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Industrialized microfluidic cartridges with photonic chips

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Summary:

Integrating Photonic-Integrated Circuits (PICs) into microfluidic devices for diagnostics faces several challenges such as handling small PICs, ensuring interface access, managing temperature and UV sensitive coatings, and maintaining bubble-free sample transfer. CSEM offers unique services merging cleanroom packaging, microfluidic design, and prototyping, aiding PIC and diagnostics industry partners. Collaborations with different partners have led to tailored PIC integration solutions for sepsis detection, bioreactor contamination detection, food safety testing, and extracellular vesicle detection.

Keywords: hybrid PIC, microfluidic cartridge, chip integration, assembly, high volume production

Introduction

The integration of Photonic-Integrated Circuits (PICs) into microfluidic devices has wide ranging applications in the field of diagnostics. However, the requirements for the integration of PICs into microfluidics can vary significantly depending on the design and application of the PIC. For example, difficulties with handling due to the small size of PICs, the accessibility of optical and/or electrical interfaces, temperature and UV sensitive coatings, and bubble-free sample transfer are all challenges that are faced in microfluidic PIC integration. To aid our partners in the PIC and diagnostics industry, CSEM provides a unique combination of services by leveraging our in-house cleanroom packaging technologies and expertise with our microfluidic prototyping capabilities that are compatible with mass production.

CSEM has successfully collaborated with numerous partners on various integration solutions for PICs used for diagnostics, sepsis detection, contamination detection in bioreactors, food safety, as well as detection and counting of extracellular vesicles. Often, these solutions are specifically designed for passive or hybrid PICs, which may or may not have integrated light sources and photo detectors. Additionally, after several years of development, CSEM has developed a process for packaging small PICs (around 10 mm^2), allowing our partners to drastically reduce costs up to 10-fold, and significantly increase their market competitiveness.

Finally, CSEM has developed innovative solutions for in-line degassing, on-cartridge heating, and on-cartridge liquid storages.

Challenges

Chip geometry - Every customer uses a different PIC as outline in Figure 1. They have either been used for research purposes or towards a diagnostic disposable product.

Figure 1. (1) Bialoom PIC on stage – size 25mm x 25mm; (2) PHOTO-SENS PIC with VCSEL, photodiodes and NTC thermistor on chip – PIC size 3mm x 5 mm.

Reusable or low-cost fluidics - During the development phase, our customers often prefer to work with a reusable microfluidic solution while in the final application a disposable solution is inevitable. CSEM has therefore developed different PIC integration methods as outlined in Figure 2.

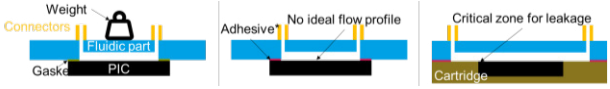

Figure 2. PIC integration methods. (left) sandwiching with a gasket, (middle) double adhesive bonding, (right) in-cartridge integration (not necessarily a PCB, also plastic substrate possible).

High sensitivity by preventing fouling - To prevent the loss of analytes from the sample reservoir to the detection site an antifouling surface is required. We have successfully applied

several different coatings from CSEM Optodex B, CSEM blocking agent but also Surfix's Coat & Close process. However, these coatings require solvent cleaning and plasma activation steps.

No air bubbles on sensor allowed - Depending on the PIC technology and measurement procedure, air bubbles passing the sensor might be detrimental to the measurement. For this reason, we have developed a miniaturized degassing solution. A degassing membrane is integrated inline with the fluidic channel which allows for efficient degassing.

UV-sensitive bio-functionalization - Depending on the application (such as sepsis detection, food safety and others), the sensing areas of the PICs have to be bio-functionalized with the appropriate receptor such as an antibody or aptamer. To ensure the highest sensitivity, these receptors need to be locally deposited on the sensing element. Examples will be shown.

Continuous and non-pulsating flow with preloaded liquids - CSEM has developed different ways to store and deliver liquids. In the project BIOCDx, liquids were stored in pre-filled syringe-like structures. In the project PHOTO-SENS, an alternative approach used pre-filled blisters. Emptying these blisters, however, results in a very high flow variability. To minimize this variability, we integrated an intermediate reservoir in the shape of a meander in which the volume of the blister can be emptied before being transferred to the PIC in a controlled way for priming, calibration, and washing.

Implementation example

In the project BIOCDx the goal was to detect protein signatures indicative of breast or prostate cancer for companion diagnostics. Lionix provided PICs (10mm x 10mm = 100mm^2) preassembled with a VCSEL and two arrays of 4 photodiodes which were encapsulated to protect the active components during the functionalization and spotting process. The PIC was bonded with a double adhesive tape onto a PCB from where wire bonds were made, and glop topped. This assembly was then bonded with a double adhesive onto the fluidic channel. The syringes are pre-filled and use a sacrificial valve to minimize the evaporation. Furthermore, the cartridge contains a blood separation membrane and on-cartridge valves to control the processes. In Figure 3 the cartridge is shown in the assembled state.

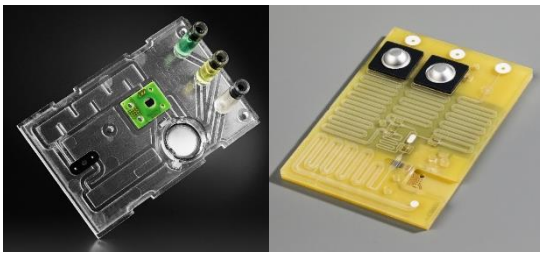

Figure 3. Photographs of the cartridges developed for (left) BIOCDx (right) PHOTO-SENS.

In the project PHOTO-SENS (www.photo-sens.eu) the goal was to detect pathogens in aquacultures to minimize the amount of antibiotics used. Surfix provided PICs (3mm x 5mm = 15 mm^2) which have been assembled with VCSEL, two arrays of 4 photodiodes and an NTC by PHIX (see figure 1 (images 2)). The cartridge designed by CSEM features a PCB bottom part and COC fluidic lid, which have both been anti-fouling coated by Surfix. Before encapsulation by CSEM, the hybrid PIC was placed flush to the PCB surface, and conductive glue was locally applied on the backside of the PIC for electrical contact with the on-chip heater. The fluidic lid was equipped with a double adhesive tape and blisters and sent to Surfix for bio-functionalization. In a final step, the lid was placed onto the PCB and a compression force was used to activate the adhesive.

The cartridge was then placed into the measurement instrument developed by LRE medical. where the cartridge is positioned, and the blisters are compressed to initiate fluid flow.

Summary and Conclusion

So far with every new PIC a different use case (e.g. sepsis detection, contamination detection in bio reactors, food safety, detection and counting of extra cellular vesicles, pathogen detection in aquacultures, cancer detection) was addressed, which resulted in a different microfluidic cartridge design and assembly strategy. Specific building blocks such as heaters, liquid reservoirs, sample injection, metering, flow front detection, degassing, and sample preparation have been developed alongside different PIC integration strategies. Currently, these different blocks can be combined to fulfill unique requirements for new use cases. A strong focus is always put on the compatibility with mass producible strategies (design for manufacturability) to ensure seamless technology transfer.

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