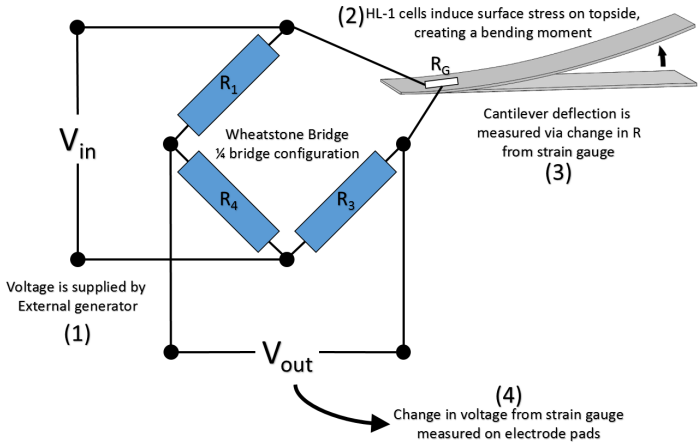
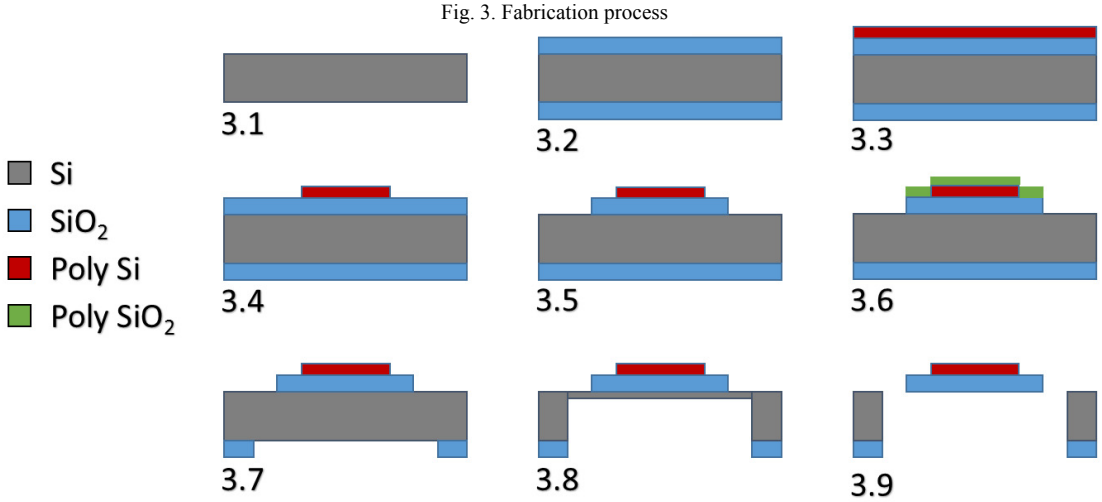


Fig. 2. Device design and operational scheme

Fig. 3. Fabrication process



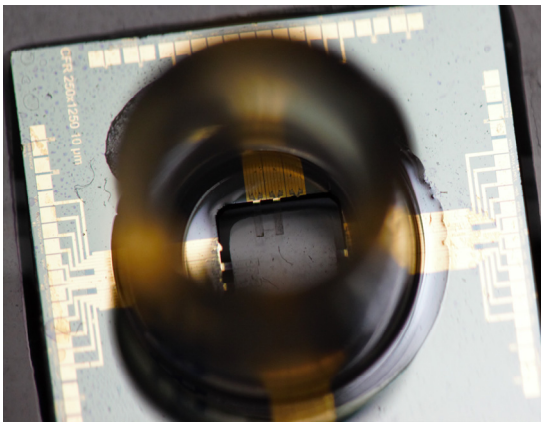


Fig. 4. Mini-Well affixed to sensor

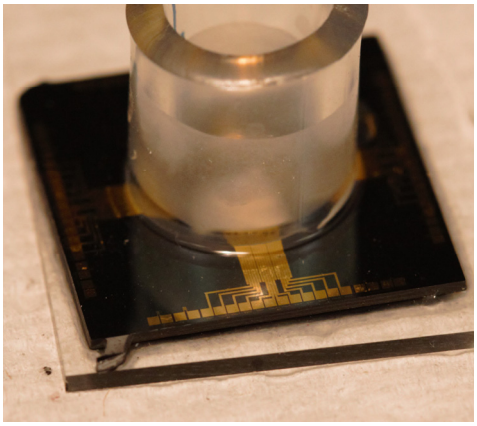


Fig. 5. Electrode pads at edge