MEMS Based Real-Time Non-Invasive Biological Cell Diagnostics

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Introduction:

Scientists have been trying for years to learn about the inner functioning and mechanisms of cells, and why cells behave the way they do. One major area of research is the reaction of cells to mechanical forces. However, scientists often come across the problem of knowing for certain when a cell is actually reacting to the applied force.

Many scientists have explored the use of impedance measurement technology to characterize normal cell growth and function in culture [1, 2]. We propose that the use of this same technology can be used in tandem with the experimental loading of the cell to tell us whether or not the cell is reacting to the applied forces and the extent of its reaction. These data will prove useful in future research involving *in vitro* chondracyte formation as well as a better understanding of how sudden impact on cells affects the functioning of those cells.

Fabrication Process:

A silicon wafer coated with silicon dioxide was obtained. Using the thermal evaporation process of a Kurt Lesker E-Gun/Thermal Evaporator, a thickness of 1000Å of Aluminum was then evaporated onto the wafer to provide electrical contact pads with the oxide as the insulating layer.

Photolithography was then performed using a mask specifically designed for our needs with various electrodes patterned to our specifications. A Shipley 3012 photoresist was used to coat the wafer with 1.5 μm of resist. The wafer was exposed in a Karl Suss MA6 contact aligner for 6.3s. It was then placed in CD-26 developer solution for 50s. The wafer was then hard baked for two minutes at 110ºC to preserve the patterned resist. The wafer was then etched using ACT 935 Aluminum etch for approximately 5 min or until the oxide layer became visible.

Experimental Setup:

Mouse myeloma cells were cultured in Delbeco's Modified Eagle Medium until they reached confluency. Approximately 1 mL cell-media solution was then placed on the electrodes of the MEMS device and, using micromanipulators, a cell was positioned between two electrode tips. The electrodes were then placed in a parallel circuit to a variable capacitor (between 2 and 6 pF). An AC power source (variable but maximum voltage of 0.4V), an impedance monitor, a resistor (330 Ω) and inductor (100 μH) were connected in series to the electrodes and capacitor (see Figure 1). One of the micromanipulators (sharp probe tip) was positioned to contact the cell and the other was positioned to contact an electrode.

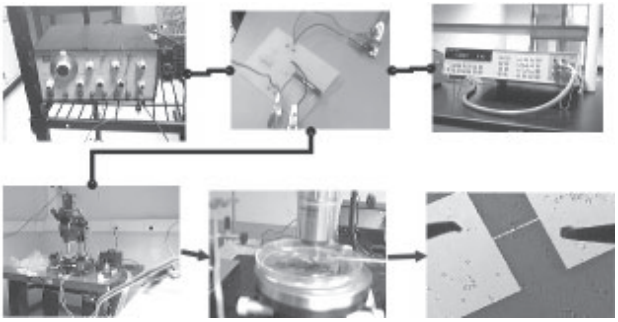

Figure 1: Experimental setup and images as seen through microscope (lower right).

The AC power source in the circuit is then adjusted to match the resonance frequency of the cell. The system was allowed to equilibrate for approximately ten minutes. The cell was then placed under load using the sharp probe tip. The impedance values for the cell were then recorded every five minutes for a two hour time span (see Figure 2). A sample of only media was also run to ensure that the media was electrically stable and that the devices were running properly.

Graph (A) shows the data collected from the cell under control conditions. This was done to rule out any ambient conditions that might have affected the cell and to compare the loaded cell's electrical behavior to that of the control. Graph (B) shows the loaded cell. The data collected from the loaded cell

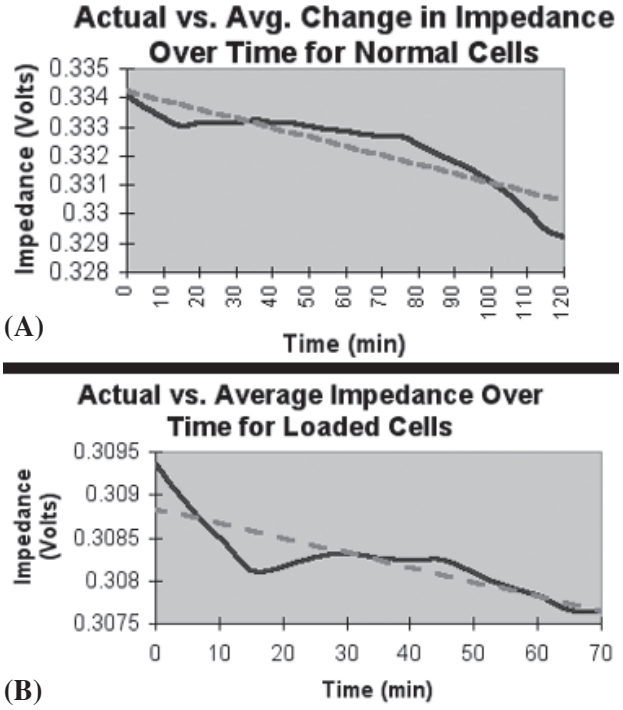

Figure 2: A) Data for cells in control conditions. B) The loaded cell.

and the control cell is compared not only using the average impedance changes (the dotted line in the graphs) but the initial change as well.

Results and Conclusions:

We found that the cells do in fact react internally to mechanical loading. The impedance values in both the average calculations and actual data points were dramatically different. Data we collected led us to the conclusion that the cell reacts initially to the load and then over time becomes accustomed to the load and approaches normal cell function. This is consistent with data found in previous studies (see Figure 3) [3]. These data show that in order for mechanical loading to effectively change a cell's behavior, the length of the loading and how often the cell is loaded must be carefully monitored and adjusted to achieve the desired results. While we did not have time to further study how the length or frequency of load and rest times affect the cells longevity and health, these results were encouraging.

Future work might include a refining of the fabrication process of our electrodes and possibly successful fabrication of cantilevers of various specifications in order to determine whether different types of loading affect the cell in different ways. We would also like to study a dynamic loading situation as well as various displacement levels of the cell. Long term goals include applying this technology to stem cell work and hopefully learning more about why stem cells differentiate the way they do.

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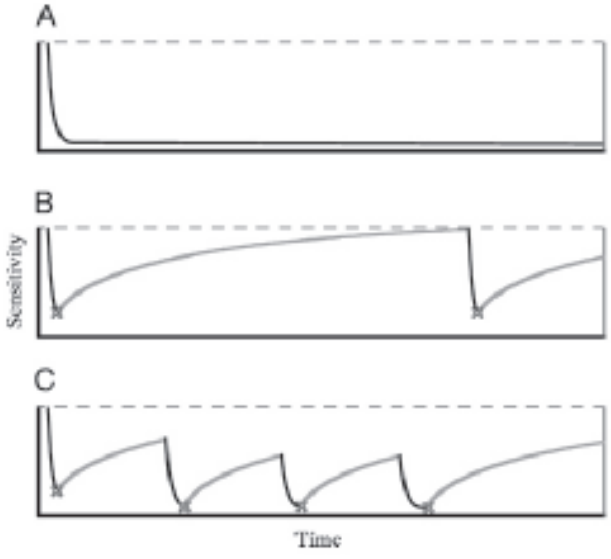

Figure 3: Data from previous study [3]. Graph is the comparable load regimen.