Sensor integration

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Integration of functions, as well as of materials and components, is one of the main hot topics within microfluidics manufacturing. The call for autonomously operating labs on chips, in particular for in vitro diagnostics and point-of-care applications, is heavily depending on innovative integration solutions to achieve the shift of complexity from external handling steps to the microfluidic platform.

Integration of sensing elements

There is an abundance of sensors that could be incorporated on-chip. At Micronit, we mainly focus on optical sensing, temperature sensing and voltage/ current sensing.

Optical sensing

On-chip integration of semiconductor light sensors allow the readout of colorimetric or fluorescent immunoassays.

Temperature sensing

By using thermistors/thin film resistors (differences in) temperature can be observed. Often this is performed in combination with heating or cooling elements, for example in PCR assays.

Voltage/current sensing

Thin/thick film conductors can be integrated on chip for electrical impedance measurement. This is used in

- electrical impedance spectroscopy chips, that are designed for electrical characterization and counting of droplets, cells or particles
- capillary electrophoresis chips, that make use of an electric field to separate molecules according to size and charge.

Or capacitively coupled contactless conductivity detection: electrodes are placed on the outside of a chip, with only a thin layer of a dielectric between the electrode and the solution.

Goals of sensor integration

The goals of sensor integration into microfluidic systems are:

- Enhance performance or add functionality
- Allow miniaturization
- Simplify external hardware

To put it simple: by increasing the on-chip functionality, you concentrate complexity and move it away from peripheral surroundings, like the external system or separate handling steps. Two trends in health care in particular ask for an increase of on-chip functionality: decentralization and personalization.

Trend 1: Decentralization of health care

Diagnostics are moving from centralized labs, via point-of-care into the patients' home. From robotized large scale processing to a diagnostics test that can be performed by the patient him- or herself. Decentralization of health care asks for greater simplicity and ease of use of diagnostics tools.

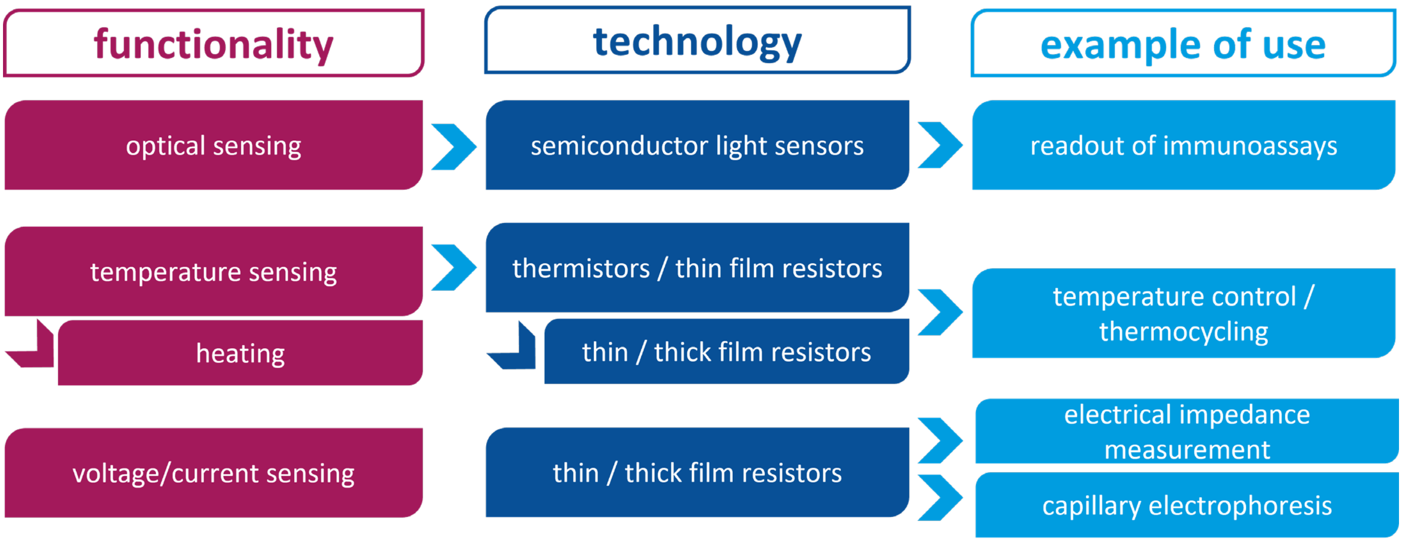
Trend 2: Personalization of health care

Personalized medicine focuses on offering the right treatment to the right patients at the right time. This trend is based on adjusting treatment to personalized measurements and needs, which can only be realized when testing and drug administration can be performed and adjusted on-the-spot.

Both trends link to an increase in tests throughout the whole patient care cycle (diagnostics, prognostics, therapy monitoring). These point-of-care test products should be easy to handle (without the need to perform any off-chip handling steps), which can only be achieved by adding complexity on-chip.

When incorporating sensors into the consumable, smart choices need to be made with regard to manufacturability and costs. The use of sensors can have large measurement advantages, it simplifies instruments and off-chip interfacing and offers great ease-of-use. It does however heavily rely on the availability of affordable sensors and on the volumes that need to be produced. Overall, one would need medium to large volumes to make the consumables cost effective.

From a centralized lab... **via point-of-care...** **to the patient's home**



Microfluidics and CMOS integration

Traditionally, on-chip sensing elements were relatively simple, like electrodes or color changing dots. Nowadays, more complicated sensing elements like CMOS based sensors are included. We refer to the addition of such elements as 'sensor integration'. CMOS image sensors (electrical and optical) are semi-conductor based, and typically use off-chip signal processing. They are increasingly used in several areas of microfluidics, including DNA sequencing, point-of-care testing and-organ-on-a-chip. Combining fluidic and integrated circuit elements into one system can be challenging, however. These platforms can be created for instance by manufacturing a microfluidic layer on top of a sensing element (CMOS meets microfluidics). In such a system, a microfluidic structure controls the flow to create the optimal measurement conditions for the sensor.

CMOS-based genomics

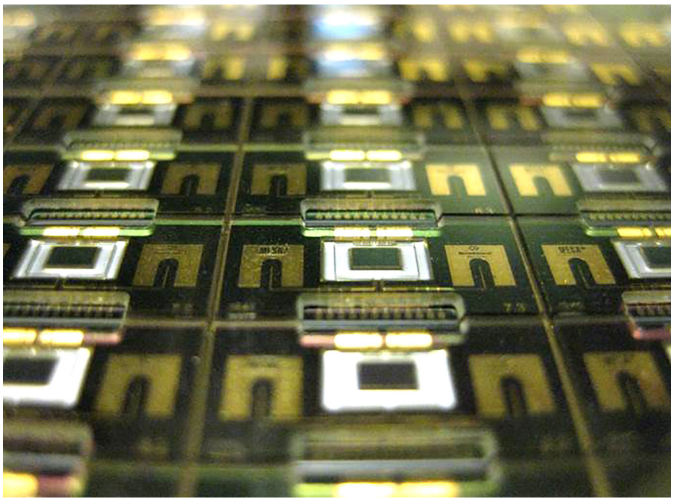
Although the overall microfluidics market calls for an increase of on-chip functionality, the genomics market in particular evolves towards applications that benefit from the microfluidics-CMOS combination.

DNA sequencing

In the DNA sequencing market, a considerable increase in hybrid flow cells (glass/silicon) can be observed. For instance CMOS-based sequencing flow cells and nanoimprinted patterned flow cells. Traditionally, Next Generation Sequencing instruments are relatively expensive, which limits the install base. To simplify the instrument, intelligence is moved from the instrument to the sequencing chip (consumable), using CMOS based sequencing. The cost of good for the consumable will increase, but the simplified instrument will require substantial lower initial investments. This will significantly improve the accessibility of DNA sequencing technology to a larger customer base. These consumables with integrated functions answer to the call for higher data output and respond to the trend of sequencing moving towards diagnostics.

DNA synthesis

Traditionally, oligonucleotide synthesis (a process to create synthetic DNA) was performed on enormous machines that were placed in specialy conditioned environments. By use of CMOS technology, large arrays of valves and tubes can be reduced to a single chip which combines microfluidics and CMOS technology. Just like in the sequencing process, in DNA synthesis too moving complexity towards the consumable leads to lower instrument costs and a smaller instrument footprint.



CMOS-based sensors.

CMOS-fluidics processing

Which materials are used as a basis for these platforms with increased functionality? And which manufacturing techniques are needed for the integration of the different elements? Let's take a look at a couple of processes we often perform at Micronit. In all cases, a silicon wafer (CMOS device wafer) is used as the basic platform to add functionalities on.

Creating a CMOS-fluidics platform

To enable the full power of sensor integration in lab-on-chips, we strive for CMOS-fluidics integration. There are a few possibilities to achieve this:

- Add CMOS dies by using pick-and-place into a larger fluidic carrier.
- Create a silicon-glass hybrid product using anodic bonding (no additional adhesives needed).
- Create a temporary fluidic cover on top of a CMOS sensor using a resealable lid.
- Attach a fluidic layer on top of the CMOS sensor.

CMOS post-processing

CMOS fabs use a well-defined set of processing steps. However, for complex integrations often additional layers on top of this standard CMOS wafer are required. At Micronit, we have applied additional metallization or permanent photoresist on top of CMOS wafers. We are also able to anodically bond microfabricated glass wafers onto CMOS wafers, to add for instance waveguides. We collaborate with strategic partners that are able to finish the CMOS wafers in functional and tested dies, assembled on printed circuit boards or other carriers.

Showcases of sensor integration

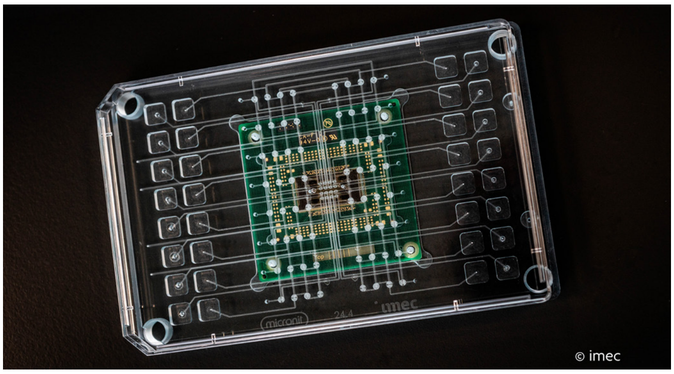
Are you curious for the practical use of sensor integration? Let's take a look at a selection of products that Micronit has contributed to.

Showcase 1: Take the lab to the home

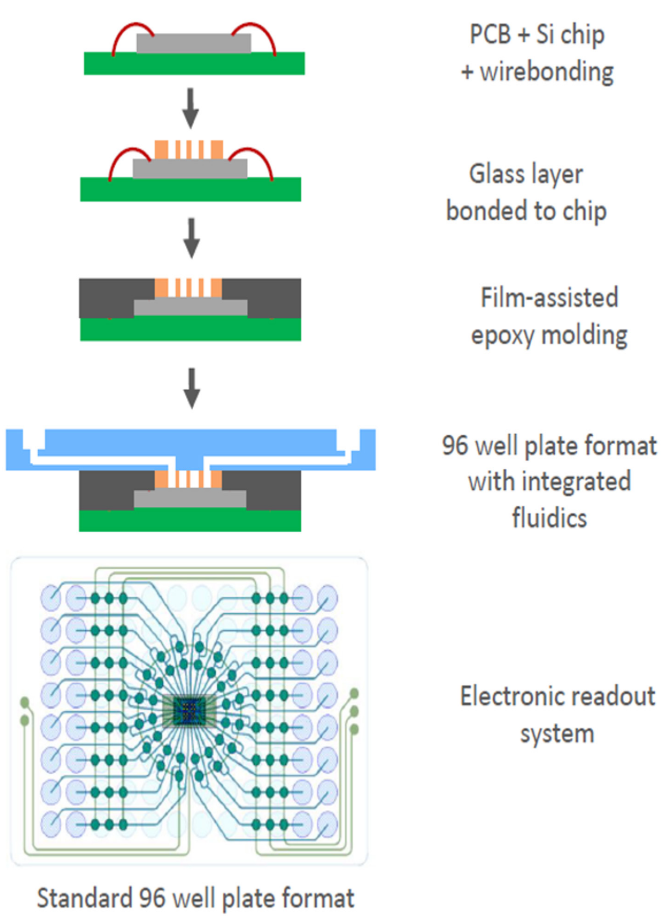
In a collaborative project between Janssen Diagnostics, NXP Semiconductors and Micronit, a microfluidics-based diagnostic device was developed by mounting a CMOS sensor on a microfluidic flow cell equipped with electrical traces. This stand-alone device is used for the detection of (low concentrations of) biomarkers and is a typical point of care product that was designed to be used outside of medical environments.

Showcase 2: Organ-on-chip platform

Collaborating with imec, R&D hub for nano- and digital technologies, Micronit created a CMOS meets fluidics cell culture platform. This device consists of a microfluidic well plate, combined with a high density multi-electrode array (MEA) chip. Cell material can be grown in the 16 cavities in the well plate. The chip handles signal processing and analog-to-digital conversion. It has 1,024 electrodes for each of the 16 microfluidic wells (for a total of 16,384 electrodes). Each of the 16 wells can be individually assessed, so multiple tests can be performed in parallel.



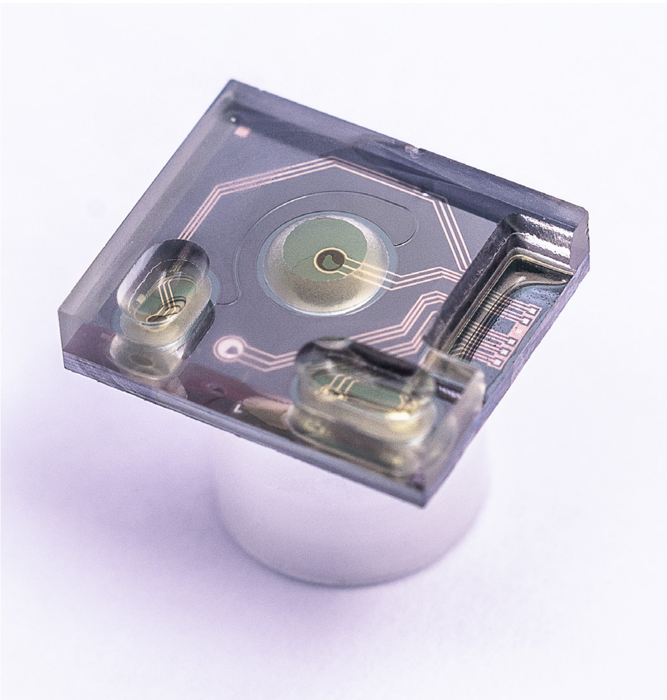
Multi-electrode array organ-on-chip platform.



Production steps of the organ-on-chip platform.

Showcase 3: Chips for water quality monitoring

In order to analyze the quality of water, Micronit and imec developed a glass-silicon hybrid sensor chip. The chip consists of a silicon base with ion sensitive electrodes. On top of this, two layers of glass have been manufactured. The middle layer contains a cavity, which forms a well, and the top layer holds two inlets for the water to enter the chip. The ions that can be measured with this chip include chloride, sodium, nitrate, and calcium as well as pH. By massive use of these consumables, a dense sensor network for real-time water quality monitoring is to be created in Flanders: the Internet of Water.



Water quality monitoring with a microfluidic chip.

Conclusion

By the incorporation of on-chip sensing elements, reliable test platforms can be created that provide immediate insight into the performed measurements. Miniaturization and the possibility to perform complex functions on-chip lead to greater ease of use, so that these devices can also be used at a patient's home or even spread around a wider area as is done in the Internet of Water project. The digital data output lends itself for remote processing and assessment. In this way, a valuable combination of on-the-spot measurements combined with central data interpretation and indication can be achieved.

Pieter-Jan Kwant

Product Manager
Sensor integration expert

In 2013 Pieter-Jan Kwant joined Micronit as an Account Manager and today he holds the position of Product Manager. In this role, he is a key figure between engineering and sales. Pieter-Jan completed his Master's Degree in Mechanical Engineering at the University of Twente in 2008 and then held several consultative and engineering postitions at tech driven companies. Within Micronit Pieter-Jan is the point of contact for customer solutions and prototyping and he is responsible for the range of catalogue products.

About Micronit

Micronit bv, founded in 1999, with development and manufacturing facilities in the Netherlands and Germany, provides innovative lab-on-a-chip and MEMS solutions using micro- and nanotechnologies. Solutions that help customers improve their products and research, contributing to the quality of life.

Micronit is ISO 9001 and ISO 13485 certified.

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