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Microfluidic packaging of high-density CMOS electrode array for lab-on-a-chip applications

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ABSTRACT

Effective packaging and integration of microfluidic components with a small electronic chip, such as a complementary metal–oxide–semiconductor (CMOS) chip, is crucial for the ultimate realization of lab-on-a-chip (LOC) devices. Hence, the methods and materials used for the integration should provide good reproducibility, reliability, biocompatibility, and capability for mass production. This paper introduces a new concept that allows the miniaturization of microfluidic packaging and the integration of CMOS chips. The photosensitive polymer material used in this study serves not only as a photoresist to pattern diverse shapes of microfluidic structures at the wafer level, but also as an adhesive to bond the Indium-Tin-Oxide (ITO) coated glass chip to the CMOS die. The patterning process, using conventional photolithography, was demonstrated with a wide range of thicknesses from 10 μm to 80 μm, and reliable seamless bonding was achieved with a conventional flip-chip bonder. We also validated that the proposed packaging can be utilized in biological experiments by culturing live cells (MCF-7) for three days and by measuring the auto-fluorescence from the polymer material in the test-vehicles. In addition, the performance of the proposed packaging method was demonstrated by applying it to the microfluidic/CMOS hybrid chip for preliminary electrochemical testing (impedance measurement), and particle entrapment testing (dielectrophoresis experiment). The proposed fabrication procedure is expected to facilitate the wide adoption of CMOS technology in LOC applications.

1. Introduction

Complementary metal-oxide-semiconductor (CMOS) integrated circuits (ICs) based on microsystems have been adapted in the field of microfluidics for biomedical applications [1,2]. These systems have the potential to ultimately become a lab-on-a-chip (LOC) for analyzing chemical or biological samples as they can perform both direct sensing and data processing on the same device without the need for bench-top instrumentation [3]. Therefore, the integration of sample-handling technologies using microfluidics and biochemical sensing functions presents new possibilities for simple, low-cost, low-power, portable systems in applications such as high-throughput screening, point-of-care diagnosis, and neural activity sensing [4–8]. In addition, miniaturization and parallelization based on the development of micro- and nano-fabrication technology either allow different analytes to be detected concurrently or parallelism redundancy to be leveraged for increased specificity and accuracy in a compact device [9]. The combination of microfluidics with CMOS ICs would therefore enable the development of a complete LOC microsystem as a viable solution, especially for a variety of clinical diagnostic applications.

The use of CMOS ICs in LOC applications requires post-CMOS fabrication processes to integrate the sensing interface with the CMOS ICs and deliver sample fluids in a controlled manner between the different on-chip components [10,11]. The applications also require the CMOS ICs to be protected from the fluidic environment as leakage of the sample fluids may affect the circuit characteristics [12]. Therefore, the materials and methods for microfluidic packaging on CMOS-ICs need to be carefully chosen. Advances in electronics and micro/nano-fabrication technologies have made it possible to produce high-functionality low-cost devices with a small footprint. In terms of CMOS fabrication, small-sized CMOS chips are preferred as the cost of these chips increases in direct proportion to the silicon

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area [3]. However, small-sized CMOS chips of the order of millimeters remain a major challenge for microfluidic packaging because they are typically much smaller than the current microfluidic components. Several strategies involving enlargement of the area using the carrier attached to the CMOS chip have been proposed to address the problem of unmatched sizes. For example, a small CMOS chip was attached to a pin grid array (PGA) and electrically connected with it by wire bonding. After encapsulating the bonding pads and wires using epoxy resin, a microfluidic channel was created on both the epoxy-encapsulated area and active sensing region in the CMOS chip by a direct-write microfluidic fabrication process (DWMF) [13]. However, the pattern size in the approach is determined by the viscosity of the polymeric material as well as the size of the dispensing needle used for creating the pattern by direct writing, thereby limiting further miniaturization with finer features. The serial process, moreover, may increase the production cost. Another approach reported previously involved attaching a CMOS chip to a polyimide ribbon cable to enlarge the area and the application of conformal-coating of a low-viscosity waterproof adhesive for bonding wires [14]. The microfluidic components are separately prepared from poly(dimethylsiloxane) (PDMS), using soft lithography. The separately fabricated CMOS chip and microfluidic component were bonded to the adhesive encapsulated zone. In a different way, a CMOS chip was attached to a larger substrate that contained lithographically patterned electrical leads [15]. Microfluidic channels were then formed on the larger area by double-layer lithography using a SU-8 epoxy-based negative photoresist. However, misalignment between the chip and carrier, and the interface bonding strength in a hybrid structure for leakage-free integration remain a difficult challenge.

A variety of materials for microfluidic packaging have been developed and adopted to deliver the sample and/or perform biochemical reactions before the actual measurement for the intended bioassay [16,17]. Among the materials, polymeric materials are most widely utilized in microfluidic integration on CMOS IC chips. Two aspects need to be considered when selecting the appropriate materials: post-processing compatibility [18] and reliable bonding [19]. Several polymers have been used for the fabrication of microfluidic structures [18]. For example, PDMS is widely used in microfluidics because it enables easy fabrication, flexibility, and biocompatibility [20]. Typically, PDMS microfluidic components are separately fabricated and then bonded to CMOS chips. Prior to the bonding process, accurate alignment of the two components is challenging because of the transparency and flexibility of PDMS. In this regard, SU-8 has attracted great interest for microfluidic structure fabrication [21] because SU-8 structures can be easily patterned onto CMOS wafers using conventional UV photolithography. However, bonding of SU-8 to the ceiling of the microfluidic structure remains challenging owing to a relatively large proximity gap and handling problems associated with non-crosslinked SU-8 [18]. A water-resistant medical epoxy was also used to encapsulate the bond wires and pads of a CMOS chip, mounted and wire-bonded to a custom-designed PCB [22]. However, poor adhesion of the epoxy to the chip substrate caused leakage of the cell culture media into the bonded wires, resulting in electrolysis and corrosion. Therefore, new materials and methods for CMOS microfluidic packaging should be investigated to address the various problems mentioned above.

In this paper, we introduce a simple and potentially mass-producible lab-on-CMOS integration procedure for a fully integrated microsystem, applicable to industry-standard packaging. A new photosensitive material, which is transparent and biocompatible, is adopted to fabricate a microfluidic structure using a conventional photolithography technique on a CMOS wafer and utilize it as an adhesive to bond the top glass substrate. Its mechanical and optical properties were characterized and the potential utility and limitation for biochemical experiments were validated by culturing live cells in the microfluidic chamber and measuring the autoflorescence of the material. In addition, impedance sensing and dielectrophoretic entrapment of the microparticles in fully packaged microsystems were carried out for a proof-of-concept demonstration of this novel approach.

2. Materials and methods

2.1. Device packaging and integration

Custom-designed CMOS wafers were fabricated by a commercial foundry company (GLOBALFOUNDRIES Inc., Singapore). The incoming CMOS wafers were post-processed and diced in an in-house cleanroom (Institute of Microelectronics, Singapore). A photosensitive polymer, (PA-S321, JSR Corp., Japan), which served as a microfluidic layer as well as an adhesive layer, was spin-coated and patterned onto the CMOS wafers using an EVG 6200 mask aligner (EV Group, Austria). ITO-coated glass substrates (CB-40IN-0111, DELTA Technologies, LTD, USA) were purchased for utilization as both a counter electrode and a ceiling for the microfluidic structures. Ultrasonic machining was used to drill holes in the ITO-coated glass substrates to create inlet and outlet ports (Bullen Ultrasonics, USA) and diced for individual assembly on the post-processed CMOS die. Prior to assembly, 150-μm solder balls (SAC 305, Sn96.5Ag3.0Cu0.5, Indium Corp., USA), for interconnection between the top counter electrode and the bottom CMOS circuitry, were jetted directly onto the diced ITO-coated glass surfaces using a laser solder jetting system (SB2-JET, PacTech, Germany). The separately prepared CMOS part and glass part were then thermally bonded using an automated die/flip chip bonder (FC150, SET Corp., France). The bond quality was tested using a bondtester machine (DAGE 4000, Nordson Corp., USA).

The bonded assembly was then attached to a ceramic pin grid array (PGA) substrate using an adhesive (Silicone 3140, Dow Corning Corp., USA). Au wire bonding from the CMOS chip to the substrate completed the electrical connections and was insulated using glop top silicone encapsulants (Silicone 3140, Dow Corning Corp., USA). Tygon tubing (#AAD04091, Saint-Gobain S.A.) was put in the tapered holes at the inlet and outlet, and fixed with epoxy (LOCTITE M-31CL, Henkel Corp.) using a syringe with a hypodermic needle. The PGA substrate was finally plugged into a microcontroller system for laboratory tests. During the tests, a uniform electric field was generated between the CMOS electrodes and ITO, thus allowing impedance detection and manipulation of cells utilizing dielectrophoresis (DEP).

2.2. Cell culture

MCF7-GFP cells (Cat# AKR-211, Cell Biolabs Inc., USA) derived from breast adenocarcinoma were cultured in DMEM High Glucose (Cat# L0102-500, Biowest, France) supplemented with 10% fetal bovine serum (FBS) (Cat# S1620-500, Biowest, France), 1 mM sodium pyruvate (Cat# 11360-070, Gibco), 0.1 mM MEM nonessential amino acids (Cat# 11140-050, Gibco), and grown at 37 °C under an atmosphere of 5% CO_2 in T75 flasks.

2.3. System set-up

An electrochemical impedance spectroscopy (EIS) measurement system comprising a customized PCB, FPGA card (PXI 7811, National Instruments Singapore Pte Ltd.), PXI Waveform Generator (PXI 5402, National Instruments Singapore Pte Ltd.), and a computer with LabVIEW software was customized to measure the electrical impedance spectrum of the microelectrode arrays and cell position manipulation. A function generator (Array 3400, Array