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SPECIAL ISSUE- ORIGINAL ARTICLE

Polymer lab-on-chip systems with integrated electrochemical pumps suitable for large-scale fabrication

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Abstract A low-cost, polymer-based microfluidic platform is described that not only includes passive microfluidic parts, but also pumps based on an on-chip electrochemical gas generation by electrolysis. A hydrogel is used as electrolyte material, which allows a simple fabrication process by screen printing or stencil printing. Test structures were designed and fabricated to illustrate the feasibility of the approach for batch processing. Microfluidic chips including reservoirs and channel structures were fabricated by microinjection molding and used to demonstrate the movement of liquids inside microchannels by the proposed micropumps. The channel system was furthermore functionalized by a plasma surface treatment to form hydrophobic and hydrophilic areas. For sealing of the channel system, as well as for bonding the microfluidic part to glass-like sensor parts, laser-cut adhesive tapes were applied.

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1 Introduction

A new polymer-based lab-on-chip platform for protein detection in point-of-care applications is currently being developed, aiming to integrate active optical components like a planar surface plasmon resonance (SPR) sensor as well as microfluidic actuators inside the polymer chip [1]. While the integration of additional functionality can improve the performance and/or usability of such a device significantly, cost per chip and analysis remains a critical factor. Thus, not only should passive components like channels and reservoirs be "low-cost" components, but also the new functionalities like pumps or valves should be selected and developed according to cost considerations.

The paper therefore focuses on the fabrication aspects for the different key elements of the lab-on-chip system. This includes especially the channel surface treatment, bonding, and sealing, as well as a new approach for the integration of low-cost micropumps.

1.1 Surface treatment

Microfluidic channels in a lab-on-chip system may have to be functionalized for certain applications. Capillary filling and, therefore, hydrophilic behavior may be desired for sample taking and to avoid bubble trapping, while capillary flow stops may be necessary, e.g., for sample liquid metering. As the presented lab-on-chip platform mainly targets protein sensing applications, the surface treatment should also prevent or at least not increase protein adsorption at the channel walls. The prevention of protein adsorption or biofouling is a key issue for various biotechnological and biomedical applications, and thus, the ability to produce protein-resistant or antifouling coatings is a critical factor in the engineering of advanced biotechnological and biomedical devices.

A variety of polymers have been synthesized to reduce adsorption of proteins, cells (direct or protein-mediated cell adhesion), and bacteria at interfaces with biological tissues. For instance, several hydrophilic polymers can be immobilized onto surfaces forming what is effectively a steric stabilization barrier to shield the underlying surface from biomolecular adsorption. These antifouling polymers include polyacrylamide, polysaccharides, phospholipids, and poly(ethylene glycol) (PEG), with PEG generally considered the most effective [2–4]. In aqueous environments, tightly packed PEG chains with a sufficiently large molecular weight are thought to form a flexible and highly solvated brushlike coating on a substrate surface [5]. Even though several techniques have been reported for the surface immobilization of PEG, only a few can be integrated into biotechnological or biomedical devices. Indeed, existing immobilization strategies often require the presence of specific surface functional groups and extensive optimization, and they have a limited capacity to be used for modification of a variety of materials. Thus, there exists an ongoing need for versatile immobilization strategies that are capable of robustly anchoring PEG and other antifouling polymers, with less susceptibility towards oxidative degradation and chain cleavage in aqueous environments, onto a variety of medically relevant material surfaces [6].

The alternative approach presented in this paper relies on a strong teflon-like polymeric backbone (-CF2–CF2- cross-linking) functionalized with PEG-like bonds (C–O, O–H). This material is deposited as thin films by plasma-enhanced chemical vapor deposition (PECVD). Synthesis of PEG chains through plasma polymerization has been widely investigated using different precursors, such as acrylic acid [7] and dimethoxyethane (ethylene glycol dimethyl ether) [8], which are nevertheless costly and not environmentally/human friendly chemistries. Furthermore, these chemistries rely on monomer fragmentation under mild plasma conditions, which raises process control and repeatability concerns. Such limitations are overcome in the current approach where (a) the chemistry is not toxic and relatively less expensive and environmentally aggressive, (b) the material synthesis relies on nucleation/growth mechanisms but not fragmentation, (c) the surface energy is tuneable (unlike PEG) from hydrophilic to hydrophobic states, (d) various materials and substrates can be coated at low-temperature ($< 80^\circ$C), and (e) the active PEG chains are embedded within the teflon structure such that the film may act as a functional reservoir.

1.2 Sensor integration

Typically, not all components of lab-on-chip systems can be made of low-cost polymers. Highly sensitive sensors, e.g., those based on SPR (http://www.biacore.com), wavelength interrogated optical systems (evanescent optical fields) [9], or electrochemical detection (http://www.abbottpointofcare.com/istat/), are still often high-value components based on glass or silicon chips. Other sensing applications require glass or silicon chips for DNA or protein detection where the biochemical immobilization of capture (probe) molecules on the chip surface is based on a particular surface chemistry. The most common surface chemistries on biochips are thiol and silane chemistries [10]. With silane chemistry, the probe molecules are immobilized directly on the silicon or glass substrate. With thiol chemistry, the probe molecules are immobilized on metal spots or electrodes (e.g., gold), which are fabricated by photolithography on glass or silicon chips. There are also surface chemistries for silicon or glass chips based on organic double bonds, e.g., a surface chemistry for silicon chips based on etching the oxide of the silicon chip away with HF acid and attaching functionalized 1-alkene self-assembled monolayers to the resulting Si–H surface [11].

These high-value sensor components need to be integrated into low-cost thermoplastic microfluidic systems. In a previously published work [12], direct clamping, clamping with laser-cut polydimethylsiloxane (PDMS) gaskets, gluing, and hybrid bonding with laser-cut adhesive tapes were tested. Based on the results obtained in this work, laser-cut adhesive tapes were chosen for the hybrid integration of glass-based SPR sensors into the low-cost thermoplastic microfluidic system described here. The use of tape gaskets allowed the presence of biomolecules (probe molecules) on the sensor chip during the bonding process.

1.3 Micropumps

As the controlled transport of liquids like a sample or buffer solutions is essential for an integrated lab-on-chip for point-of-care use, on-chip microfluidic actuators are desired, which are small in size, inexpensive, and easy to integrate, but, on the other hand, able to generate large displacements. Classical approaches for micropumps that consist of a pump chamber, an oscillating membrane, and passive or active valves are usually very complicated and difficult to integrate in a polymer platform. Despite these "conventional" micropumps, certain nonconventional pumping principles have been investigated and developed during the past few years.

One type of "nonconventional" pump is surface-based actuators, which employ, e.g., electroosmotic effects, electro-/thermocapillary effects, or surface acoustic wave effects. While all of these techniques are very attractive for certain applications, it is usually very difficult to flexibly apply them to a low-cost, polymeric, channel-based lab-on-chip system. Furthermore, these principles also strongly depend on certain properties of the moved liquids and/or the used substrate/wall material.

In contrast, applying a direct pressure to a liquid inside a channel seems to be a more "universal" approach. Also, for direct pressure actuation, different "nonconventional" approaches have been investigated. For example, paraffin actuators have been proposed by Carlen and Mastrangelo [13], which make use of the large thermal expansion of wax paraffin when melting (phase change). Another type of very promising actuators uses expandable microspheres incorporated in an elastomeric matrix, and was first proposed by a group around G. Stemme [14]. Both of these actuation principles use heating to generate a pressure, which leads to a high power consumption. Furthermore, these actuators may not be suitable for temperature-sensitive applications, like, e.g., protein assays.

Another interesting approach, first demonstrated for microactuators by C. Neagu et al. [15], is the electrochemical generation of gas bubbles by the electrolysis of water. Actuators based on electrolysis have a very low power consumption, as well as almost no heat generation, while still being able to generate large deflections or displacements and high pressures. Due to its low complexity, the principle is well suited for low-cost applications.

1.3.1 Electrolytic microactuators based on hydrogels

The electrolysis of water is the dissociation of water molecules into oxygen and hydrogen gas by means of an electric voltage. The reaction is given by:

$$\begin{aligned}\text{Anode}: &\ 2H_2O \rightarrow 4H^+ + 4e^- + O_2(g)\\ \text{Cathode}: &\ 2H_2O + 2e^- \rightarrow 2OH^- + H_2(g)\end{aligned}$$

The amount of generated gas molecules is directly proportional to the current flowing through the electrolytic cell. Assuming that all charges contribute to the generation of H_2 and O_2, and no back reaction takes place, the theoretical volume V_{gen} of the generated gas mixture can be calculated as the sum of the generated oxygen and hydrogen volumes.

$$V_{\text{gen}} = V_{H_2} + V_{O_2} \tag{1}$$

Per elementary charge, $\frac{1}{2}H_2$ and $\frac{1}{4}O_2$ molecules are generated. One mole of a gas has a volume of $V_m = 24.46$ l/mol under standard conditions and contains about $N_A = 6.022 \cdot 10^{23}$ mol^{-1} molecules (Avogadro number). The generated gas volume can then be calculated as follows:

$$V_{\text{gen}} = \left(\frac{1}{2} + \frac{1}{4}\right) \cdot \frac{N}{N_A} \cdot V_m \tag{2}$$

For a current $i(t)$, the number N of the elementary charges e flowing during a certain period of time dt is

$$N = \frac{\int i(t)dt}{e} \tag{3}$$

Using this equation, the finally generated gas volume as a function of current and time is given by

$$V_{\text{gen}} = \left(\frac{1}{2} + \frac{1}{4}\right) \cdot \frac{V_m}{N_A \cdot e} \cdot \int i(t)dt \tag{4}$$

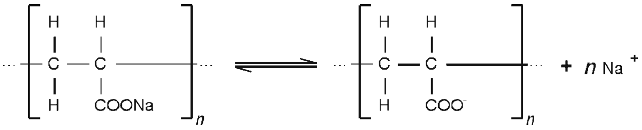
or using the Faraday constant $F = N_A \cdot e$

$$V_{\text{gen}} = \frac{3}{4} \cdot \frac{V_m}{F} \cdot \int i(t)dt \tag{5}$$

As an example, for a current of $I = 1$ mA a volume of 0.19 µl of the oxygen–hydrogen mixture is generated during 1 s.

The generated gas can either be used to deflect a membrane or to drive a fluid by directly applying the gas pressure to the fluid without an intermediate membrane. Bubble actuators based on electrolysis have already been successfully demonstrated for microfluidics [15–17]. Within these works, a liquid (usually water or a water-based liquid) had to be integrated in the electrolytic reservoirs. However, the integration of a liquid can be critical for mass production and may also cause problems concerning long-term stability.

A hydrogel based on sodium polyacrylate was therefore investigated in this work for its applicability as electrolyte, which combines the electrolytic and gas-generating properties of water-based electrolytes with a good processibility by screen printing or stencil printing. It is available at very low cost and is nontoxic.



$$[-CH_2-CH(COONa)-]_n \rightleftharpoons [-CH_2-CH(COO^-)-]_n + n\,Na^+$$

Fig. 1 Working principle of sodiumpolyacrylate-based gels: when brought into (deionized) water, sodium ions are split from the polymer chain. The repelling forces of the negatively charged COO^- groups are responsible for the swelling of the gel

Crosslinked sodium polyacrylate is a so-called super absorbing polymer that is able to dramatically swell in water. The swollen state is referred to as a hydrogel, which mainly consists of up to 99 wt.% of water, but has a very high viscosity. When sodium polyacrylate is brought in contact with water, the weakly bonded sodium is split off, leaving negatively charged polymer chains and movable sodium ions (Fig. 1).

2 Passive microfluidic part

2.1 Design and fabrication of the microfluidic channel system

A microfluidic system was designed according to the requirements of an integrated lab-on-chip system for point-of-care diagnostics [20]. The microfluidic layout incorporates three inlet reservoirs, one waste reservoir, and a channel system that connects all these reservoirs and delivers the liquids to a sensor area.

In addition, each inlet reservoir is connected to the "pump region" (Fig. 2) by a thin hydrophobic channel ("gas delivering channel") of a cross section of 100 × 100 μm^2. The pump region mainly consists of the gel reservoirs in which the gas will be generated by electrolysis. The gel reservoirs can be covered by a thin membrane that should open automatically when a certain gas pressure within the gel reservoir is reached. The working principle of the pump is explained in Fig. 2. The bottom picture reflects the "real" setup and layout of electrodes and channels, which has been also used in Section 3.2.

The layout described above was transferred to a double-sided mold (Fig. 3) by micromilling. The mold was then used in a "Battenfeld Microsystem 50" microinjection molding machine to fabricate the passive microfluidic polymer parts (Fig. 4). As material, the Cycloolefin-Copolymer (COC) TOPAS 5013 by TOPAS Advanced Polymers was used for its low water absorption and low autofluorescence.

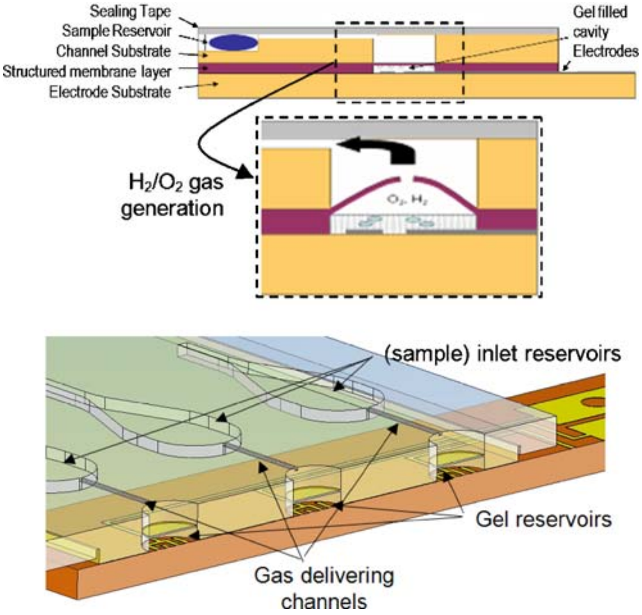


Fig. 2 Schematic drawings of the pump region of a lab-on-chip system with a gel pump. *Top*: principle of pumping, *bottom*: cross section through gel reservoirs

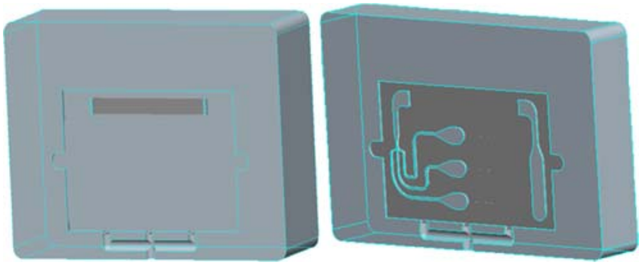


Fig. 3 Double-sided mold

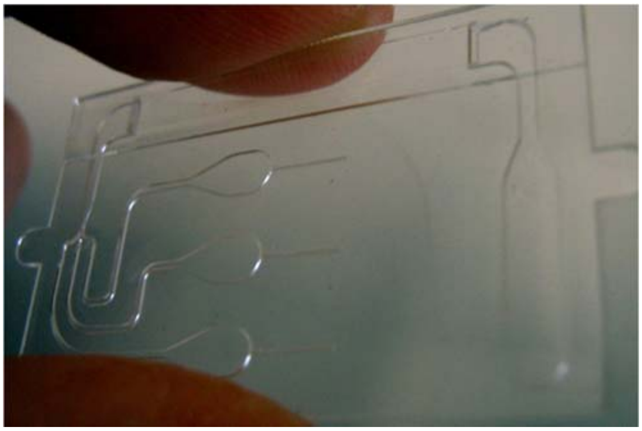


Fig. 4 Passive microfluidic channel substrate fabricated by microinjection molding of the COC TOPAS 5013

2.2 Microchannel surface treatment by PECVD

Certain applications for lab-on-chip systems have further requirements to the passive microfluidic channel system. For example, capillary filling and/or capillary flow stops inside the channel system may be desired. Protein sensing applications furthermore demand for a low protein adsorption at the channel walls.

Processes for hydrophilic, hydrophobic, and nonfouling applications have therefore been developed based on the PECVD technique (Table 1). Plasmas are produced inside a cylindrical stainless steel vacuum chamber (diameter 30 cm) with a parallel plate configuration (Fig. 5). Substrates to be coated are positioned on the lower grounded electrode. The precursours' vapor is uniformly distributed in the reactor by the upper showerhead electrode (with pinholes' diameter of 1 mm). The upper electrode is externally connected, through a semiautomated matching network (Dressler VM1000A), to a 13.56-MHz-RF power supplier (Advanced Energy Cesar® RF power supply), which provides a RF voltage with respect to the grounded chamber. Before operating the discharge, the device is evacuated below $5 \cdot 10^{-3}$ mbar by means of a rotary pump (Alcatel ADS 501). During plasma deposition, the chamber is evacuated by means of the rotary pump.

For the presented work, fluoropolymer coatings were used for the functionalization of the microfluidic channels. Octafluorocyclobutane (C_4F_8) is a gaseous monomer at room temperature that can be polymerized during plasma treatments by rearranging the radicals produced by its dissociation induced by electron impact. Soft coatings of CFO with high content of fluoromethane groups are obtained by mixing C_4F_8 and oxydant carriers (e.g., water vapor) in plasma process yields [21]. At low oxygen content, the hydrophobic behavior of CFO is related to fluoromethyl groups (C–F and F–C–F bonds), while increasing oxygen content leads to hydrophilic hydroxyl and carbonyl groups (O–H and C=O bonds).

Table 1 PECVD process conditions for depositing CFO films

Parameter	Value
Precursors	C_4F_8 (80 scmm)
Carrier	Water vapor (Partial pressure 0.15 to 0.3 mbar)
Working pressure	0.50 mbar
Power	200 W
Process temperature	80 °C
Plates spacing	20 mm
Deposition rate	typ. 5 nm/s

Fig. 5 In-house built PECVD reactor (CEA courtesy)

As shown in Fig. 6, adding oxygen into CFO coatings substantially increases their surface energy and turns hydrophobic CF material into hydrophilic CFO material as oxygen content goes up (CF→CFO1→CFO2→CFO3). At low oxygen content, CFO1 coating retains the hydrophobic character of CF before changing to hydrophilic with higher oxygen content (CFO2, CFO3). This transition is mainly due to the increase in the surface polar energy, which is induced by the presence of hydroxyl, carbonyl, and other polarized bonds of oxygen components.

This physicochemical effect can be coupled to an oxygen plasma roughening of the COC polymer substrate prior to depositing the coatings. Thus, the added nanotexture (Rms < 200 nm) makes hydrophilic surfaces more hydrophilic (superhydrophilic) and hydrophobic surfaces more hydrophobic (superhydrophobic). This approach has been described for superhydrophobic polymer coatings by Katsuya Teshima et al. [22].

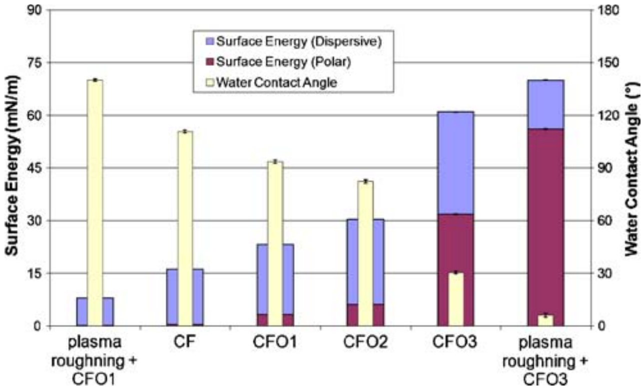


Fig. 6 Surface energy and contact angle of CF and CFO coatings

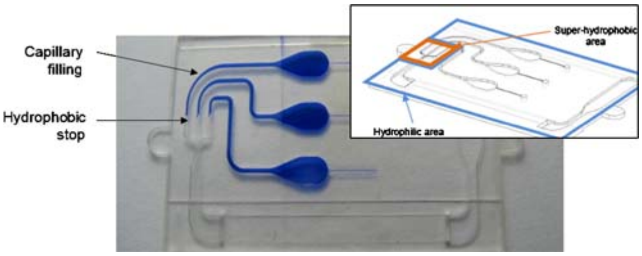


Fig. 7 Capillary flow stops realized by selective deposition of different CFO films on injection molded COC parts

The process described above has been used to functionalize the channels of the injection-molded COC substrates. Some parts of the chips, like the inlet reservoirs and inlet channels, as well as the sensor channel, were treated hydrophilically to allow good capillary filling and to avoid bubble trapping. The "fork" area (Fig. 7) was treated superhydrophobically to establish a capillary flow stop. Filling with inked water (Fig. 7) visualizes the desired behavior.

2.3 Sensor integration with laser cut tape

Double-sided polyester-based laser cut adhesive tapes were used for hybrid bonding of the glass-based sensor to the thermoplastic microfluidic system. A one-sided polyester-based laser cut adhesive tape was used to seal the microchannels of the prototypes. The laser cutting and bonding process have been described elsewhere [12]. The leak tests showed that the glass-thermoplastic sealing using microstructured adhesive tape gaskets was good. No leaks were observed both under the microscope and in the pressure measurements up to the gage pressure of about 30,000 Pa generated by the syringe pump. The sealing is therefore strong enough for typical microfluidic pump pressures. Figure 8 shows the laser-cut tapes used for hybrid sensor integration and for microfluidic channel sealing. Figure 9 shows a typical leak test curve.

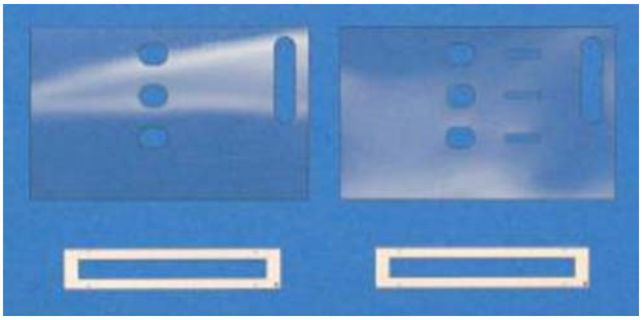


Fig. 8 Laser cut double-sided adhesive tape gaskets for sensor integration (*bottom*) and one-sided adhesive cover tapes for microfluidic channel sealing (*top*)

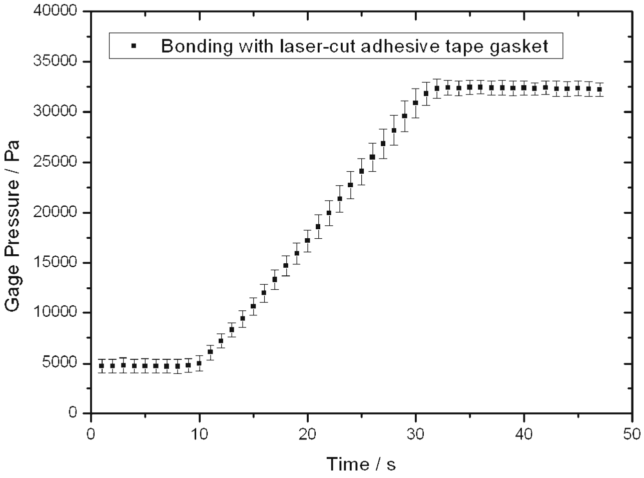


Fig. 9 The sealing of the tape bond between glass chip and thermoplastic fluidic channel was strong enough to withstand typical microfluidic pump pressures (here, ca. 30,000-Pa gage pressure generated by a syringe pump)

3 Active microfluidic part

The active microfluidic part of the lab-on-chip system provides pumping functionality by using electrolysis of water. In contrast to previous works, the water is not integrated as liquid but is incorporated in a hydrogel. The gel will be interfaced by planar electrodes on an electrode substrate.

Two types of structures were designed and fabricated. The first one uses silicon and polymer wafer technologies to allow the development of the gel integration process by stencil printing and the investigation of the electrolytic behavior (=electrode test structures, Section 3.1).

The second type of structure was developed to be suitable for integration with the injection-molded substrates described in Section 2. It was designed and fabricated to demonstrate the feasibility of the gel actuators as pumps in a lab-on-chip system (Section 3.2).

3.1 Towards gel integration: electrode test structures

For developing and illustrating the stencil printing process and to investigate the actuator's performance, a set of test electrodes was designed and arranged in a 4-in. wafer layout together with cavities, which are placed around the electrodes. These test structures were also used to measure membrane deflection, e.g., for use as a valve. The performance of these electrode

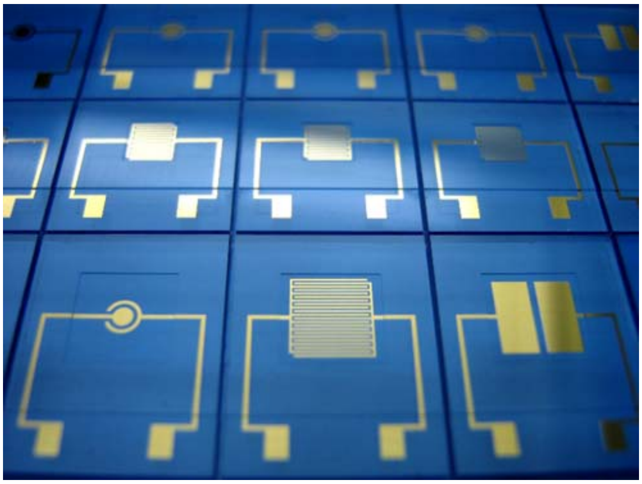


Fig. 10 Diced COC chips on blue dicing tape with gold electrodes and SU-8 chambers

designs with and without membrane was already presented in [19], where, e.g., a 70-μm-thick PVC membrane with an area of 3 × 3 mm^2 was deflected more than 300 μm.

In this paper, special attention is being put to the feasibility of the approach for large-scale fabrication by stencil printing, which allows us to fill a large number of flat electrolytic reservoirs at the same time.

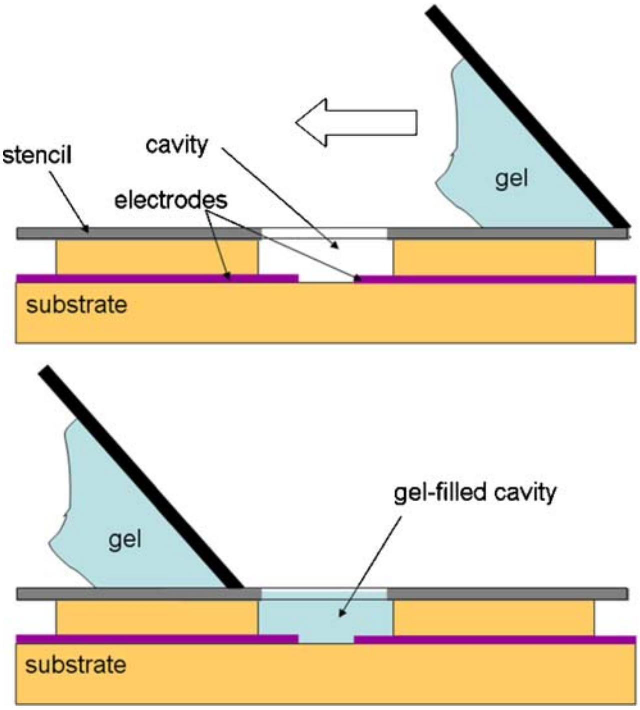


Fig. 11 Filling of an electrolysis chamber with gel by using stencil printing

Gold electrodes were fabricated by sputter coating, standard lithography, and wet etching on both 4-in. silicon wafers (with thermal oxide for insolation) and 4-in., injection-molded, thermoplastic wafers made of the COC TOPAS 5013. Cavities around the electrodes were subsequently formed by SU8 lithography. SU8 is a negative photoresist frequently used in microtechnology for applications in which large film thicknesses (up to 1 mm) and/or high aspect ratios are required. The SU8 cavities formed in this study had heights between 80 and 300 μm. Figure 10 shows a set of electrode test structures fabricated on a COC substrate, Fig. 12a on a silicon wafer.

The SU8 chambers were filled with the sodium polyacrylate gel by stencil printing on the wafer scale. The process is illustrated in Fig. 11. As a stencil, a commercially fabricated 50-μm-thick stainless steel stencil was used. The openings were chosen to be slightly smaller than the dimensions of the SU8 chambers.

Figure 12 shows a successfully finished stencil printing batch process on a silicon wafer with SU8 chambers. As sealing of the gel by a thin membrane directly after printing the gel is desired, current investigations focus on membrane material selection and process integration of these materials.

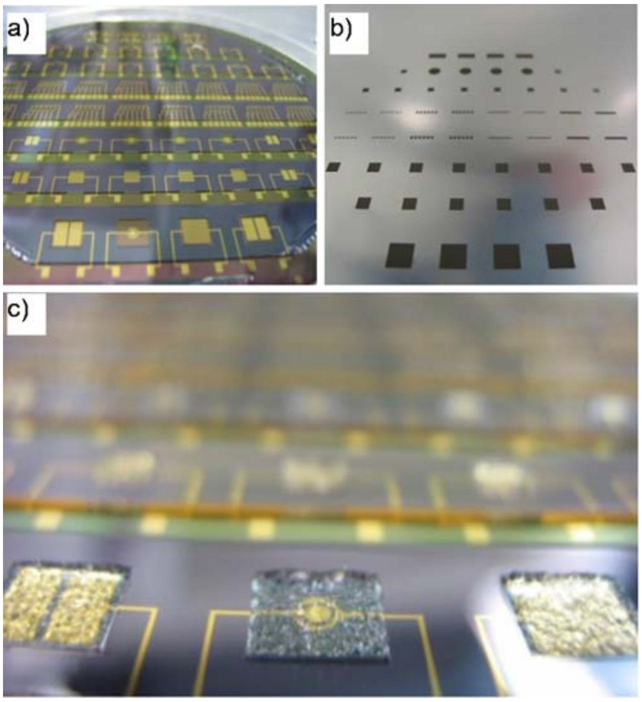


Fig. 12 Filling of an electrolysis chamber with gel by using stencil printing. **a** Four-inch silicon wafer with electrode test structures and SU8 cavities (see Section 3.1), **b** stainless steel stencil, and **c** gel filled in cavities by using the stencil on a conventional screen printer

3.2 Pump integration

As the integrated system should be as inexpensive as possible, thin-film technologies for electrode fabrication (like sputter coating as described above) proved to be not feasible for mass production. Thus, the electrode structures for the integrated system were finally fabricated by standard printed circuit board (PCB) technology. The copper electrodes on the PCB were subsequently coated with an electroplated nickel/gold bilayer for electrochemical passivation.

The gel was placed on top of the electrodes in the pump region without the need for an additional frame around the electrodes (in contrast to Section 3.1). The so-formed actuator part was clamped together with the injection molded channel substrate. Proper sealing between both parts was achieved by an intermediate silicone membrane. This membrane layer incorporates holes in the area where the gel was placed on the electrode substrate. The membrane layer was fabricated by PDMS casting. It has to be noted that this is considered to be a prototyping technology only suitable for the proof of concept. For a later large-scale fabrication, the PDMS gasket layer can either be replaced by a thermoplastic elastomer gasket or by the same structured, double-sided adhesive tape used for sensor bonding.

3.3 First results

The parts described in Section 3.2 were used to demonstrate the operation of the integrated pumps. After filling the reservoirs and contacting the electrodes, a constant current was applied for the three actuators separately, resulting in an emptying of the reservoirs. Figure 13 shows the emptying of the middle of three reservoirs at different times. Flow rates in a typical range between 5 and 200 μl/min can be achieved and easily adjusted by the applied current. Back pressures may reach up to several hundred millibar. One pump consumes a chip area of typically 3×3 mm^2 and a gel height of between 0.1 and 1 mm, which allows us to integrate these pumps also in very flat substrates (like chip-cards).

Interestingly, almost no fluid entered the channels back to the other reservoirs, even if they were already emptied. This is caused by two effects: The first reason is that the flow resistance was selected to be higher from the junction of the channels towards the inlet reservoirs than to the outlet reservoir. The second (even more important) reason is that only the waste reservoir (outlet) has an opening, while the air/gas in the channels towards the inlet reservoirs would have to be compressed to allow a flow in this direction.

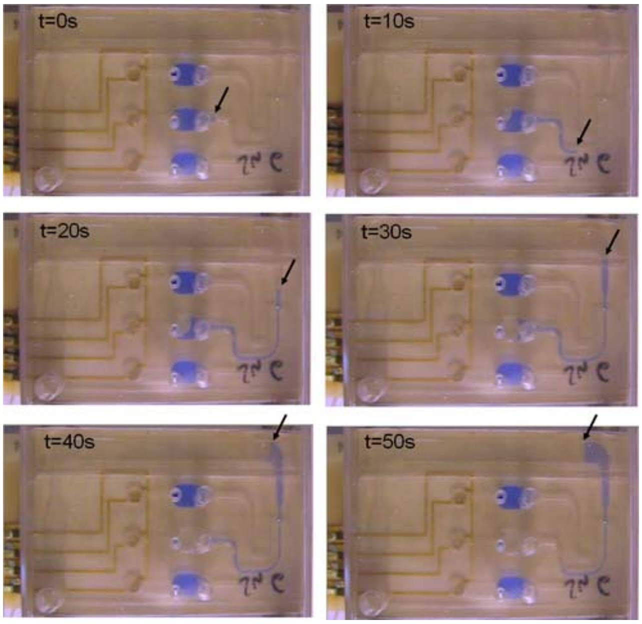


Fig. 13 Emptying of the middle of three reservoirs. The *arrows* are indicating the fluid front

4 Conclusion

A set of technologies suitable for complex polymer microfluidic systems has been described, including channel substrate fabrication by microinjection molding; channel surface treatment for adjusting the wetting behavior; channel sealing and sensor bonding by laser-cut adhesive tape; and low-cost, low-temperature pump integration. On-chip gas generation by electrolysis was successfully used to empty reservoirs and drive fluids through channels inside a polymer-based microfluidic system. The water used for electrolysis was “stored” inside a super absorbing polymer and could therefore be easily integrated, e.g., by stencil printing. The next steps will focus on complete integration of all components and the development of an in situ integration of the gel-covering membrane directly after the stencil printing process.

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