SINGLE HEART CELL FORCE MEASURED IN STANDARD CMOS

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SUMMARY

Active force from living individual heart cells has been measured using a standard CMOS piezoresistive force transducer. Signal-to-noise ratio of over 10:1 was achieved with a Wheatstone bridge and on-chip CMOS amplifier. The sensing mechanism involves the deflection of a cantilever beam with a strain gauge at the base. The system response is roughly 2.4 V/μm in both air and saline environments. To date we have measured contractile forces up to 32μN in response to an externally applied calcium stimulus.

Keywords: piezoresistor, force transducer, heart cell

DEVICE DESCRIPTION

Standard force transducer technology has been used to measure active force from rat heart cell contractions in response to chemical stimuli [1]. These transducers are inherently limited in frequency response and sensitivity due to relatively large mass of the transducer system compared to that of the cell. By necessity the force transducer must be positioned outside the cell's saline bath. Glass pipettes are required to enter the solution meniscus to contact the cell and are subject to surface tension forces.

MEMS technology allows the development of extremely low mass, highly sensitive, fully submersible force transducers which offer the possibility of higher frequency response. We have fabricated such a force transducer using a standard CMOS process [2]. The silicon dioxide structure is released via a maskless post-processing XeF_2 etch and assembled using tungsten needle probes (Figs. 1 and 2). A living heart cell is attached between the oxide clamps using a silicone sealant. When the cell contracts, it deflects a cantilever beam with a polysilicon strain gauge in the base. The electrical signal is transmitted back from the foldover structure via aluminum hinges [2].The estimated spring constant in the beams is 10N/m. The strain gauge is part of a Wheatstone bridge attached to an on-chip amplifier (Fig. 3). Off-chip amplification and filtering were added.

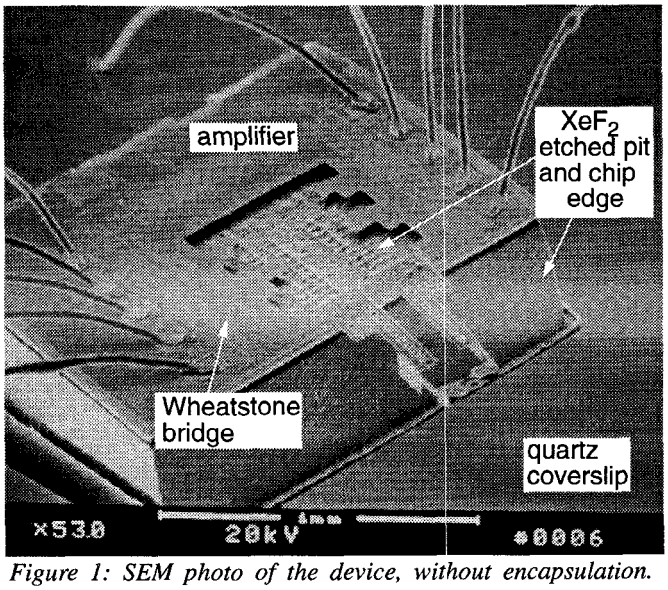

Figure 1: SEM photo of the device, without encapsulation. Chip is attached to a quartz coverslip with aluminum interconnects (not visible here).

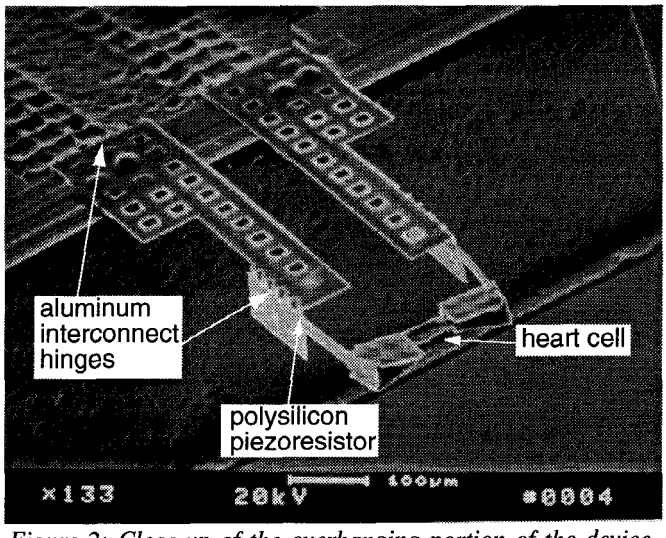

Figure 2: Close-up of the overhanging portion of the device. Heart cell shown glued between the silicon dioxide clamps. CMOS aluminum interconnects also serve as hinges.

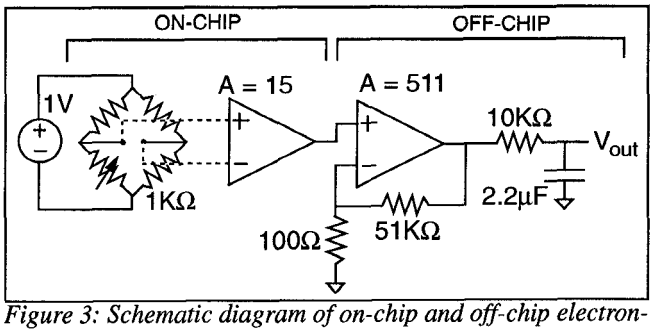

Figure 3: Schematic diagram of on-chip and off-chip electronics. Each resistor in the bridge is nominally 1KΩ

The CMOS chip is attached and wirebonded to a custom-made interconnect package. Aluminum lines are patterned on one half of a quartz coverslip. Quartz allows transmissive imaging of the cell. External wires are then attached to the aluminum lines along one edge of the coverslip via silver epoxy.

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Finally the entire package (including the chip, but not the structure) is encased in epoxy and nail enamel for electrical isolation.

RESULTS AND DISCUSSION

Cells have been successfully attached to the CMOS structure (Fig. 4). The sensor was calibrated in both air and saline by deflecting the beam with a probe and measuring the change in voltage. The deflection produced similar changes in output voltage in both environments (Fig. 5). Eight other devices showed this behavior as well.

A typical force record resulting from calcium activation solution infusion is shown in Fig. 6. Upon solution exchange, a transient spike arises from the fluid deflecting the sensor beam.

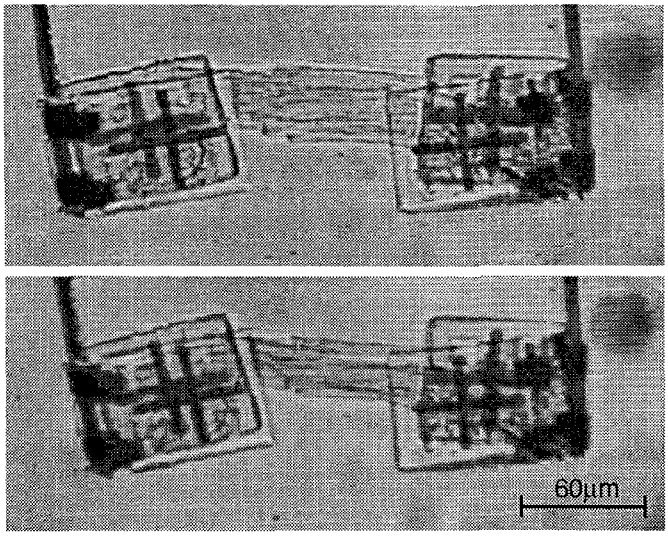

Figure 4: Optical micrographs of the same heart cell attached between clamps before (top) and during (bottom) contraction. Note that during contraction the cell has narrowed and the beams have deflected approximately 2μm.

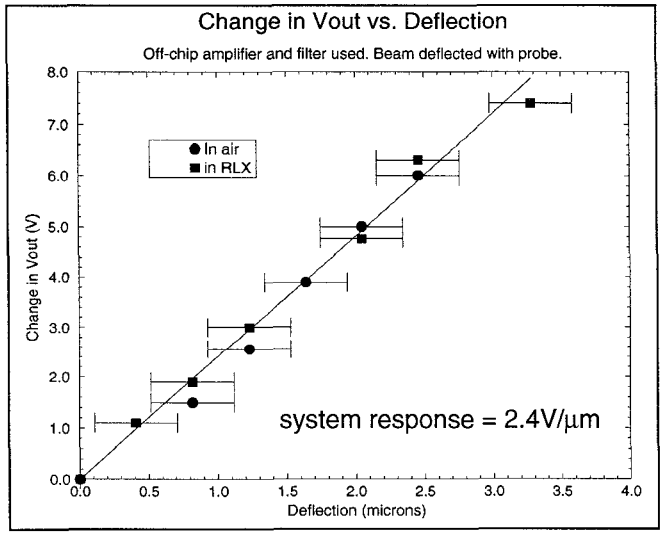

Figure 5: Typical calibration curve in air and in saline (relaxing solution = RLX). Slope of the best fit line is 2.4 V/μm

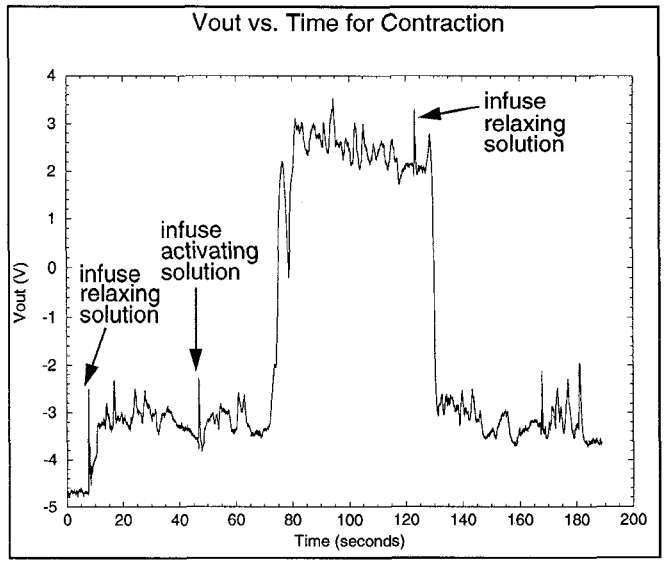

Figure 6: Trace recorded via data acquisition during cell contraction in response to a calcium activating solution and during relaxation in response to a relaxing solution.

The change in output voltage due to the cell contraction corresponds to about 2.5μm of deflection (via Fig. 5). Given the estimated spring constant in the sensor beam (k = 10N/m), this corresponds to 25μN of force. The noise level is approximately 1μN. The fluctuation in the record is caused by fluid currents during solution exchange. The delay in activation/relaxation following the introduction of a new solution is due to its transit time in the chamber.

To date we have measured contractile forces from 15 - 32μN. The range is primarily due to variations in the size of the cell. Since the force generated by the cell is dependent on cell length, we can alter the clamp spacing externally and measure the cell's response. By infusing varied levels of calcium, preliminary results have indicated that intermediate levels of activation can be resolved ranging from relaxation to full activation.

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