Micromagnetic Manipulation of Cardiac Tissue

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Abstract:

Studies of failing heart tissue have shown numerous changes in the cellular microenvironment. More specifically, changes in the cell shape, alignment, and gap junction distribution suggest that stresses and strains within the cell have caused both structural and electrical changes.

The focus of this project is to fabricate a device capable of stressing and straining cells in patterns that mirror the experimental findings. We hope to elucidate how these changes in the cellular microenvironment can affect the electrophysiological functioning of the cell and perhaps precipitate arrhythmias.

We attach matrix-protein coated magnetic beads to specific receptors on the cell membrane, and then, by running currents through nanoscale gold wires below the cells, we are able to create highly localized magnetic field gradients. The resulting magnetic field is highly controllable and capable of exerting forces on the membranes of the cells via the beads.

Introduction:

Research on failed heart tissue has shown changes in the intercellular environment, suggesting that mechanical stress can contribute to ventricular arrhythmias [1]. The most common method for testing the mechanoelectrical properties of cardiac tissues is through the inflation of a balloon within the heart. The action potentials across the cardiac surface can be measured and correlated with the magnitude of the strain on the heart tissue.

The problem with this method is that it is not specific to individual molecules or even cells; thus it is not only not known which cell proteins are responsible for the impulse that causes these changes within the heart, but it is not even clear which cells are responsible.

In our experiment, we are looking to explore the influence of specific integrin proteins on the functioning of the cell. By attaching specific matrix-proteins to the surface of magnetic beads, we are able to select specific proteins on the cell surface for binding. Once the protein has bound to the cell surface, we can manipulate the beads by generating controlled magnetic fields.

To generate these highly controllable magnetic fields, we used a series of twenty microwires, each connected to a computer-controlled current source. By placing the beaded cells above these wires, we are able to exert forces on the beads by running currents through the wires, generating a magnetic field gradient above the wires.

Our specific aims for this setup are threefold: to test if mechanical strains exerted on the integrin proteins will alter the action potential propagation; to test whether the changes in the Ca^{++} metabolism of the cell due to micromechanical stimulation contribute to arrhythmias; and to test whether some integrin proteins are more efficient transducers of mechano-electrical coupling.

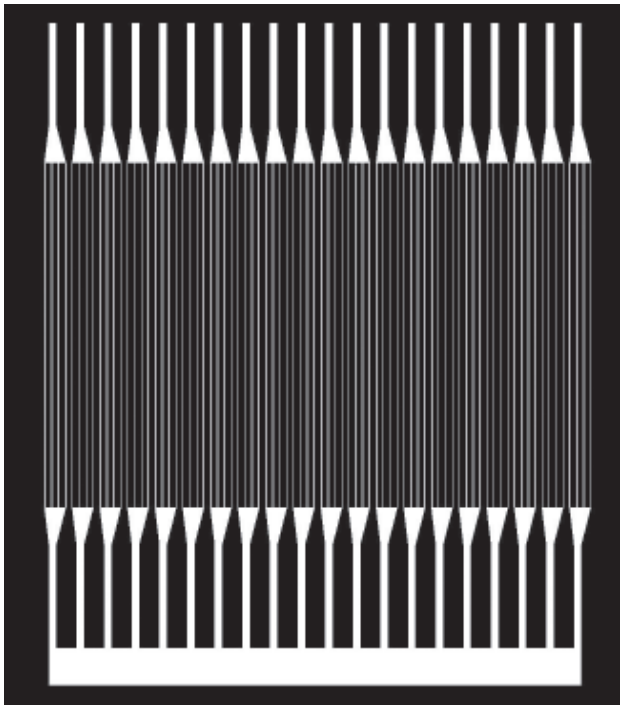

Figure 1: The pattern of wires printed onto our samples.

Procedure:

Our samples were fabricated using a standard photolithography process. We started with a 2.5 cm diameter sapphire window. We then spun on a layer of Lift-off Resist (Microchem Corp.) followed by a layer of Shipley 1813. We followed that by exposing the photoresist through a chrome mask (Figure 1), in an AB-M UV aligner for 2.6 seconds. The sample was then developed in Shipley CD-26 developer for 60 seconds, with gentle agitation, followed by a wash in DI water, and nitrogen drying. Finally the sample was placed in a Sharon Thermal Evaporator, where 75 Å of titanium and 500 Å of gold were evaporated onto the sample. The remaining resist was then removed using Remover PG (Microchem Corp.).

The sample was then electroplated for four hours in Oromerse BR (Technic Inc.) at 0.2 mA, plating on approximately 2.5 μm of gold onto the exposed regions. Finally the sample was coated with a 9 μm layer of SU-8 (Microchem Corp.), forming a protective biocompatible coating over the wires.

Result and Conclusions:

We were able to generate magnetic fields capable of exerting forces on the 4.5 μm magnetic beads, attracting beads suspended in water to a current carrying wire. Nevertheless, the forces generated were not of the magnitude we were aiming for. To that end, a redesign of the chip will be necessary to facilitate an increase in the forces generated. Since the magnetic field is proportional both to the current running through the wire and the distance from the wire, proposed designs will bring the wires closer together as well as making the wires larger, to allow for a lower resistance and therefore an increase in the allowable currents.

Also, due to constraints imposed by the optical mapping setup, the entire device must be translucent. This, unfortunately, requires that copper or other metals not be used as a heat sink. The wires, however, generate enough heat that temperature control is necessary, mandating a new design. Current plans include using a water chamber in contact with the bottom of the wires, allowing for temperature controlled water to be run below the wires, dissipating excess heat and allowing the device to be held at a fixed temperature.

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References:

[1] Hansen DE. Mechanoelectrical feedback effects of altering preload, afterload, and ventricular shorting. Am J Physiol. 11993 264(2 Pt 2):H4234-32.

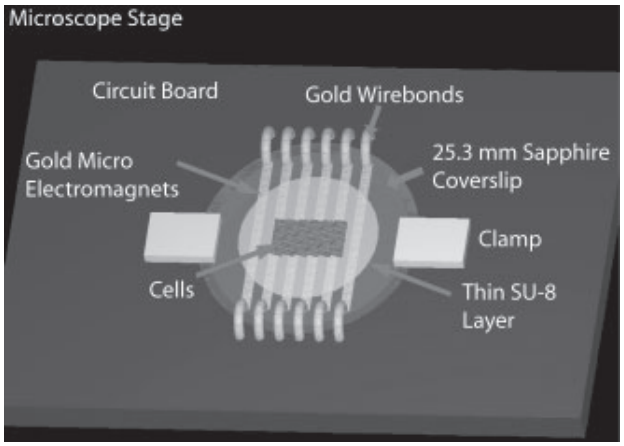

Figure 2: Schematic diagram of our experimental setup.