A CMOS Multi-Functional Cellular Thermal Actuation/Sensing Array for Reconfigurable Localized Cell Heating and Manipulation

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Applying thermal stress on biological tissues has been widely utilized in numerous clinical applications. Raising the ambient temperature can result in denaturation of biomolecules, i.e., DNAs and protein complexes, and drastic alteration of the cellular biochemical reactions, which thus change the physiological behaviors of the tissues. However, existing thermal stress applicators are mostly designed for macroscopic scale clinical applications. To study the cell-level biological responses under thermal stress, a desired thermal applicator platform should provide (1) single-cell resolution and (2) arbitrary and reconfigurable thermal stress location.

We utilize the standard CMOS IC process to achieve a cellular thermal actuation/sensing array with reconfigurable localized thermal stress and temperature monitoring. The chip has been designed and fabricated (Fig. 1a). All the excitation and reference electrodes can be individually programmed to provide reconfigurable and localized thermal actuation. To accurately measure the local temperature, on-chip proportional-to-absolute-temperature (PTAT) temperature sensors are implemented at each pixel, forming a joint thermal actuation/sensing pixel. Full characterization of the CMOS cellular thermal actuation/sensing array will be started soon.

In parallel, we have developed a bio-compatible packaging solution, as a prerequisite for cell-based actuation/sensing applications. Since the CMOS chips are directly interfacing with living cells and the corrosive culture medium in the measurements, high solution resistance and biocompatible electrodes are critical to prevent chip damage and permit the study of long-term drug effects. To protect the aluminum electrodes from the culture medium, a standard electro-less gold plating procedure with aluminum-zinc-nickel-gold is developed. First, the CMOS chip is bonded to the glass substrate with black wax for easy handling. The chip is then washed with acetone, methanol, and isopropyl alcohol, and further cleaned with oxygen plasma ions. Next, the CMOS chip on the glass substrate is immersed in aluminum etchant and then nitric acid to completely remove the aluminum oxide layer. Finally, the CMOS chip on the glass substrate is sequentially immersed into off-the-shelf zinc, nickel, and gold solutions. As a last step, the chip is immersed in autocatalytic gold solution to thicken the gold layer up to 1μm. A chip microphotograph of a gold-plated CMOS test chip is shown in Fig. 1b.

Once being verified, our CMOS cellular thermal actuation/sensing array will serve as a novel low-cost cellular analysis platform to realize microscopic cellular thermal stress and thermal monitoring with high spatial resolution and reconfigurability, directly applicable for a plethora of high-impact biomedical applications, such as cancer studies, neural network characterizations, cell-based assays, and low-cost drug screenings.

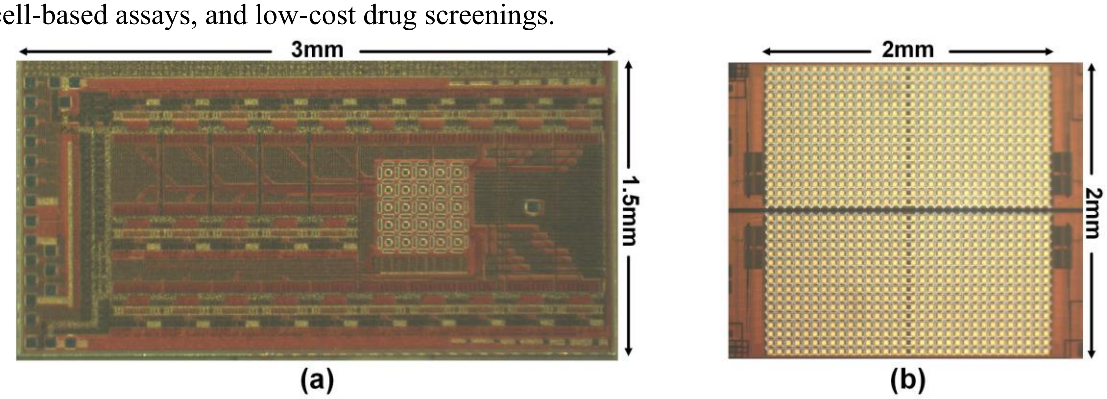

Fig. 1. (a) Chip microphotograph of the CMOS cellular thermal actuation/sensing array. (b) Chip microphotograph of a gold-plated CMOS test chip.