

Packaging of silicon sensors for microfluidic bio-analytical applications

Citation for published version (APA):

Wimberger-Friedl, R., Nellissen, A. J. M., Weekamp, J. W., van Delft, J. A., Ansems, W., Prins, M. W. J., Megens, M., Dittmer, W. U., de Witz, C., & Iersel, van, A. W. M. (2009). Packaging of silicon sensors for microfluidic bio-analytical applications. *Journal of Micromechanics and Microengineering*, 19(1), 015015-1/7. <https://doi.org/10.1088/0960-1317/19/1/015015>

DOI:

[10.1088/0960-1317/19/1/015015](https://doi.org/10.1088/0960-1317/19/1/015015)

Document status and date:

Published: 01/01/2009

Document Version:

Publisher's PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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Packaging of silicon sensors for microfluidic bio-analytical applications

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Received 9 May 2008, in final form 29 October 2008

Published 28 November 2008

Online at stacks.iop.org/JMM/19/015015

Abstract

A new industrial concept is presented for packaging biosensor chips in disposable microfluidic cartridges to enable medical diagnostic applications. The inorganic electronic substrates, such as silicon or glass, are integrated in a polymer package which provides the electrical and fluidic interconnections to the world and provides mechanical strength and protection for out-of-lab use. The demonstrated prototype consists of a molded interconnection device (MID), a silicon-based giant magneto-resistive (GMR) biosensor chip, a flex and a polymer fluidic part with integrated tubing. The various processes are compatible with mass manufacturing and run at a high yield. The devices show a reliable electrical interconnection between the sensor chip and readout electronics during extended wet operation. Sandwich immunoassays were carried out in the cartridges with surface functionalized sensor chips. Biological response curves were determined for different concentrations of parathyroid hormone (PTH) on the packaged biosensor, which demonstrates the functionality and biocompatibility of the devices. The new packaging concept provides a platform for easy further integration of electrical and fluidic functions, as for instance required for integrated molecular diagnostic devices in cost-effective mass manufacturing.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

During the past years rapid progress has been made in the development of integrated microfluidic sensors for the detection of specific bio-molecules, such as DNA or proteins [1–3]. Such sensors are of great importance in the fields of diagnostics for healthcare and safety [4–6]. In these applications fast response, high sensitivity and robustness are required. This is particularly challenging since the concentrations of target molecules can be extremely low. A frequently used approach is to up-concentrate the target molecules at the sensor surface by binding them to capture molecules, such as oligo-nucleotides and antibodies, which are immobilized at the pertinent sensor surface. The detection can be based on a change of the local surface properties by the presence of the target molecules themselves (label free) or by

the presence of a label, which is attached to the target molecule. Generally, label approaches achieve a higher sensitivity than label-free methods, since the label properties can be optimized for the employed detection technology. Various optical, (di-)electrical, mechanical and electromagnetic effects have been proposed for sensitive detection [7]. Certain detection principles require substrates with specific electrical, chemical and/or optical properties. Here we make use of a giant magneto resistive (GMR) sensor [8–11], which detects the presence of super-paramagnetic bead labels. The labels are spheres of typically 200–500 nm diameter containing nanometer-sized iron-oxide grains and having immobilized capture probes at their surface. The presence of such particles at the surface of the sensor changes the electrical resistance of the GMR layer in the presence of a magnetic field. The resistance change can be detected with a very high accuracy.

So in essence it is an electrical detection principle induced by a magnetic label. A major advantage of magnetic labels is the fact that they can be actuated by magnetic fields which can speed up the total assay time.

In order to carry out a diagnostic test, the sample needs to be brought in contact with the sensor surface. In many cases, several (bio-)chemical reactions need to be carried out before the actual measurement. For robust and easy operation as required for use outside the laboratory, these steps need to be integrated in a single device, such that it can be used by untrained people in the field or at home. This requires the integration of sample ports as well as on-board reagents in the disposable device. The well-established dip stick formats, as for instance used in pregnancy tests, do not facilitate the integration of new types of sensors, or more complex assays. Microfluidic, lab-on-chip or micrototal analysis system (μ TAS) approaches have been proposed for a large variety of analytical applications [12]. Most commonly fluidic channels are created in elastomeric PDMS by casting from a lithographic or micromachined master, which is bonded to the sensor substrate [13, 14]. Such an approach is very convenient for proof of principle studies, but is not attractive for commercial application in diagnostics for several reasons: (i) A large silicon or glass chip is needed because the chip is also used as mechanical support outside the actual functional area of the sensor. (ii) PDMS is expensive from a material cost and processing point of view and (iii) the electrical interconnection of the sensor chip to the instrument is insufficiently robust. Currently there is a lack of technology for low-cost, robust integration of sensors in diagnostic disposable devices, which hampers commercial application of new sensing and actuating technology as developed in the academic μ TAS community.

We present a sensor-fluidics integration concept, which is commercially feasible in terms of processing, robustness and costs. This is achieved by an approach which minimizes the surface area of sensor substrate, uses mass manufacturing processing technologies, is scalable and provides a convenient fluidic and electrical interface. Biomolecules are required on board the disposable device for biological assays. Therefore all processing and assembly steps after the reagents application need to be biocompatible. Basically, the module consists of two parts with a flat and accessible interface to facilitate reagent loading and surface treatment steps. The first part contains all electrical functions, such as the sensor, or heating elements if required, including the electrical interface to the control instrument. The second part contains all passive microfluidic channels and the physical interface to the macroworld (sample port). The concept will be described and demonstrated in more detail by the example of a flow-cell immuno-sensor that is used for sensor development. In this paper, we report on the concept, the total technology chain and the performance of the processes as well as the device.

2. Design concept of integrated sensor prototype

For an industrial application, cost considerations are of highest importance. Therefore the various processes must be carried

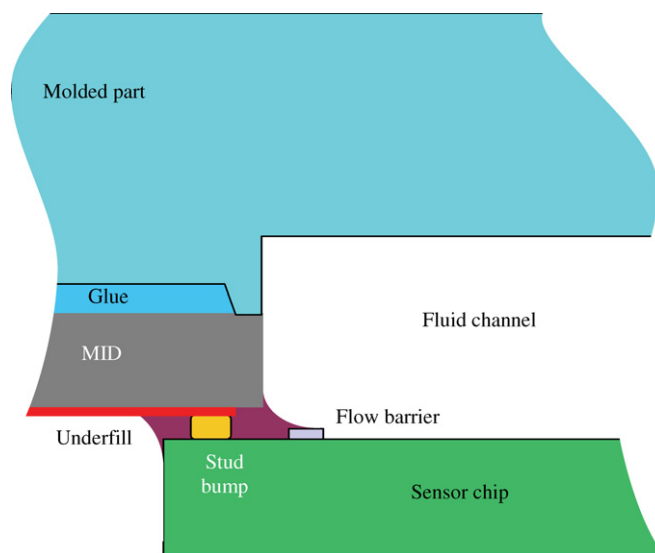


Figure 1. Schematic cross-section of the sensor device in the plane perpendicular to the flow direction of the sample fluid.

out in an efficient way and the order of the various steps is important. The design of the flow-cell sensor is such that assembly efforts are minimized and biological materials are introduced just before the last step, which is the closure of the system. This is done with room temperature processing.

The prototype is an assembly of two major subassemblies, i.e. the electrical and the microfluidic part, respectively. The former is composed of three main components: (a) a silicon biosensor chip, (b) a molded interconnection device (MID) with the electrical interconnection circuitry and (c) the flex foil for connection to the readout electronics. The microfluidic substrate consists of an injection-molded part and tubes for the in- and outlet port, which can be connected to reservoirs and pumps for the testing purposes of this device. The fluid enters through one of the tubes and is then guided through a microfluidic channel, which is formed between the features in the injection-molded part and the MID part. At the position of the silicon sensor, a square opening is provided in the MID with tapered edges in the flow direction to give access to the sensor surface. Copper interconnection tracks run at the backside of the MID up to the edge of the fluid cavity. The biosensor chip is bonded to the MID with the aid of Au stud bumps provided at the periphery for interconnection to the MID. Sealing the gap between the sensor chip and the MID is achieved by applying an underfill resin. To prevent this resin from flowing over the active sensor area, a flow barrier is present at the chip sensor surface. The microfluidic cover is bonded to the MID by a UV-cured resin which is applied in two steps.

In figure 1 a sketch of the cross-section of the assembled device at the position of the sensor in the direction perpendicular to the flow direction is shown. From the cross-sectional view it can be seen how the electrical interconnection is made to the sensor at the same time allowing fluid access. The MID with electrical wiring is placed upside down on the chip on which Au bumps are present. In this way no vias are required on the chip. By making the MID very thin the fluid access to the chip can essentially be in plane with the sensor

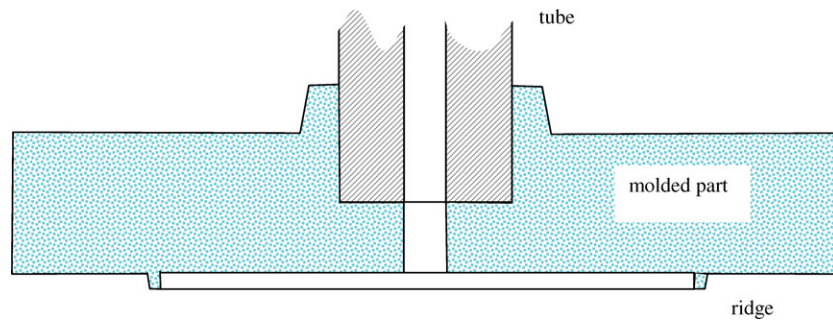


Figure 2. Schematic cross-section of the tube inlet port to the fluidic substrate.

chip. The fluid channel is defined by the sensor surface, the underfill resin pinned by a lithographic stop feature on the chip and the inner cavity on the fluidic part. As can be seen, the channel in the fluidic part is defined by ridges rather than being a recess in the substrate. This serves several purposes: (i) it minimizes the contact area of glue with the fluid in the channel (ii) it reduces the requirements with respect to flatness for injection molding, (iii) the features are independent of the layout which facilitates mastering and replication of the features and (iv) most importantly, it enables dispensing of a defined amount of glue independent of the channel lay out. Glue is applied to the ridges in a dipping process. The part is positioned on the MID and the glue is cured by UV illumination. In a second step, glue is also applied in the gap which is created between the fluidic part and the MID. The glue fills the gap by capillary forces and is cured after complete filling either by UV illumination or is self curing (cyanoacrylate). The fluidic part is slightly larger than the MID for convenient application of glue.

The tubing attached to the fluidic part is encapsulated during molding by the molten plastic and forms a via to the channel at the opposite interface, as sketched in figure 2. The edge of the fluid channel is defined by a ridge in the molded part. This ridge is pressed against the MID during the bonding process, as described above.

3. Manufacturing process

The manufacturing process is a multistep process starting from silicon wafer processing up to the application of the biological reagents and closure of the system. The different steps for the processing of the components and their assembly are described in more detail below.

3.1. Components

3.1.1. Sensor chip. Silicon biosensor chips are manufactured in a clean room on the wafer scale using thin film techniques such as sputtering, photolithography and etching [9]. GMR multilayer stacks are applied and patterned as well as the current carrying wires. Bond pads are Au metalized. Each chip contains 32 interconnect positions (I/Os) at the edge. The chips are provided with a photoresist feature on the wafer level, manufactured by photolithographic patterning of a 15 μm thick SU-8 layer (Micro Resist Technology, Germany).

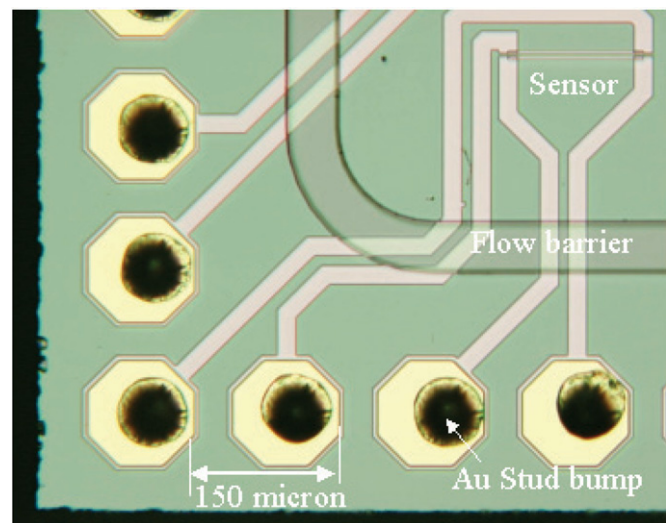


Figure 3. Photograph of a part of the biosensor chip, showing one sensor element, the SU-8 flow barrier feature, and Au stud bumps on the interconnect areas.

In the following step, Au stud bumps are applied on the bond pads. After Ar-plasma cleaning of the wafer in a barrel type reactor (Chemex Plasma Equipment) stud bumps are placed on the bond pads using a wire bonder (Kulicke and Sofa 1484, LXQ Turbo) with a 18 μm thick gold wire.

After stud bumping the wafers are provided with a thick polymer coating to prevent contamination of the sensor surface during dicing. Dicing into individual chips is performed on an adhesive so-called blue tape, using a Disco NBC-Z2040 machine. After dicing, the chips are removed from the tape and the protection coating is stripped in acetone. Finally, the chips are rinsed in iso-propanol and dried in air flow. A photograph of a section of a completed sensor chip is shown in figure 3.

3.1.2. MID. Manufacturing of the MID is done according to the Ultrathin technique [15]. It starts with formation of a Au/Ni/Cu interconnection pattern on a thick copper carrier foil. This is achieved by conventional photolithography and electroplating techniques. Arrays of 21 MIDs are patterned on the carrier foil. The arrays are punched out of the foil, provided with registration holes to facilitate alignment in the molding tool and inserted in the mold. Alignment between carrier foil and mold is important since it determines the position of the

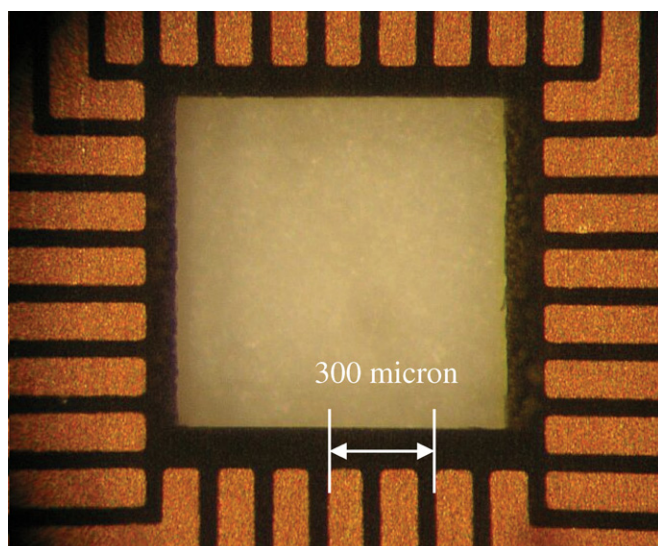


Figure 4. Photograph of the MID showing the copper interconnection pattern around the sensor cavity.

fluid cavity with respect to the interconnection pattern. Epoxy transfer molding is done in a Fico MMS12M molding machine (BESI, NL). 9220HF13 epoxy pellets (Hitachi, J) are used as the molding material. After demolding, the copper carrier foil is completely removed by wet chemical etching. Then the epoxy part is separated into 21 individual MIDs by sawing on the blue tape using a Disco NBC-Z2040 machine. The resulting interconnection pattern around the sensor cavity on a completed MID is shown in figure 4.

3.1.3. Flex. The flexible interconnect foil that connects the MID to the readout electronics is obtained from QPI. It consists of a 100 μm thick polyimide substrate with Cu interconnection tracks. The Cu tracks are protected by solder resist and the contact pads are Au plated.

3.1.4. Microfluidic substrate. The microfluidic part of the prototype is designed to serve sensor development purposes and is not yet meant to be used by customers. To that end, a convenient connection to syringe pumps is realized and the internal microfluidic channel is only a straight interconnection leading over the sensor surface. Short PEEK tubes of 1.6 mm (1/16") outer diameter (Upchurch, UK) are used just to allow convenient coupling with a standard tube connector. To avoid leakage problems or the necessity of gluing, the tubes are encapsulated by the plastic during the molding process. The prefabricated tubes are inserted in the mold on metal pins, where the molten plastic encapsulates the tubes. This leads to a tight sealing and a smooth transition from the tube to the microfluidic channel. The microfluidic channel is defined by ridges. In this way, the bonding process is facilitated. The ridges are replicated from grooves in the mold. The ridges (70 μm high) were machined directly in steel rather than derived from a lithographic master via electroplating. Manufacturing of the microfluidic part is performed by injection molding on an Arburg Allrounder 220-S-205-60

machine, with a clamping force of 60 ton. Cyclo-olefine copolymer Zeonex E48R (Nippon Zeon, Japan) is used. The mold is a one-cavity steel mold with two holders for the tubes. The cavity has a rectangular sprue at one of the short edges of the part. Part thickness is 1.5 mm. The molding conditions were as follows: mold temperature 140 $^{\circ}\text{C}$, melt temperature 270 $^{\circ}\text{C}$, injection rate 2.5 $\text{cm}^3 \text{s}^{-1}$ and packing pressure 500 bar. For the prototype runs, the tubes are inserted in the mold by hand. This leads to a cycle time of about 1 min.

3.2. Assembly

The assembly process starts with ultrasonic bonding of the sensor chip to the MID, which is accomplished in a Toray FC-2000 US bonder. Total bonding time is in the order of 1 s. After chip bonding the gap between the chip and the MID is filled using underfill resin (Namics 8437-2) containing carbon particles. The resin is applied at the edge of the silicon chip and fills the gap by capillary force. The flow stop feature on the chip ensures that the resin does not reach the active sensor surfaces. The underfill polymer is cured for 20 min at 150 $^{\circ}\text{C}$ in a convection oven. Then the flex is attached to the MID. This is performed by thermo-compression bonding on a Weld Equip flex bonder with an anisotropic conductive adhesive foil of Hitachi. Bonding is done for 20 s at a pressure of approximately 10 N mm^{-2} , and at a temperature of 150 $^{\circ}\text{C}$. Finally, the biosensor cartridge is electrically tested using dedicated test equipment and is visually inspected.

At this point the biosensor substrate is ready for biochemical preparation. The current devices contain four or eight individually addressable sensors with an 80 nm thick Au layer on the surface. A self-assembled monolayer (SAM) of a mixture of PEG-alkane-thioles containing carboxyl groups and alkane-thiols is applied from the solution. Each sensor surface is functionalized with a specific capture antibody, by covalent coupling with the aid of the well-known EDC-NHS coupling chemistry [16]. All wet-chemical preparation is done by pipetting solutions on the surface, instead of immersing whole devices in solutions. After application of the biomolecules, the sensor cartridge is closed by joining the fluidic part to the MID part. This process starts with degreasing the injection-molded fluidic part in iso-propanol followed by treatment in UV ozone. A thin layer of UV-curable acrylate mixture (Dymax 136 M) is applied on a wafer by spin coating. The UV resin is then transferred to the ridges of the fluidic part by dipping. After careful alignment with respect to the MID using a Fineplacer (Finetech, FRG), it is bonded by illumination with UV light (365 nm) from a fiber for 1 min. Next a cyano-acrylate adhesive (Loctite 406) is dispensed manually at the edge of the assembled device. Due to capillary forces the adhesive fills up completely the gap between the MID and the fluidic part. The ridge on the fluidic part prevents the adhesive from flowing into the fluid channel before curing. The adhesive is allowed to postcure at room temperature for at least 12 h. The room temperature processing ensures that the biomaterials inside the cartridge remain functional. Alternatively, instead of the cyano-acrylate Dymax 136 M can also be used, which requires UV curing after capillary filling. Finally, the

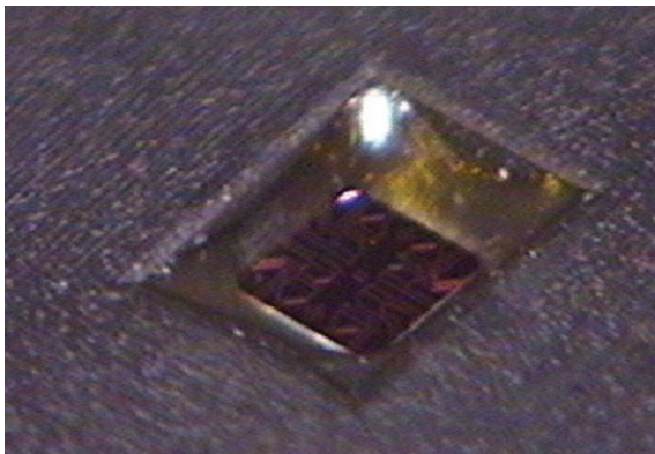


Figure 5. Optical micrograph of the chip mounted on the MID viewed from the top. The underfill resin can be clearly seen covering the slopes of the cavity and not covering the sensor surface.

cartridge is visually inspected and is then ready for functional testing.

As an alternative to this procedure, the flex foil can be designed such that it takes over the function of the MID part. In that case the sensor chip is bonded directly to the flex foil which contains a laser-cut opening at the chip position. The fluidic substrate is bonded to the flex foil after the appropriate surface treatments.

4. Results

4.1. Device processing

A critical element in the assembly is the alignment of the chip with the electrical interconnects because of the small pitch

and at the same time aligning the stop feature for the underfill with the aperture of the MID part. The latter is defined by the molding operation, while the former is determined in the aligner for the ultrasonic bonding. From the optical micrograph in figure 5, it can be seen that the sensor structure is aligned well with the cavity of the MID. The picture also shows that the underfill resin effectively fills up the gap between the sensor chip and the MID and rounds off the sharp transition to enable an undisturbed flow of the fluid over the sensor surface. No underfill polymer has flowed into the active sensor area, so the SU-8 ring acts as a good flow barrier for the underfill resin. In figure 6, a machined cross-section is shown an assembled device, which very much resembles the schematic cross-section depicted in figure 1. In the zoomed-in section, one can identify the MID resin from the large and polydisperse spherical filler particles, differing from the much smaller particles in the underfill and the unfilled SU-8 ring. The image also shows the Au stud bump and the interconnection track on the MID.

After careful optimization of the process settings for chip bonding, a good electrical interconnection between the sensor chip and the readout electronics was obtained, with a nearly 100% yield for all 32 I/Os. Endurance testing (24 h at 85 °C/85% RH, and 1 h in boiling water) revealed no degradation of electrical interconnection and no leakage of the fluidic channel. This is important for applications, such as DNA amplification reactions, where cyclic heating is required.

Critical to the quality of the injection-molded part are the sealing of the tubing, the complete filling of the ridge and the flatness of the part. A photograph of the injection-molded fluidic cover is shown in figure 7. With the optimized settings, the molding process gives a practically 100% yield. The pull-out force of the tubes from the plastic is too high to pull out by hand. This is sufficient for the application. The channels

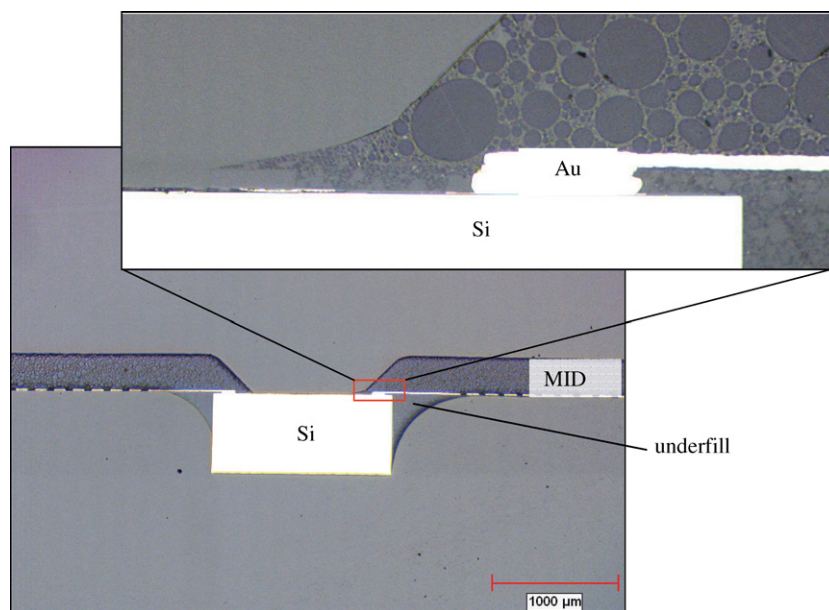


Figure 6. Optical micrograph of polished cross-section of the assembled biosensor substrate cast in epoxy resin.

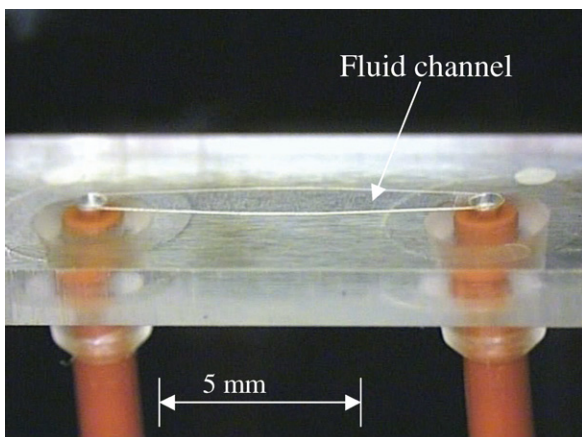


Figure 7. Photograph of injection-molded fluidics substrate with insert molded tubing, viewed from the channel side. The ridge defining the channel is clearly visible.

are always open, and the ridge, which defines the microfluidic channel, is replicated well. The flatness of the ridge is within $5\ \mu\text{m}$, which is important for the gluing step.

The biosensor cartridge with the fluidic part attached is shown in figure 8. This flow-cell cartridge is used as the device for the development of bio-molecular assays. The same technology can be used to fabricate a cartridge that has a form-factor which is more suited for a product.

4.2. Device performance

For a proper functioning of the biosensor the sample fluid needs to be guided smoothly and reliably over the sensor surface. No chemical interference from any of the materials which are in contact with the sample and reagents may occur with the assay. The biomolecules, in this case antibodies, must be functional for binding of target molecules and, last but not least, the sensor must not be deteriorated by chemical or electrochemical interferences. To verify the performance of the packaged sensors, measurements were conducted in which the sensitivity of the GMR sensor to super-paramagnetic particles was measured. A solution of super-paramagnetic particles with 300 nm diameter (Ademtech, France) was applied to a cartridge without a fluidics part. The particles were allowed to sediment toward the sensor surface, and the sensor signal was recorded with a home built electronic board, while observing the sensor surface through a microscope. A linear relation between the sensor signal and the bead coverage was observed over a broad range as described elsewhere [17].

Immunoassays were performed in the assembled cartridges to validate liquid tightness and the biocompatibility of the integrated device. As an example a sandwich assay was performed by first injecting a solution of parathyroid hormone (PTH) and biotinylated anti-PTH polyclonal antibody into the device with the aid of a syringe and incubating for 60 min. (All reagents are commercially available as part of the STAT platform from Future Diagnostics, NL) Then a PBS-buffered solution of streptavidin-functionalized magnetic

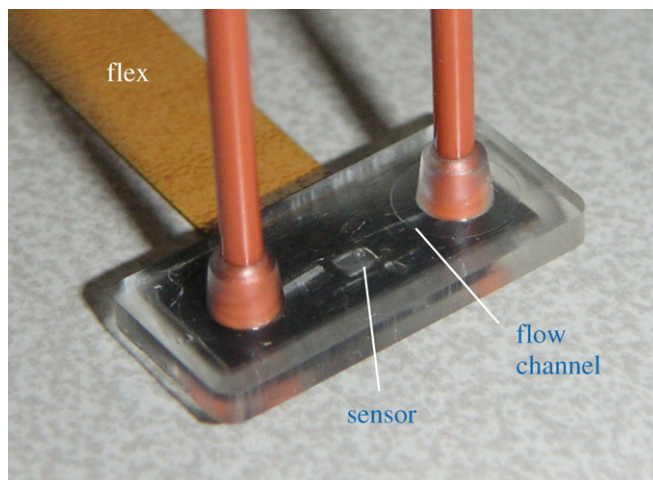


Figure 8. Photograph of a completed flow-cell biosensor cartridge.

beads (0.1%w/w, 200 nm Ademtech, France) was pumped over the sensor surface with the aid of a syringe pump (Harvard, UK) at a rate of $190\ \mu\text{l}\ \text{min}^{-1}$ until the channel was completely filled. The resulting increase of the sensor signal with time was recorded with the stagnant liquid. A typical result is depicted in figure 9. As can be seen, the kinetics of binding can be followed in real time. From the response, it can be inferred that the signal increase is proportional to the concentration of PTH during the incubation step. At $t = 0$ a small signal drop is observed which can be explained by a small temperature change at the moment the solution touches the sensor surface. These results should merely demonstrate the functional performance of the integrated device and do not represent the sensitivity of the assay, since neither the assay conditions nor the actuation of the magnetic beads was optimized. From a device packaging point of view, it is important to see that the signal responds immediately as soon as the liquid contacts the sensor surface and is stable for long periods. The drift of the signal in the case of zero PTH concentration is due to the electronic drift of the readout electronics and is not related to the device packaging. Every curve in figure 9 was obtained with a different device. The cavity was filled completely in all cases without air inclusions.

From these results, it can be concluded that the packaging technology presented here enables immunosensing in a compact, robust way. No problems with non-specific adsorption of biomolecules and magnetic beads were encountered. The capture probes at the sensor surface remained functional during processing of the device. In particular, the bonding with UV-curing is a potential source of problems, since both cyano-acrylate as well as UV light can affect the biofunctionality. By the two-step process and limited UV dose, we were able to avoid these.

The concept can be extended to other kinds of microfluidic sensors which require the combination of an inorganic substrate with an electrical interconnection and a fluid sample which needs to be introduced in a convenient way. It is especially suited for rugged use and for single use applications,

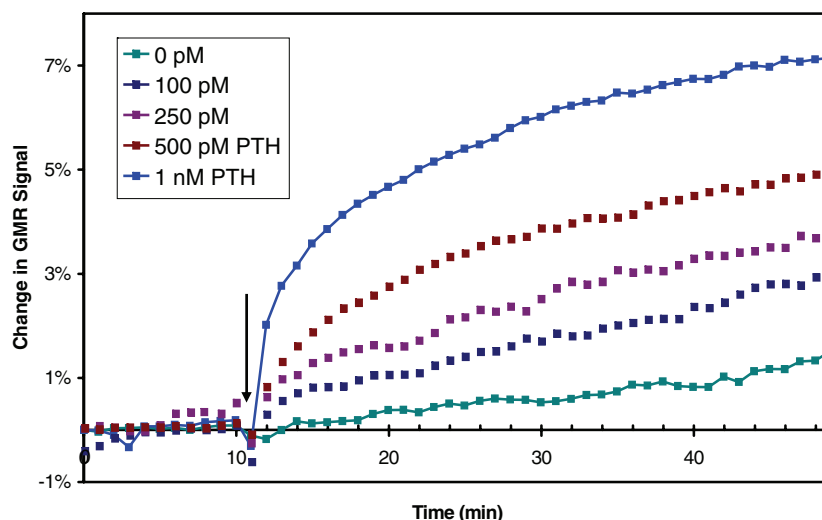


Figure 9. Sensor response during incubation with a solution of streptavidinated beads of 200 nm diameter. The different curves represent different pre-incubations of the sensor with solutions of PTH and anti-PTH. The concentration of PTH is indicated in the graph. The bead solution is injected at the time point indicated by the arrow.

such as blood testing, where the device is used only once for safety reasons.

5. Conclusions

We describe an industrial concept for the integration of small sized silicon-based biosensor chips into a microfluidic disposable package. In this approach the size of functional substrates is minimized to reduce cost. The inorganic substrate is incorporated in a plastic environment to enable convenient interfacing with the macroworld. Electrical and fluidic interfaces to the active sensor surface are combined without the need for vias and wirebonds.

The package was proven to be feasible and robust in manufacturing and use. Electrical testing of the interconnection between the sensor chip and the readout electronics showed nearly 100% yield. Temperature and humidity tests revealed no degradation of the interconnection.

Sandwich immunoassays were performed successfully on the integrated devices with magnetic bead labels demonstrating the functionality of the electrical sensor as well as the compatibility with biomolecular reagents.

By combining molded plastic with silicon and electrical interconnects, an optimum balance is achieved between flexibility, performance and cost. The latter is of great importance to open up commercial application of microfluidic sensing devices in medical diagnostics.

The technology can be applied to a wide range of device architectures wherever electrical and microfluidic interconnections need to be combined.

Acknowledgments

The authors would like to acknowledge many colleagues, who have contributed to this work in various ways, in particular

Mrs E Janssen, M Olde Riekerink, A van der Lugt, J Nieuwenhuis, J van Eemeren and P Lemmens,.

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