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Integration of CMOS Biosensor into a Polymeric Lab-on-a-Chip System

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***Abstract*—**We present an integration approach of a CMOS biosensor into a polymer based microfluidic environment suitable for mass production. It consists of a wafer-level-package for the silicon die and laser bonding process promoted by an intermediate hot melt foil to attach the sensor package to the microfluidic chip, without the need for dispensing of glues or underfiller. A very good condition of the sensing area was obtained after introducing a protection layer during packaging. A microfluidic flow cell was fabricated and shown to withstand pressures up to $\Delta p = 780$ kPa without leakage. The employed biosensors were electrically characterized in a dry environment.

***Keywords*—**CMOS biosensor, laser bonding, silicon polymer integration, wafer level packaging.

I. Introduction

LAB-on-a-chip (LOC) systems provide ever more elaborate fluidic procedures, enabling integrated and automated solutions to process biochemical assays [1]. Besides sample preparation, the detection of the target analyte is a main function of a LOC. This is often realized by optical detection methods like microarrays, usually requiring external benchtop devices for readout [2].

As an alternative, electrical detection promises to combine high sensitivity with compact external periphery. Although increasing the complexity of the LOC, especially CMOS biosensors are suitable for this purpose, since their high level of miniaturization combined with standard fabrication processes enables cost levels low enough for single-use devices. Hence, since most microfluidic platforms are polymer based [3], a combination of microfluidic sample preparation and microelectronic detection requires technologies to integrate silicon into polymer, while maintaining mass production capabilities for applications beyond research.

The integration of a CMOS based sensor into a microfluidic environment poses several challenges, e.g. spatial separation of fluidic and electric interfaces, fluidic tightness, low resistance electrical contacts and an approach to functionalize the sensing area. Existing solutions often use serial processes and glues or underfiller to seal and fluidically connect the sensing area, requiring additional dispensing steps and structures to avoid clogging of fluidic channels [4]-[6].

Here, we present the application and expansion of a recently proposed integration concept [7] in combination with a CMOS biosensor with 2 x 3mm^2 footprint and 36 electrical interfaces surrounding the sensing area. With 65.536 Cu nanoelectrodes the biosensor is capable of measuring biomolecule binding events by the associated capacitance change at the interface between nanoelectrode and liquid [8]. The packaging approach consisted of two main steps: First, a *wafer-level package* was fabricated by embedding the silicon dice into mold compound, yielding a reconstituted mold wafer. Afterwards, a lithography based redistribution to fan-out the electrical interfaces was employed [9], [10]. Second, a *laser bonding process* was used to integrate the singulated sensor package into a microfluidic multi-layer stack by means of a flexible hot melt foil.

II. Concept

To illustrate the concept, Fig. 1 shows a schematic cross section of a fully assembled system consisting of several polymer layers and an embedded sensor package. Between the sensor package and the lower polymer substrate, a flexible laser-activated hot melt foil is arranged, which provides mechanical attachment and sealing. It also contains a spared-out part, in which the microfluidic feeding channel is situated, forcing the sample to flow very close to the sensing area. Another opening allows for electrical contacts to the sensor package, e.g. via contact spring probes. The flow cell is covered by the upper polymer substrate, which provides a recess to house and protect the sensor package and, in combination with the flexibility of the hot melt foil, can be used to realize additional fluidic functions such as valves and pumps [11].

Compared to existing techniques, this approach provides mass production capability both for sensor packaging and assembly of the microfluidic system. For wafer-level-packaging, process steps involving lithography, sputtering, electroplating and etching are standard in microsystems engineering and can be easily ramped up. Also laser bonding is suitable for high throughput at low costs as it is a contact- and wearless assembly technology with low cycle times due to readily available high power laser sources. Additional steps like dispensing of glue are completely avoided in the presented packaging concept.

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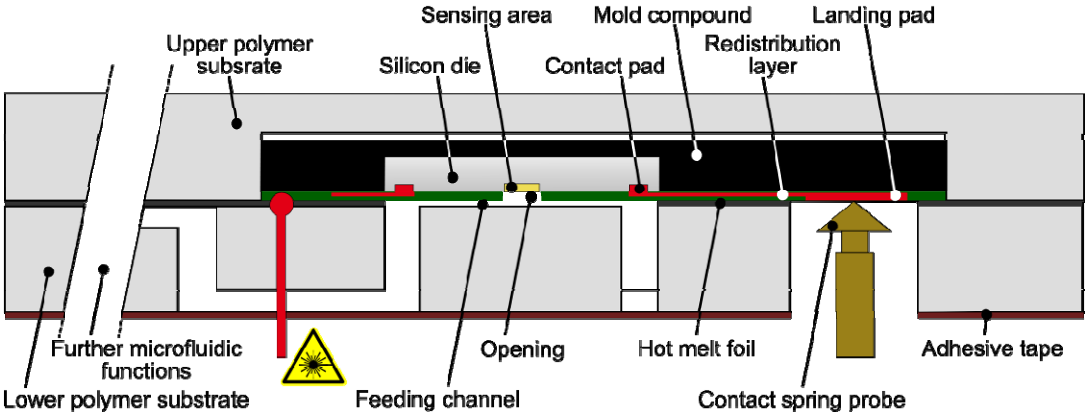

Fig. 1 Schematic cross section showing a fully assembled system consisting of several polymer layers and the sensor package; the intermediate hot melt foil is used attach and seal both the sensor package and the polymer substrates with each other by a laser bonding process

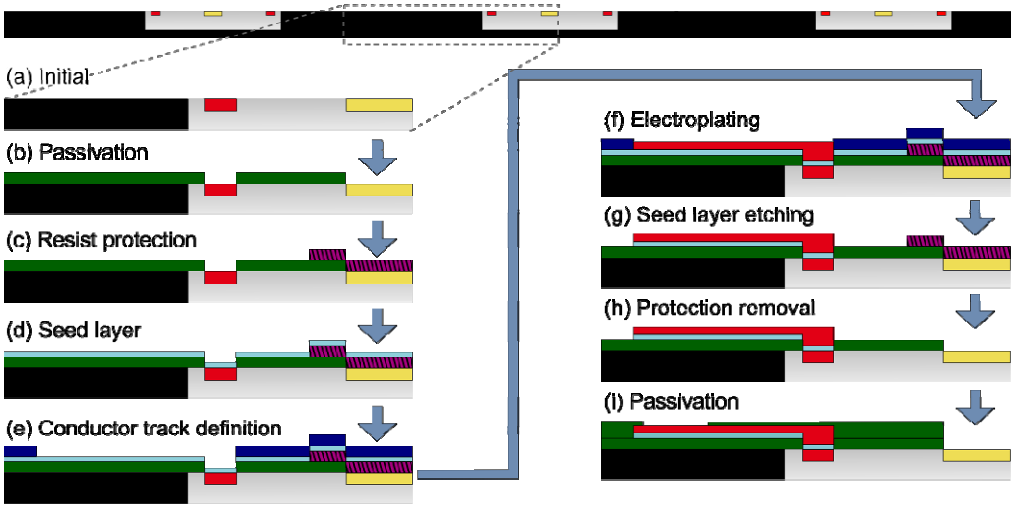

Fig. 2 Schematic cross section of a mold wafer and details showing layer configurations during the redistribution process; a temporary protection layer was applied above the active area at step (c) and removed after seed layer etching in step (h)

III. Methods and Materials

A. Mold Wafer Fabrication

Singulated silicon sensors were picked and placed onto a temporary carrier with a thermal release tape (RevAlpha 3195V, Nitto). For die placement a high speed chip assembly machine (CA3, ASM) was used for chip assembly with an accuracy of ± 15µm. Reconfigured wafer encapsulation was done by compression molding (120 t press, TOWA) with a liquid mold compound (R4202-26, Nagase). After molding wafers were released by a temperature step from the carrier.

B. Wafer Level Redistribution

Lithography on mold wafers was performed with photoresists for passivation, definition of conductor tracks and protection layer (WPR5100, JSR Micro Inc and AZ4562, Microchemicals GmbH) with a spin coater and mask aligner (RC8 and MA-150, Karl Süss KG). A sputtering unit (von Ardenne Anlagentechnik GmbH) was used for thin film deposition of Cu and Ti, followed by Cu electroplating (Rena GmbH). A plasma unit (Nano, Diener electronic GmbH) was used for cleaning and activation. Ammonium persulfate (APS) and buffered oxide etch (BOE) were used for etching of Cu and Ti, respectively. Mold wafers were singulated using a wafer saw (DAD 3120, Disco Hi-Tec Europe GmbH).

C. Flow Cell Fabrication

Microfluidic structures were milled from 1.5mm thick injection molded polycarbonate slides (Makrolon 2605, Bayer Material Science). The employed hot melt foil (Platilon LPT 2185, thickness 40µm, Epurex Films) was based on a thermoplastic polyester-polyurethane. Laser bonding was performed with a laser power of 1500mW in cw mode, a spot size of 300µm and a spot velocity of 90mm/s. The spot was routed in lines with a distance of 400µm. To cover channels running on the backside of the polymer stack, an adhesive tape (Polyolefin sealing foil, HJ Bioanalytik) was applied.

D. Electrical Functionality Tests

Resistivity tests on sensor packages with daisy chain dies were conducted on a wafer prober by 4-wire-testing. A source measure unit (K4200, Keithley Instruments Inc.) was used to apply five driving currents between -50mA and 50mA and

determine the corresponding voltage drops. For sensor readout, contact spring probes were used to interface the sensor package to a driving PCB.

IV. Sensor Package Fabrication and Evaluation

A. Fabrication Process

Reconfigured wafers containing 50 embedded biosensors were assembled and encapsulated on an 8" carrier and laser cut to 6" after release. Die shift compensation were performed by die position measurement before and molding and consequently die assembly position adaptation. Mold wafer thickness was selected due to wafer warpage. Lowest wafer warpage of 450µm was achieved with a combination of 400µm sensor thickness and 480 µm overall mold thickness.

Redistribution was performed according to the process flow shown schematically in Fig. 2. As a first step, a resist to passivate the mold wafer surface was applied and opened above the contact pads and the sensing area (a, b). Afterwards, to protect the nanoelectrodes from the subsequent process steps, a resist was applied above the sensing area (c). This avoided direct contact to the Ti/Cu seed layer (d), as well as to the temporary resist defining the conductor track layout (e). After copper electroplating (f), the temporary resist was removed and the seed layer was etched (g). A final passivation layer was applied after removal of the protection material (h) to provide a virtually flat surface for laser bonding into the microfluidic cartridge and to avoid contact between sample liquid and conductor tracks (i).

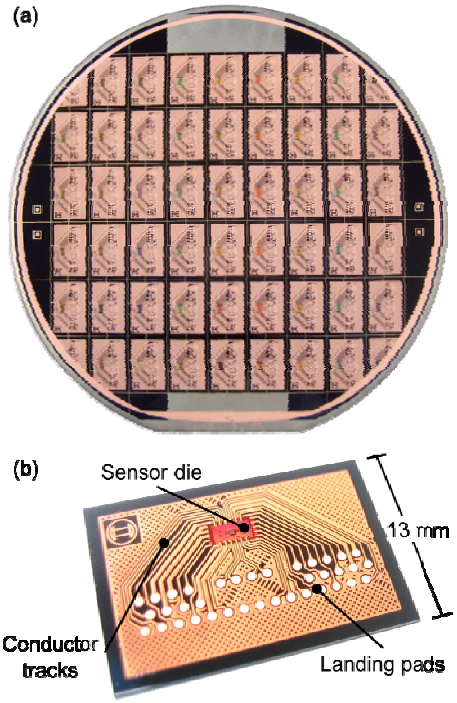

Fig. 3 Fully processed samples after redistribution (a) Mold wafer containing 50 redistributed sensor dies (b) Singulated sensor package. Electrical contacts on the sensor die were routed towards landing pads for interfacing with contact spring probes

Fig. 3 (a) shows a fully processed 6" mold wafer resulting in 50 sensor packages with dimensions of 13 x 19mm^2. As can be seen from the singulated sensor package in Fig. 3 (b), the electrical contacts on the silicon die were spatially separated from the active area and routed towards landing pads for contact spring probes. With a cross section of 100 x 4µm² resistances below 1 Ω were expected for conductor tracks with few cm in length.

B. Condition of Active Area

With the nanoelectrodes being a central part of the detection principle, the main challenge during packaging was to maintain their integrity and to avoid damage by aggressive steps. Especially etching of the seed layer (Fig. 2 (g)) was considered to be the most harmful process, since, without further protection; the metal seed layer was in direct contact to the nanoelectrodes. Hence, during etching of the seed layer, the employed etchants also directly acted on the sensing area. To gain more insight into the condition of the nanoelectrodes after the redistribution process and to study the effectiveness of the protection layer, SEM investigation was performed.

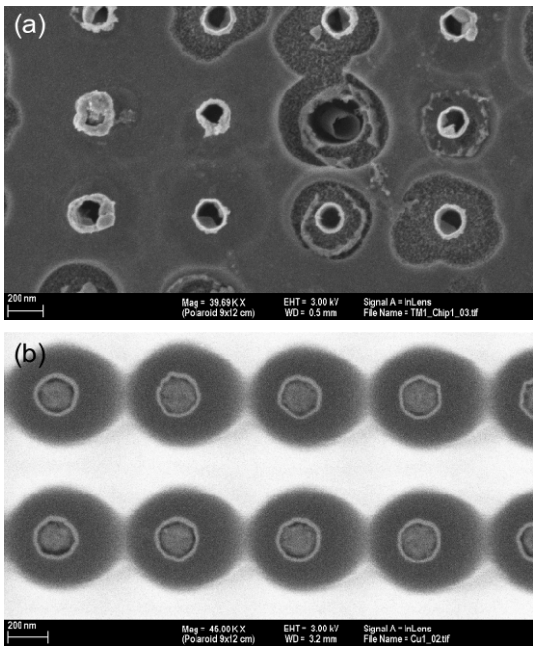

Fig. 4 SEM images of nanoelectrodes (a) Active area without protection layer, Nanoelectrodes and isolation material in between were heavily affected (b) Active area with protection layer. A very good condition of the nanoelectrodes was obtained

Fig. 4 (a) shows a part of the active area of a typical sample without protection layer. As can be seen, both the nanoelectrodes and the isolation material in between were heavily affected by the etching steps during redistribution. The nanoelectrodes seemed to be completely etched, leaving holes in the active area. In contrast to this, samples with protection layer (Fig. 4 (b)) showed a very good condition of the sensing area. No deformation of the nanoelectrodes was observed and they were obviously still filled with material.

Moreover, since bright areas in SEM images indicate isolating surfaces due to charging effects, the isolation material between the nanoelectrodes was still intact. Hence, the employed protection layer improved the condition of the nanoelectrodes drastically.

V. Laser Bonding and Microfluidic Flow Cell

Standard laser transmission welding relies on material interdiffusion at the interface between a transparent and an absorbing polymer, which requires comparable melting temperatures of the adjacent materials [12]. For the material combination used in this work, the glass transition temperature of the passivation material ($T \approx 210$ °C) was too high to employ standard laser welding, since this came close to the onset of thermal decomposition of polycarbonate. In contrast to existing laser welding approaches including a flexible polymer membrane [9], the hot melt foil introduced in this work incorporated gluing properties activated at a temperature of $T = 110$ °C. Hence, this membrane enabled a laser based bonding process between the sensor package and the polymer substrate.

A microfluidic flow cell with integrated sensor package was successfully fabricated based on the cross section shown in Fig. 1. As can be seen from Fig. 5, a homogeneous laser bond was achieved without any entrapped air bubbles, which would indicate thermal decomposition. For a differential pressure of $\Delta p = 20$kPa between inlet and outlet of the flow cell a flow rate of $Q = 20$µl/s was obtained, whereas the corresponding fluidic resistance was dominated by the thin feeding channel. Even for pressures up to $\Delta p = 780$kPa, no leakage was observed at the bond between sensor package and polymer substrate.

Fig. 5 Fabricated flow cell with integrated sensor package; A homogeneous bond was observed, without any indication of thermal decomposition

VI. Electrical Functionality Tests

Sensor packages were electrically investigated in a dry environment by applying different test routines. First, the resistance of the electroplated conductor tracks was determined with silicon dies containing daisy chain structures. All conductor tracks were reliably connected with absolute resistances generally below 1 Ω. The resistance per track length of $r_{exp} = 52 \pm 5$ mΩ/mm was comparable to the expectation for pure copper ($r_{theo} = 42$ mΩ/mm).

Different DC and AC (50 MHz) test routines were applied to analyze the response of packaged sensors. First, a probe-needle setup was used to contact the dies directly above the silicon where the conductor tracks started. The sensors responded as expected for both DC and AC operation and capacitance values determined by the nanoelectrodes were comparable to unpackaged sensors. This indicated that both the sensor internals as well as the nanoelectrodes survived the packaging process. Measurements including the full readout path using contact spring probes are currently ongoing.

VII. Conclusion

A silicon-into-polymer integration approach based on wafer level packaging of CMOS biosensor and a laser bonding process was investigated. A CMOS biosensor was successfully packaged including a protection for the nanoelectrodes on the sensing area. Since a standard resist was applied, this step can be adapted to a variety of different materials on the active area. Laser bonding of materials with different melting temperatures was shown by fabrication of a flow cell withstanding pressures up to $\Delta p = 780$kPa, which is high enough for most common microfluidic applications. Low resistances were obtained for the electroplated conductor tracks, enabling applications where low losses are required.

The presented approach is easily adaptable to other biosensor designs. Moreover, since during laser bonding the heat entry is locally confined, the sensing area does not experience elevated temperatures. This, in principle, allows functionalization of the sensing area on wafer level before laser bonding. Since a large amount of sensors can be packaged in parallel and all employed process steps are suitable for mass production, this approach enables cost-effective integration of CMOS biosensors into single-use polymer LOC devices.

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