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NOVEL HIGH-THROUGHPUT HEART-ON-A-CHIP PLATFORM WITH MEA AND STRAIN SENSORS FOR ELECTRO-MECHANICAL SENSING

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ABSTRACT

This work demonstrates a novel biosensing platform for in vitro characterization of cardiomyocytes. This cantilever-based platform has the capability to measure the electrophysiology as well as the contractile profile of cardiomyocytes simultaneously with high throughput. This platform has been used to measure the contractile profile and field potential of cardiomyocytes day-wise, and understanding propagation of cardiomyocytes along the cantilever. The proposed platform has the potential to be used for high-throughput drug-induced toxicity screening.

KEYWORDS: Cardiomyocytes, High-throughput, Microelectrode Array, Strain Sensor

INTRODUCTION

Till date, several platforms have been developed for cardiac biosensing applications [1,2]. However, these platforms either only measure the contractility or the electrophysiology of the cardiomyocytes. There are some platforms that measure electrophysiology and contractility both at the same time [3,4]. These platforms, however, either involve complex algorithms for analysis or have low throughput. Hence, there is a need for such a platform that can record both electrical and mechanical activity of the cells, is easy to record, analyze and has high throughput. Herein, we propose a novel cantilever-based biosensing platform that incorporates all the above-mentioned features, in addition to being non-invasive. Electrophysiology is measured using microelectrode array (MEA) patterned on a cantilever. Strain sensor is patterned on the fixed end of the cantilever that measures the contractile activity. Cardiomyocytes were cultured on this platform and simultaneous measurements were analyzed.

THEORY

The proposed high-throughput cardiac biosensing platform consisted of polymer cantilever-based devices. Each cantilever consisted of (1) a strain sensor at the fixed end of the cantilever, (2) laser reflecting area near the free end of the cantilever and (3) MEAs between the laser reflecting area and strain sensor. Cardiomyocytes cultured on the cantilever deflected the cantilever with their contraction force. The resistance of the strain sensors patterned at the fixed end changed upon deflection. Simultaneously, field potential was recorded using MEAs.

EXPERIMENTAL

Figure 1 (a) shows the schematic of the high-throughput cardiac biosensing platform connected to the printed circuit board (PCB). The cantilever-based device was fabricated using SU-8 polymer and the strain sensor and MEAs were patterned using Ti/Au. First was the cantilever layer (14 µm thick), on which Ti/Au were patterned for MEAs, strain sensor and the laser reflecting area. Then, the cantilever area was isolated using SU-8 except the MEAs and reference electrode. Finally, the body was formed to provide strength to the device. Thickness of each layer is shown in figure 1 (b). Figure 1 (c) describes the dimensions of each pattern.

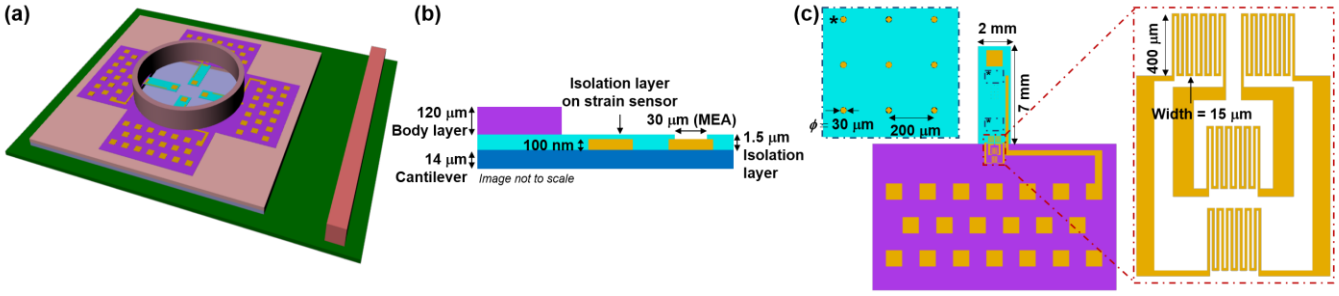

Figure 1: (a) Schematic of the novel high-throughput cardiac screening platform, (b) cross-section of the various layers of the cantilever-based device fabricated using photolithography, (c) schematic of the cantilever-based device showing dimensions of the cantilever, MEA and the strain sensor.

RESULTS AND DISCUSSION

As shown in figure 2 (a), the resistance of our strain sensor was stable in cell culture. It was not influenced by the culture medium even when measured for a long time. Figures 2 (b) and 2 (c) show the strain sensor measurement and field potential duration (FPD) measured from day 6 to day 9 after cell culture. As can be seen from figure 2 (b), the change in resistance increases with increase in the cantilever displacement. Cantilever displacement was measured using the laser vibrometer by focusing the laser on the laser reflecting area. FPD decreased with increasing culture day (figure 2 (c)).

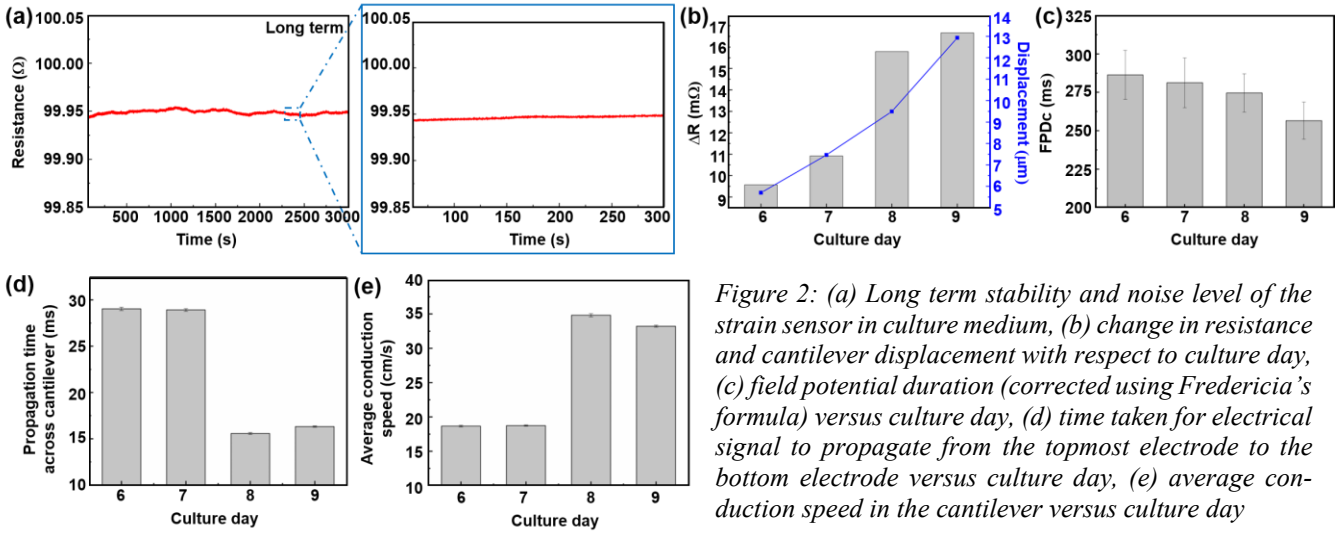

Figure 2: (a) Long term stability and noise level of the strain sensor in culture medium, (b) change in resistance and cantilever displacement with respect to culture day, (c) field potential duration (corrected using Fredericia's formula) versus culture day, (d) time taken for electrical signal to propagate from the topmost electrode to the bottom electrode versus culture day, (e) average conduction speed in the cantilever versus culture day

Figure 2 (d) shows the time taken for the electrical signal to propagate from the topmost microelectrode to the bottom-most microelectrode of the cantilever. It can be seen that the time taken for the signal to propagate across the cantilever revealed an overall decreasing trend with increasing culture day. The propagation time was 29 ± 0.17 ms on day 6. It decreased to 15.56 ± 0.1 ms on day 8 and 16.32 ± 0.07 ms on day 9. Inversely, the average conduction speed, as shown in figure 2 (e), increased with respect to culture day, beginning from 18.67 ± 0.11 cm/s on day 6 to 33.22 ± 0.15 cm/s on day 9.

CONCLUSION

The combination of MEA with strain sensor was demonstrated and the high-throughput biosensing platform was discussed. The propagation of electrical activity across the cantilever was analyzed and discussed. It can be seen that this novel platform can be used to study the combined effects of drugs on electrophysiology and mechanophysiology of cardiomyocytes.

ACKNOWLEDGEMENTS

This study was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No.2017R1E1A1A01074550).

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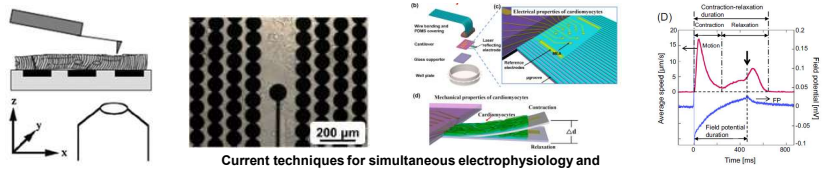
INTRODUCTION



- Several drugs only show changes in contraction force but not electrophysiology of cardiac cells, and vice versa.
- Simultaneous electrophysiology and mechanical recordings not analyzed extensively till date
- Objective is to develop a high throughput integrated cardiac sensing drug screening platform for simultaneous measurement of electrophysiological and mechanical properties of cardiomyocytes

DEVICE CONCEPT

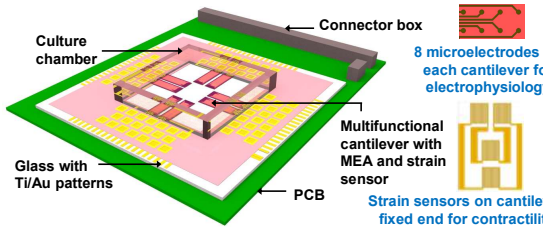


Figure 1. Schematic of the proposed multi-functional biosensor platform. Total 8 cantilevers with MEA and strain sensors each. Diameter of MEA = 50 µm, pitch = 350 µm.

DEVICE FABRICATION

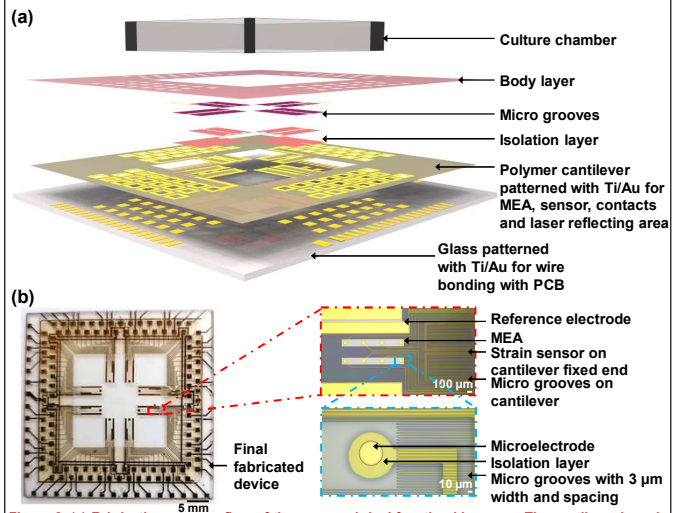


Figure 2. (a) Fabrication process flow of the proposed dual-function biosensor. The cantilever layer is deposited first using photolithography using a photosensitive polymer, then microelectrodes of Ti/Au, then isolation layer, microgrooves and, lastly, body layer of the device, (b) optical image of the final high-throughput biosensor showing positions of microelectrodes and reference electrode on the cantilever.

EXPERIMENTAL SETUP

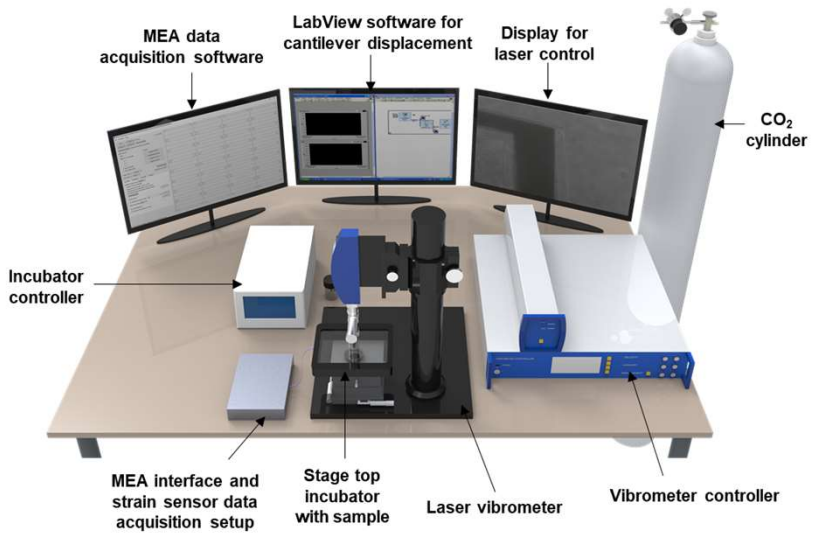


Figure 3. Experimental setup for the measurement of electrophysiology and contractility simultaneously. The high-throughput platform can measure data from 8 cantilevers using strain sensors for contractility and MEAs for field potential. Contractility output can also be confirmed using optical methods such as the use of lasers vibrometer.

EXPERIMENTAL RESULTS

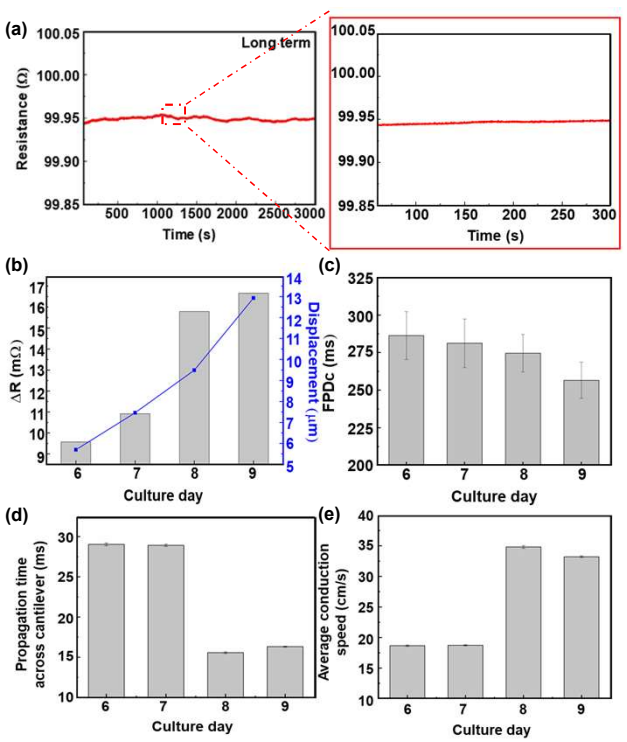


Figure 4. (a) Long term stability and noise level of the strain sensor in culture medium, (b) change in resistance and cantilever displacement with respect to culture day, (c) field potential duration (correct-ed using Fredericia's formula) versus culture day, (d) time taken for electrical signal to propagate from the topmost electrode to the bottom electrode versus culture day, (e) average conduction speed in the cantilever versus culture day.

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