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Microfluidic microchemomechanical systems

Merle Allerdißen[1,a], Rinaldo Greiner[1,b], and Andreas Richter[1,c]

Technische Universität Dresden, Professur Polymere Mikrosysteme, Dresden, Germany

[a]merle.allerdissen@tu-dresden.de, [b]rinaldo.greiner@tu-dresden.de,
[c]andreas.richter7@tu-dresden.de

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Abstract. The lab-on-a-chip (LOC) technology was expected to influence our every day live in a similarly fundamental way as integrated circuits have. Unfortunately, this demand has not been met yet. The cause therefore lies in the complexity of microelectromechanical systems (MEMS), which form the base of the current LOC technology. We present a new concept of LOC which are based on fluidic microchemomechanical systems (μCMS). During the fabrication process, these μCMS are preprogrammed by monolithic integration of special active components. These active components are holding chemical energy that can be transformed at least once into mechanical energy and thus provide a timed and quantitative exactly defined fluidic function. With our simple and inexpensive fabrication method combined with the above mentioned advantages of the invented μCMS, new and better LOC technology can be developed.

Introduction

The importance of manipulating and processing liquid flows containing molecules and organisms is comparable to the importance of manipulating streams of electrons in microelectronic information technology (IT) [1, 2, 3]. Fluidic integrated circuits (IC), so-called labs-on-a-chip, are discussed as as a major new technology of this century, able to revolutionise the processing of liquid flows. Over more than twenty years, a broad range of methods to manipulate liquids on microchips have been developed [4]. However, the expected revolution of the LOC technology has not yet happened [3].
Looking back to the rapid development the early computer technology had experienced by introducing the microprocessor, a single integrated circuit comprising the complete central processing unit (CPU) including both control and execution unit, important reasons for this development might lie within the system architecture of microelectromechanical systems (MEMS). MEMS, forming the base for the current LOC technology, have an architecture in which the most expensive subsystem, the control unit, is an off-chip component. In a current work, we present a concept of microfluidic central processing units on a single integrated chip based on the concept of microchemomechanical systems (μCHEMS) [5] which shows remarkable similarities to early electronic Von Neumann microprocessors. Control unit, execution unit and chemical power supply are integrated on one IC, thus they are expected to be able to carry out similar long, complex program sequences as early electronic microprocessors. Due to their material base of intrinsically active materials (phase-changeable polymers), the ICs are suitable for large-scale integration and offer the possibility of active decision-making capabilities regarding chemical information.

The microchip presented in this paper shows an example of such a μCHMS IC based on intrinsically active materials. It consists of three different layers: (i) a control layer that contains most of the microvalves and the micropumps and is used to manipulate the process media, (ii) a data layer in which reactions between different process media take place, and (iii) a thin, flexible membrane separating the two layers (s. Fig.1). Isolating the data layer from the control layer allows a separate processing of the two types of signals: chemical control signals and chemical data signals. The control signal processed in the control layer is a binary chemical information, here the binary concentration of water (c_{H_2O} = 0: water is not applied; c_{H_2O} = 1 : water is applied). The data signals are the actual process media, e.g. the concentrations of samples, chemicals, or analytes which can be analogue carriers of information.

Fabrication of the IC.

Channel Structure. All three layers of the microchip are fabricated using the polydimethylsiloxan (PDMS) RTV 615 A + B (Momentive) by means of multilayer soft lithography [6, 7, 8]. For the layers containing the channel structures (data and control layer), PDMS is mixed with a ratio of 30:1 (ratio of component A to component B). The mixture is poured onto a SU-8 master featuring the negative channel structures, degassed and cured at 80°C for 1,5 h. The valve seats for the opening valves and the channels in the data layer which are located above the closing valves are 70 µm high, all other channels have a height of 140 µm. The valve seats for the closing valves, the reaction chambers and the reservoirs in the reaction layer are 210 µm high and the chamber holding the actuator array for the pump has a height of 260 µm high. The separating PDMS membrane is fabricated by spin-coating degassed PDMS on a PET-substrate. Two different membranes are investigated: A double-layer membrane, each layer with a height of 30 µm and with a mixing ratio of 3:1 (PDMS A:B) and, in order two increase stability and decrease sagging, a three-coat membrane in which an additional 30 µm high layer with a mixing ratio of 10:1 (PDMS A: B) is added between the two outer layers. Measurements of the Young's Modulus (s. Fig. 2(d)) of the three-coat membrane show a good agreement with the Young's modulus of PDMS at mixing ratio of 10:1. After preparing the channel layers, the microfluidic device is assembled layer-by layer.

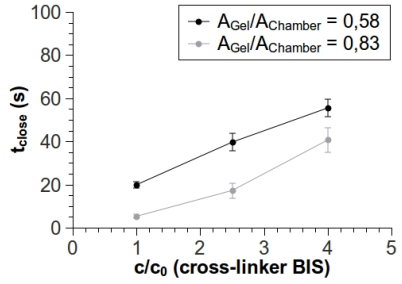
(a) Device before filling with control liquid.

(b) Device after filling.

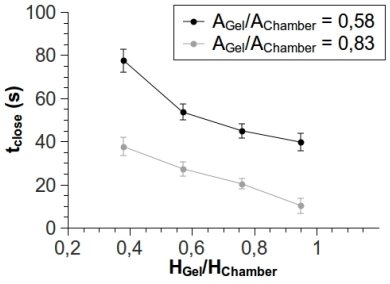
Fig. 1: Schematic cross section of the microchip.

Active Components. Closing valves are based on hydrogels. Hydrogels are cross-linked, three - dimensional networks that combine the properties of a chemical sensor and an actuator by a reversible and reproducible change of their volume in dependency of a small alteration of certain stimuli [9, 10, 11]. This change in volume allows to regulate the continuous flow of liquids in a microfluidic channel and enables the development of inexpensive microfluidic components and devices [12, 13, 14, 15]. In this paper, sodium acrylate is used as base material. The closings valves are fabricated by the photolithographic polymerization of 2 g of sodium acrylate, 0.04 g of the cross-linking agent (N,N'-methylenebisacrylamide) BIS, and 0.04 g of the photoinitiator (2-hydroxy-4′-(2-hydroxyethoxy)-2-methylpropiophenone) (all chemicals are obtained from Aldrich) dissolved in 14 ml distilled water (in the following this solution is referred to as c0).

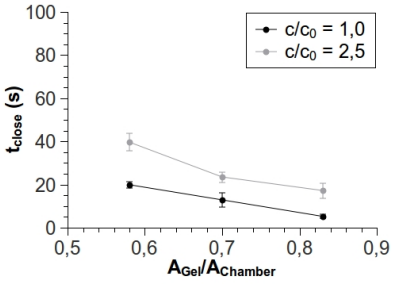
Besides production parameters, the actual response time of the closing valves depends on the dimensions of hydrogel and valve seat, the concentration of cross-linker and, in case of valves that not only regulate the flow in the control but also in the data layer, on the properties of the membrane. Fig. 2(a) shows the influence of cross-linker concentration c on the closing time of the valve. An increasing cross-linking degree of the polymer results in stiffer hydrogels with a reduced maximum swelling degree and that, in consequence, leads to an increase in the valves closing time. A second very important parameter that influences the closing time of a valve is the volume ratio of the hydrogel in its dry initial state compared to the size of the valve chamber. Fig. 2(b) shows the change in the valves closing times depending on the height H_{Gel} of the actuator, whereas in Fig. 2(c) the influence of changes in the footprint of the valves A_{Gel} are shown. In both cases the closing time decreases with increasing hydrogel size. The performance of the valves influencing not only the control, but also the data layers is shown in Table 1. Upon contact with a swelling agent (control medium), the hydrogels swell, close the valve seats in the control layer and, by deflecting the flexible PDMS membrane, also close the data channels (Fig. 2(f) ii-iv)). The relatively high Young's Modulus (Fig. 2(d) and the necessary pre-loading of the membrane leads to a significant tension. Measurements show that only



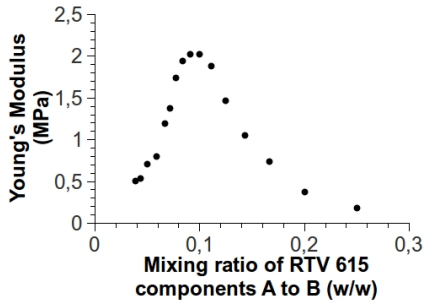
(a) Closing time depending on the cross-linker concentration c (ratio of $H_{Gel}/H_{Chamber}$ = 0,95).



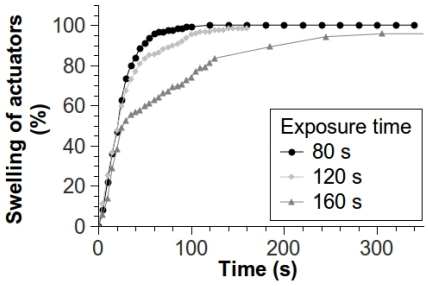
(b) Closing time depending on the height of the valve (cross-linker concentration c/c_0 = 2,5).



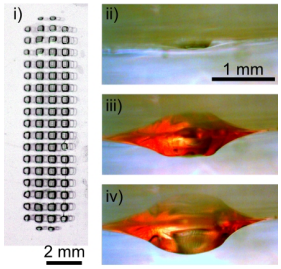
(c) Closing time depending on the footprint of the valve (ratio of $H_{Gel}/H_{Chamber}$ = 0,95).



(d) Young's modulus of PDMS RTV 615 (PDMS cured in closed cast, 80°C, 4 h).



(e) Swelling of pump actuators depending on the exposure time (SA-basd hydrogel array, c/c_0 = 1,0).



(f) i) Actuator array on foil and ii-iv) swelling of a hydrogel valve deflecting a PDMS membrane.

Fig. 2: Properties of the active elements used as closing valves and micropumps based on SA (exposure time for closing valves: 7 min).

stiff hydrogels with a high cross-linking degree are able to completely close channels in the data layer. Hydrogels with lesser cross-linking only reduce the channels cross-section and thus the devices flow velocity. In order to perform the measurements, the microfluidic device presented in this paper does not to require fast closing valves. Here, the stiffness of the valves is of much more importance.

Table 1: Closing time of valves in the data layer depending on the membrane configuration and the cross-linker concentration (SA-based hydrogels, ratio of $H_{Gel}/H_{Chamber}$ = 0,95, exposure: 7 min). a) Valves with $A_{Gel}/A_{Chamber}$ = 0,7 and a ration of width of the valve to channel width of the data layer of $d_{Gel}/d_{DataChannel}$ = 1,4. b) Encased valves with $A_{Gel}/A_{Chamber}$ = 0,63 and $d_{Gel}/d_{DataChannel}$ = 1,25.

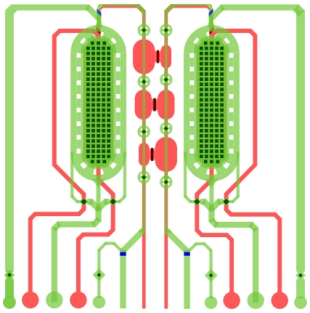
			Closing Time	
	c/c_0	Membrane Configuration	Average Value (s)	Standard Deviation
a)	4,0	two layers	11,3	3,2
	4,0	three layers	36,5	6,5
	2,5	two layers	44,0	5,2
	2,5	three layers	-	-
b)	4,0	two layers	31,5	6,1
	4,0	three layers	75,0	6,9
	2,5	two layers	-	-

The micropump also consists of photopatterned sodium acrylate hydrogels. According to Tanaka, the time constant of the swelling process of hydrogels depends on the square of its characteristic dimension [9]. On order to reduce the swelling time and to ensure an equal supply of swelling agent within the active element of the pump, the actuator is fabricated as an array of 72 square hydrogels (edge length: 50 µm, gap: 300 m). The array is photopolymerized on a 20 µm foil (Professional Flip-Frame Transparency Protectors, 3M) pretreated with 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) dissolved in Bicyclohexyl (both obtained from Sigma-Aldrich) to enhance the adhesion of the actuators. The polymerization time for the actuator array was chosen according to several measurements. Optimized results regarding stiffness, swelling time (s. Fig. 2(e)) and well separated actuators are obtained at a polymerization time of 140 s.

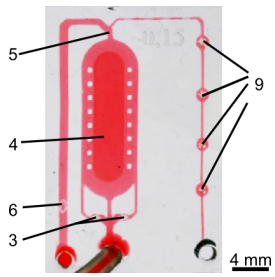
Opening valves consist of Poly(ethylene glycol) (PEG) obtained from Aldrich. The molecules of this polymer are not cross-linked, therefore a breakup of the intermolecular polymer-polymer interactions causes the opening valve to dissolve. The dissolution time of these valves depends on the polymer itself (type of polymer, chain length of polymer chain), valve length and flow rate of the passing solvent. Opening times in the range from a few seconds to several hours are possible [5]. These valves also work as pressure relief valves. Increasing the pressure in the channel leading to the valve, causes a breakthrough followed by a rapid dissolution of the valve. This way, the opening time of these active components can be also influenced.

Microchip for equidistant kinetic investigations.

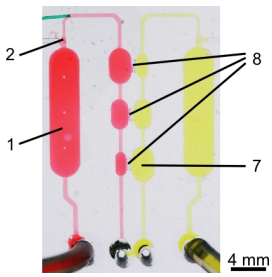
The microchip shown in Fig. 3 is designed to perform kinetic rate measurements by triggering equidistant reactions between a component, e.g. a substrate or a inhibitor, and a sample. For reasons of comparability, three reactions with varying volume ratios of component to sample can be carried out simultaneously.



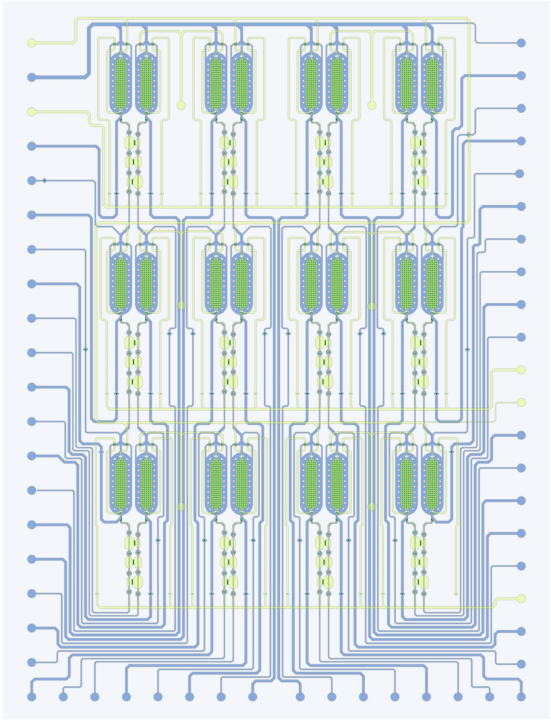
(a) Layout of one stage of the microchip (control layer: green, data layer: red).



(b) Picture of one half of the filled control layer.



(c) Picture of filled data layer.



(d) Layout of the fluidic microchip designed for equidistant kinetic investigations.

Fig. 3: Design of the microchip. For facility of inspection, in 3(b) and 3(d) control and data layer are shown separately.

To trigger a measuring cycle in which all fluidic operations necessary for sampling, sample preparation and conduction of the reaction are carried out, the inlet of control layer only has to be provided with a control liquid, in the simplest case with water. This control liquid then activates the integrated valves and pumps according to a predefined schedule completely energy self-sustaining and self-controlled. In the following, its working principle is explained on the basis of one cycle.

In the data layer of the microchip, two different process media are stored into separate reservoirs while opening/overpressure valves 2 prevent the media to flow onward into the reaction chambers. The control liquid fed into the inlet of the control layer passes valves 3 that are supposed to close inlet and the outlet of the data layer. The control liquid then flows into the chamber containing the actuator array of the pump 4. The design of the pump chamber ensures an equal supply of swelling agent for the hydrogel array and allows a continued flow of the control liquid even after swelling of the actuator array. The pump actuators 4 start to swell, deflecting the membrane into the reservoirs of the data channel. The pressure inside the data channels increases and leads to a breakthrough of opening/pressure valves 2 – the stored data liquid is pushed out of the reservoirs into the reaction chambers 7. In the control layer, the control liquid dissolves valves 5 while valve 6 closes, their opening and closing times are matched. In the control layer, valves 9, that separate the reaction chambers in the data layer are activated. Thus, a quantitatively controlled reaction between data liquids in adjoining reaction chambers can take place. Analogous to the design of the pump chamber, the configuration of valves 9 allow a continued flow of the control liquid. Thus the control fluid is able to activate the valves located at the outlet of the control layer which mark the inlet of the next measuring cycle. Setting the opening time of these valves, the interval between two measurements can be adjusted between 2 min and two hours (valves 4 made of PEG 6,000 with a length of 0.3 mm).

Summary

We introduce a microfluidic CPU with integrated control unit, execution unit and chemical power supply. The monolithic microchemomechanical ICs consists entirely of polymers - its channel structures are fabricated using PDMS, whereas its active components are composed of different phase-changeable polymers. The opening valves are made of PEG, closing valves and micropump consist of hydrogels based on sodium acrylate. On contact with a solvent, the hydrogels swell and carry out mechanical work by closing the valves or performing one pumping cycle. This material base allows for a microfluidic chip that works completely energy self-sustaining and self-controlled. The microchip presented in this paper is designed to perform kinetic rate measurements by equidistantly triggering three simultaneous reactions between a component and a sample with varying volume ratios. Adjusting the opening time of the valves separating two successive cycles, the interval between two measurements can be adjusted between 2 min and two hours. The microfluidic chip consists of three different layers, a control layer containing most of the microvalves and the micropumps, a data layer in which reactions between different process media take place and a flexible membrane separating the two layers. This layout has the advantage of a separate processing of control and data media, influences of the active elements on the process media can be reduced. To reduce the influences of the active elements on the process media further, in future works the exchange of opening valves with insoluble overpressure valves will be examined. Additionally, the research will discuss the suitability of an alternative material base to fabricate channel structures and especially the separating membranes

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