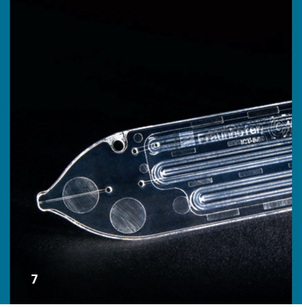
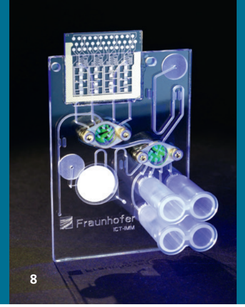
7 *Detection and dispensing of single circulating tumor cells*
8 *Breast cancer detection out of whole blood*





APPLICATION EXAMPLES

Single cell detection and dispensing

The realized cartridge for detection and dispensing of circulating tumor cells (CTCs) is a proprietary consumable for a fully automated single cell dispensing instrument. The instrument starts out with a 7.5 ml whole blood sample, a so-called "liquid biopsy", extracts all CTCs and dispenses each CTC individually into the wells of a standard microtiter plate. The CTCs are then ready for downstream single cell analysis, e.g., with next generation sequencing, to study tumor biology and ultimately to monitor therapy success. The cartridge was optimized for low-cost fabrication as it only requires one injection molded core and two cover foils to close the microfluidic structures and to form two built-in microvalves. Crucial features for the application are the surface quality in the microchannel for optical cell detection and in the dispensing port which needs to be appropriate for single cell dispensing.

Breast cancer detection from whole blood

This chip is an example of an electrochemical assay realized on a microfluidic polymer chip. Whole blood as sample is introduced into the system. Blood plasma is separated by a membrane, diluted and distributed to different channels of an electrochemical sensor array via a turning valve. With the liquid reagents stored on chip, an ELISA assay is executed and the resulting signal is calibrated by a low / high calibrator also integrated on-chip.

Amplification and detection of circulating tumor cell RNA on chip

Here, we give an example for on-chip integration of a multistep PCR followed by an electrochemical detection using high / low calibration. A lysed sample of circulating tumor cells is amplified by a variant of the polymerase chain reaction called multiplex ligation-dependent probe amplification (MLPA). This process requires four PCR steps (reverse transcription, hybridization, ligation and final PCR). The PCR reagents are stored freeze-dried on chip. After amplification the sample is diluted and spread over an integrated electrochemical sensor for verification.

FIELDS OF APPLICATION

- Biological analysis
- Medical technologies
- Water analysis
- Oil monitoring
- Food quality control
- Ion analysis
- Industry 4.0
- Polymer waveguides

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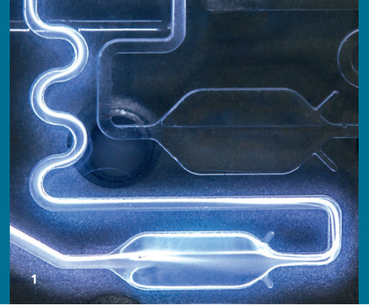
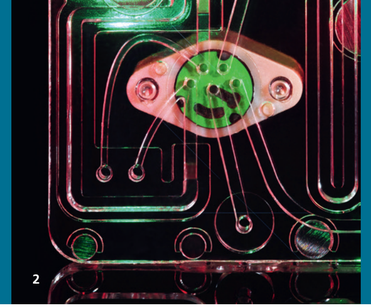
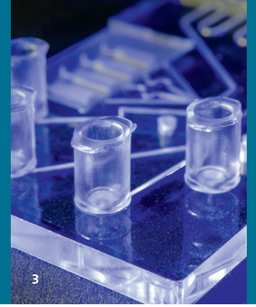
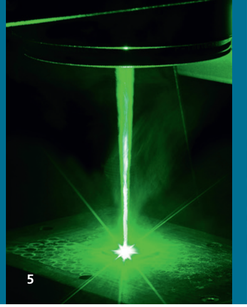
POLYMER MICROMACHINING AND PROCESSING

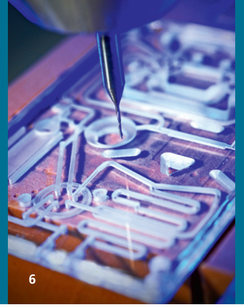






1 Plasma in microchannel for surface modification
2 On-chip turning valve for liquid manipulation
3 Ultra-sonic welded Luer interface
4 Composite foil pouches for liquid storage
5 Laser ablation with ND:YAG Laser
6 Precision milling of micro-fluidic chip





FUNCTIONS IN POLYMER

Fluid handling

Today, it is well known that the transfer of (bio-) chemical standard assays into disposable microfluidic polymer cartridges facilitates a considerable reduction of precious chemicals and resulting wastes as well. Furthermore, the option to employ highly efficient microfluidic mixing strategies for reagents and samples together with accelerated heat transfer in small volumes opens the advantage of significantly reduced processing time.

IMM possesses long-time knowledge in liquid sample handling in custom developed microfluidic cartridges of various polymer materials, allowing metering, splitting, merging, mixing, aliquoting and spotting of a wide variety of chemical agents, bio-reagents and cell dispersions as well. The related polymer devices may integrate different types of valves as well as pumping functions. This together with our expertise in design and numerical simulation of polymer-based microfluidic cartridge systems makes IMM the one-stop-shop for microfluidic handling systems.

Medium storage

A vital issue for integrated microfluidic analysis systems is how to store the required media such as liquid or dry chemical/biological reagents prior to and after the analysis. Most commonly used methods are storage directly on-chip or storage within the instrument, e.g. in bottles. However, some sophisticated applications demand more elaborate methods. We have for instance established a novel technique which enables reagent storage in chip compatible compartments instead of storing them directly on the chip. This allows decoupling of the freeze drying process from the chip manufacturing itself. In addition, for applications where very robust and/or light weight fluid reservoirs are required (e.g. in space applications) we have developed special composite foil pouches. These pouches can be manufactured in almost any size and shape and efficiently help to minimize evaporation losses making them particularly well suited for applications which require extended storage times.

Surface modification and coating

Modification of the surface properties of polymers such as hydrophilicity, hydrophobicity or the ability to specifically bind certain marker species plays an important role in microfluidics. Here, IMM has a variety of processes available to render polymer surface properties either by means of chemical or mechanical surface modification or by coatings. These e.g. can be used to manipulate fluids without valves or pumps. Through immobilization of capture agents like aptamers or antibodies we can realize specific biosensors in microchannels.

Sensor integration

IMM has also long-time experience in design and realization of custom solutions in analytical microsystems. This starts with the direct on-chip integration of passive micro-optical features like gratings, mirrors and wave guides into transparent polymer materials which e.g. provide the coupling with external non-disposable optical components such as light sources and detectors located in the operating unit. It concludes with our capabilities to integrate electrochemical sensors e.g. realized by screen-printing on foils or by thin film technology on silicon or glass dies.

Laser structuring

Different laser processes are available at IMM for structuring a variety of polymer materials. An excimer laser is employed for precise mask-based ablation in the fabrication of microfluidic channels down to a size of 5 µm with low surface roughness in the range of 100 nm. Using this technique, even optical elements of high quality like waveguides or Fresnel lenses can be fabricated. The same technology can also be applied to functionalize polymer surfaces e.g. with strip lines by selective ablation of thin metal films. For the realization of microfluidic interconnects through thin cover foils a CO_2-Laser is applied. The device can also be used for cutting of polymer substrates up to a thickness of 3 mm or to drill holes down to a diameter of 30 µm.

Polymer joining technologies

The availability of appropriate joining techniques is of crucial importance for tight and reliable sealing of microfluidic structures with cover lids and on-chip integration of further components such as e.g. fluid connectors, valves and reservoirs. IMM's expertise comprises dedicated joining processes for a variety of different polymer materials. These include e.g. ultra-sonic welding, thermal laser welding, lamination, gluing and chemically or plasma activated bonding which allow to achieve bond strengths that can withstand up to several bars of pressure. With UV enhanced thermal bonding we are for instance able to cover 10 microns deep and 500 microns wide channels. A technique employing structured double side sticky tape for joining chips or integration of sensors is also available.

FUNCTIONS ACHIEVED

- Metering
- Splitting
- Mixing
- Aliquotation
- PCR on-chip
- Cell culturing on-chip
- Electrochemical sensing
- Optical sensing
- Dry and wet reagent storage on-chip
- Positive and negative enrichment
- Cell lysis and purification on-chip
- Polymer optical waveguides

FABRICATION TECHNOLOGIES: FROM SINGLE PIECES TO SMALL BATCH SERIES

Testing and validating new ideas

Apart from direct cutting in polymer substrates via milling or laser machining for realization of prototypes on small scale we also offer manufacturing of microfluidic polymer devices by hot embossing or injection molding with in-house made, custom designed tools and mold inserts. With hot embossing we for instance can realize optical waveguide structures of high quality using a hot embossing tool made by precision milling. Mold inserts for injection molding e.g. for fabrication of fluidic channels with a small cross section of 10 microns depth and 500 microns width can be realized at IMM by a dedicated precision milling process in hardened tool steel.

In summary, IMM offers its customers a comprehensive processing platform for the realization of microfluidic polymer devices starting from design and manufacturing of first prototype samples for concept validation up to batch production of pilot series on small and medium scale.

	Milling	Laser ablation	Hot embossing	Injection molding
Smallest structure	100 µm	5 µm	10 µm	50 µm
Precision	± 5 µm	± 1 µm	± 2 µm	± 2 µm
Roughness	100 nm	100 nm	<100 nm	<100 nm
Aspect ratio	5	5	2 – 5	2 – 5

TECHNOLOGY USED

- Milling
- Hot embossing
- Injection molding
- Laser structuring
- Laser welding
- Ultrasonic welding
- Solvent welding
- Capillary gluing