Hybrid microfluidic systems – combining a polymer microfluidic toolbox with biosensors

Claudia Gärtner, Stefanie Kirsch, Birgit Anton, Holger Becker

microfluidic ChipShop GmbH, Carl-Zeiss Promenade 1, D-07745 Jena, Germany

ABSTRACT

In this paper we present polymer based microfluidic chips which contain functional elements (electrodes, biosensors) made out of a different material (metals, silicon, organic semiconductors). These hybrid microfluidic devices allow the integration of additional functionality other than the simple manipulation of liquids in the chip and have been developed as a reaction to the increasing requirement for functional integration in microfluidics.

Keywords: polymer microfluidic chip, hybrid microfluidic chip, microfluidics, biosensors

INTRODUCTION

When microfluidic system first came into existence in the late 1980ies / early 1990ies [1,2], they were fabricated using methods adopted from the manufacturing of microelectronic devices, namely photolithography, wet chemical etching and fusion bonding, as well as the material from this field, namely silicon [3] and glass [4]. In many cases, the devices were manufactured using a single material, a typical example being a microfluidic channel which was etched into a glass plate and sealed with a glass plate, yielding a monolithic glass chip. In recent years, these materials as well as the manufacturing methods described above, have been superseded by the trend to use polymers as a base material for microfluidic devices [5]. The main driver behind this development was the comparative ease of manufacturing of the polymer devices, the use as disposables in the commercial world and the wide range of polymers with a corresponding variety of material parameters available. While most of the early work was done using polymers like poly-methylmetacrylate (PMMA) or poly-carbonate (PC) for more temperature-demanding applications, two trends can be identified in recent times: firstly, novel polymeric material with better properties (optical, chemical, mechanical) are in great demand, namely cyclic-olefin-polymers (COP) or cyclic-olefin-copolymers (COC), secondly, also the need for hybrid devices is becoming noticeable. We use the word “hybrid” as opposed to “monolithic” for a microfluidic device, where for at least one functional aspect of the device another material, different from the primary material, is essential. Examples for this material combination, which we will present in this paper are polymer-metal combinations for e.g. integrated electrodes or reaction areas, the combination of thermoplastic material like PMMA with elastomeric material like PDMS, the combination of thermoplastic polymers with thermoset (epoxy) polymers like polyimide or the combination of polymers with materials from the microelectronic world, namely silicon, glass or ITO. Particularly the last case opens up the road towards the improved use of biosensors, as in most cases the biosensor includes some electronic functions, while the handling of the fluid requires other materials.

POLYMER DEVICES WITH METALLIC STRUCTURES

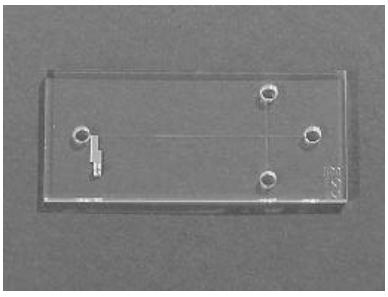

Fig. 1: CE chip with integrated Au electrode

Fig. 2: CE chip with integrated Pt electrode

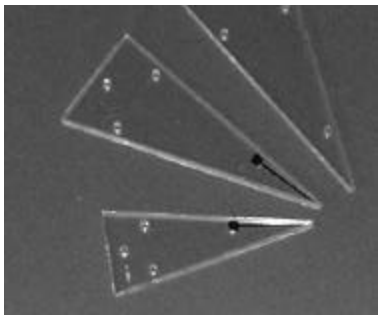

Fig. 3: Chip for CE-MS coupling with Ti/Au electrode

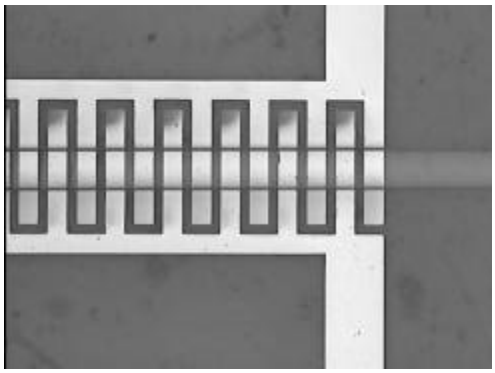

Fig. 4: Microscopic image of a 50 µm wide Pt electrode structure over a microchannel.

Figures 1-3 show various examples of integrated metal electrodes on polymeric substrates. In Fig. 1 and 2, chips made out of PMMA and COC respectively for capillary electrophoresis (CE) with gold electrodes for amperometric detection are shown. In Fig. 3, a chip made out COC with a Ti/Au electrode for the coupling of CE with nanospray-mass spectrometry is shown. In all cases, the polymer chips were manufactured using hot embossing [6] for prototyping and injection molding for higher volume production. The metal structures were manufactured using a shadow-mask technique. In this technique, a mask made out of a thin (typ. 0.2 mm) metal sheet contains open areas where the electrodes are supposed to be on the chip. Typically these structures are cut by a laser into the metal. In an evaporation system (thermally or with an electron-beam) the desired metal is then deposited through this mask onto the chip. The minimum dimensions achievable with this method depend on the accuracy of the mask cutting and are typically of the order of 100 µm. For the design in Fig. 4 an silicon mask was used which was fabricated by dry etching a thin silicon wafer. In this case the structures were below 50 µm. The critical parameter in this process is the temperature control of the polymer substrate. As the thermal expansion coefficient of polymer materials differs typically by an order of magnitude from the thermal expansion coefficient from metals (data shown in Table 1), any significant deviation of the substrate temperature from room (or later operating) temperature will lead to large stress in the metal film and ultimately will result in a cracking of the electrode. To reduce this effect and to improve adhesion of metals like platinum or chromium on a polymer, an intermediate layer of gold, titanium or aluminium can be used. Typical thicknesses of the electrode structures described above are 100-150 nm, with an adhesion layer thickness of the order of 10 nm.

Table 1: Thermal expansion coefficients of metals and polymer materials.

	Al	Au	Ti	Pt	Cr	PMMA	COC
Thermal expansion coefficient [10^{-6} /K]	23.8	14.3	29	9	7.5	248	60

Another example of a device with a larger metallized area is a sensor for surface plasmon resonance [7,8] shown in Fig. 5. The measurement principle is as follows: A thin metal film (gold) is deposited onto a dielectric material (i.e. a polymer, in this case COC [TOPAS from Topas]). If light is now irradiated onto the metal film, surface plasmons (surface electromagnetic waves) are exited and travel along the metal/dielectric interface, while most of the light is being reflected under a certain angle. If now the local refractive index of the metal film is changing due to the adsorption of e.g. biomolecules, the angle of the reflected light is changing and can be evaluated as the sensor output signal. To generate selective binding of biomolecules e.g. the human immunoglobuline G (IgG), a part of the gold surface is coated with protein A. This method allows the measurement of changes in the refractive index as little as 10^{-6}. Figure 5 shows the sensor chip, Fig. 6 the measurement result of the sensor. In the figure, the vertical grey lines indicate the switching points of the IgG solution (PBS buffer) between the concentrations 0 – 150 ng/ml – 0 – 1,5 µg/ml 0 – 15 µg/ml – 0 – 150 µg/ml - 0 – 1,5 mg/ml, the thick black line the resulting sensor signal, with the thin black line being the sensor signal of an uncoated gold surface (unspecific binding).

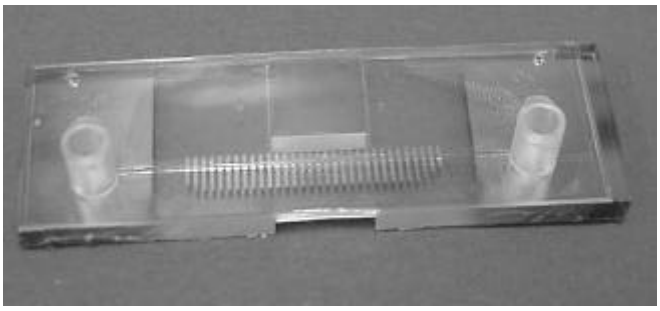

Fig. 5. Surface plasmon resonance chip

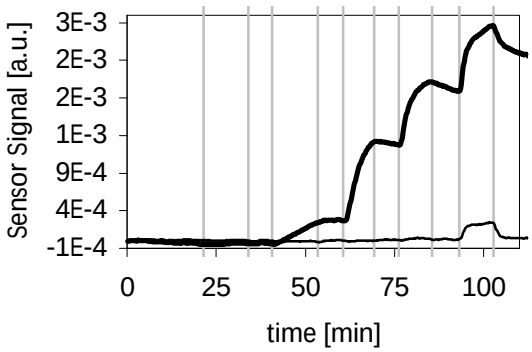

Fig. 6: Sensor response of the system to an increasing concentration of IgG in PBS buffer (thick black line), response from an uncoated Au film (unspecified binding) is shown in the thin black line

STANDARDIZED POLYMER CHIPS FOR BIOSENSOR APPLICATIONS

While in the past, most external chip geometries in the literature have been individual formats ranging from less than a cm on each side to several centimetres, most conventional equipment in the laboratory life follows two existing standards, namely the microtiterplate according to SBS standards [9] and the microscope slide with external dimensions in the range slightly below 76 mm by 26 mm. We have implemented the latter format as a standard for a toolbox-like approach to microfluidic devices, allowing for a rapid integration into the existing laboratory infrastructure. When fixing the format less tolerance for the microfluidic devices is accepted then for microscopy slides and the chips can be thinner. Standard formats are 25.5 mm x 75.5 mm x 1 mm or 1.5 mm respectively.

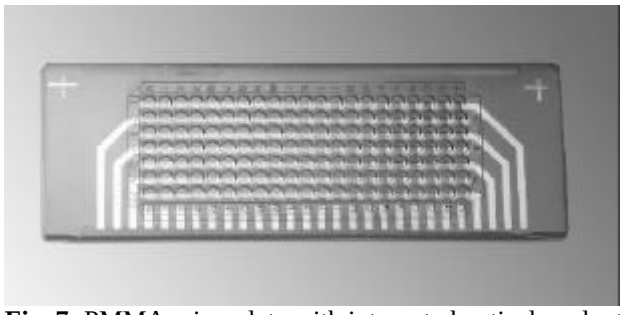

Fig. 7: PMMA microplate with integrated optical readout system.

In Fig. 7, an example for such a hybrid microstructure in the microscope slide format can be seen. The device contains 7 rows of 21 microwells with a diameter of 2 mm as reaction sites for fluorescence reactions. These plates have been manufactured in MBA, MABS or PP using injection molding. Underneath this chip, a multiplayer structure on a glass slide is mounted, containing an aluminium electrode array structure, an organic semiconductor material as a photoelectric sensor element and a transparent coating of indium-tin-oxide (ITO) to protect the photoelectrode. If a reaction takes place in the microwell which generates light, this is directly converted into easily readable electric signals at the output of the electrodes, thereby greatly reducing the instrumental effort usually associated with the readout of fluorescence signals from a microtiterplate.

Another concept currently under investigation is the use of a variety of biosensors for the detection of cancer markers [10]. In this concept, again, the above described microscope slide format acts as the geometrical frame in which a polymer based microfluidic cartridge contains biosensors made out of a variety of materials, mostly based on silicon microengineering. In Fig. 8, a simple multichannel structure is shown, where the biosensor sites are the slightly enlarged regions in the middle of the microchannels, and the final system depicted in the schematic in Fig. 9. In all cases, the interface between the polymer components and the inserted biosensor has to be realized in a manner that no leakage at this interface occurs and that subsequent assembly steps are not interfered with, which typically requires very tight geometrical tolerances in the parts used.

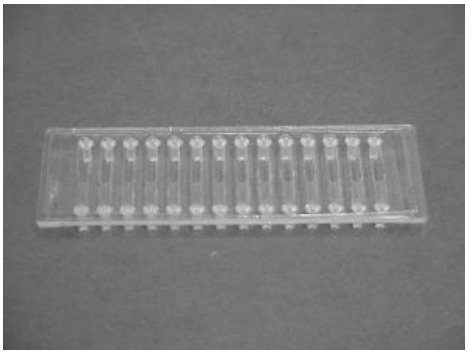

Fig. 8: 14 channel biosensor chip

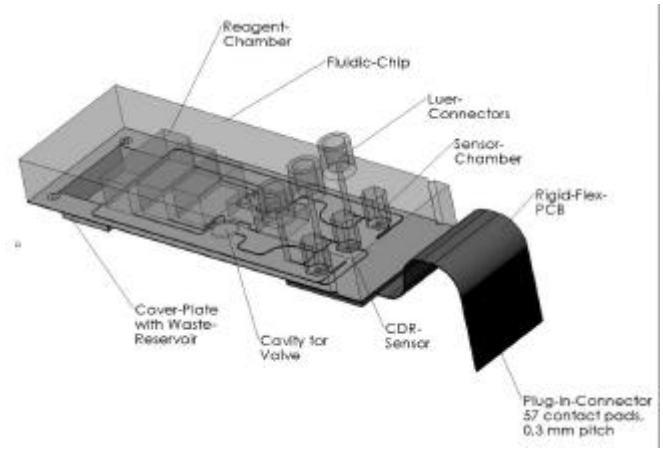

Fig. 9: Concept for a cancer marker detection chip

CONCLUSION AND OUTLOOK

In this paper we have presented different examples of microfluidic devices where the fluidic manifold has been manufactured out of polymer material and additional functional elements made out of other material have been integrated. In our opinion this trend of integrating more functional elements into the devices will continue in the future and will present a challenge mainly in the manufacturing technologies, requiring additional process steps partly with techniques which are not generally compatible (e.g. injection molding and thermal evaporation) at target costs which will only be marginally higher than the current allowable costs for simple polymer components.

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