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Hydrogel-based microfluidic systems

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Abstract. Over the last ten years, microfluidic technologies have gained considerable importance. However, realising highly integrated microsystems is a major challenge, which so far has only been solved insufficiently. Here, we present an innovative approach to fabricate low-cost, integrable microfluidic platforms. As active elements, photopolymerised hydrogels based on Poly(*N*-isopropylacrylamide) (PNIPAAm) are introduced. PNIPAAm is temperature-sensitive. Heated in water above its lower critical solution temperature (LCST), it reversibly changes from a swollen to a shrunken state (volume change in the order of 90%) and can, via an electrothermic interface, be employed as electrothermally switchable actuator. Varying specific parameters in the swelling agent, for example varying its alcohol concentration, can shift the LCST. So not only micropumps or microvalves, but also valves with an appointed threshold value, so-called chemostats or chemical transistors, can be realised. Using the example of a microchip performing enzymatic endpoint analyses, we investigate characteristic behaviour of active elements based on PNIPAAM and show the ability of integrating different fluidic operations like fluid transportation, metering, valving and mixing into one fully polymeric microchip.

Introduction

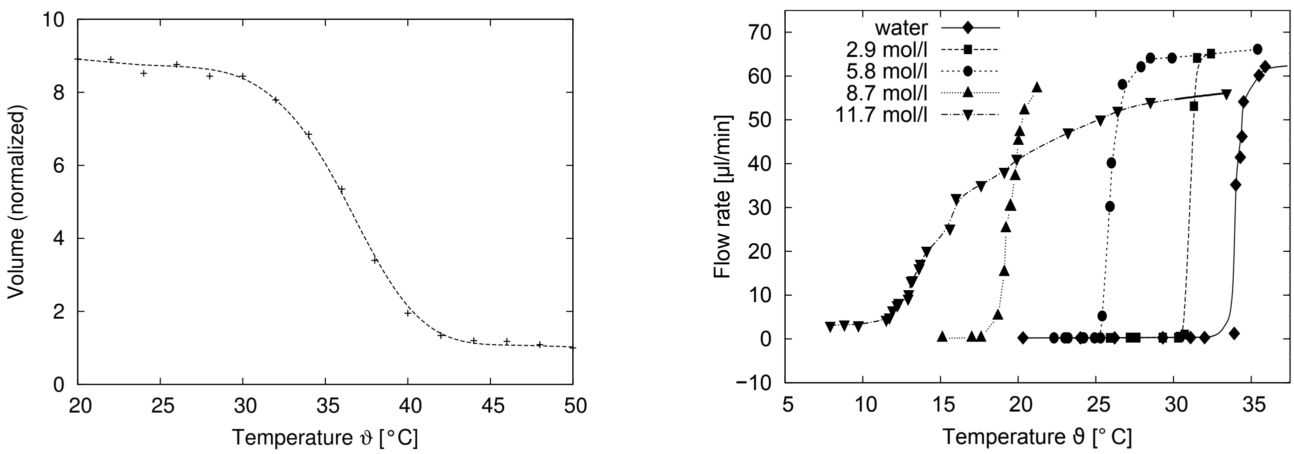
Due to the large number of potential applications, especially in the areas of biotechnology, life science and pharmaceuticals, the number of papers and patents regarding the topic of microfluidics has increased dramatically over the last ten years [1, 2]. Fluidic integrated circuits (ICs), so called lab-on-a-chips (LOCs) offer a great many advantages, including the reduction of operating time, of reagent consumption and of required sample volume [3] as well as the possibility for high-speed serial processing and a high degree of parallelisation, respectively [1]. However, until now the market for industrial applications of microfluidic devices still is limited.

An important reason is supposed to be the cost-efficiency, which is still much to high, at least for more complex microfluidic systems. Thus, a cheap technology platform is required, which still provides all needed microfluidic components like channel structures, valves, pumps and mixers. To keep the manufacturing costs down even for complex systems, these components have to be integrable and inexpensively producible.

Stimuli-responsive hydrogels like PNIPAAm have the potential to solve these problems [4]. They are cheap, electrothermically controllable and allow full integration. Here, integrable basic active microfluidic elements are shown: valves, pumps and chemostats/chemical transistors.

Temperature-sensitive hydrogels

Stimuli-responsive hydrogels are networks, that are able to change their volume significantly in response to small changes of several environmental parameters like temperature, pH, electrical fields, light and solvent composition. Upon contact with an aqueous fluid, polymer-solvent interactions replace the hitherto dominating polymer-polymer interactions of the network. Thus, the network absorbs



(a) Volume of a spherical PNIPAAm particle

(b) Influence of methanol concentration on LCST of PNIPAAm in a chemical transistor [5]

Fig. 1: Phase transition of PNIPAAm and shifting of the LCST in dependency of the concentration of methanol in an aqueous solution.

or releases the applied liquid, the so-called swelling agent, and changes its volume. If external forces are applied, these hydrogels provide considerable swelling forces. The change in volume can be more than hundredfold.

As the swelling and shrinking of hydrogels is diffusion-based, the actuation speed and thus the characteristic time constant τ depend greatly on its dimensions:

$$\tau \sim \frac{d^2}{D_{coop}}, \qquad (1)$$

where d is the final radius of a hydrogel sphere and D_{coop} the hydrogels cooperative diffusion coefficient [6].

The consequence is that for fast actuation, the diffusion ways have to kept short, thus small hydrogels have to be used. This makes hydrogels especially interesting for micro technology like microfluidics.

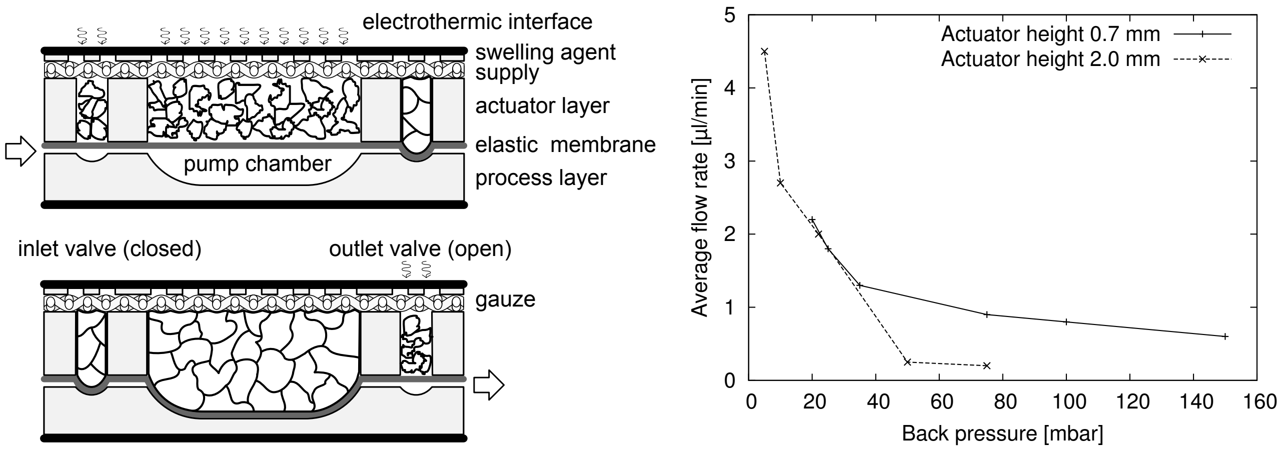
A well-known stimuli-responsive hydrogel, which is often used as actuator material, is poly(N-isopropylacrylamide) (PNIPAAm) [7]. It has a lower critical solution temperature (LCST), thus it shrinks when heated over this temperature and swells when cooled down. Typically, this LCST is around 33°C. Fig. 1(a) shows the change of volume of a PNIPAAm particle depending on temperature. Switching between the completely shrunken and the completely swollen state is possible within a temperature range of 6 K [8].

PNIPAAm can be synthesised and cross-linked in many different ways, common methods are thermally initiated simultaneous radical polymerisation and cross-linking and photo-patterning [9].

Fabrication

In order to produce integrated microfluidic processors, one fabrication method applicable for all necessary elements has to be found.

The substrates of the valves and pumps were fabricated with soft lithography methods based on poly(dimethylsiloxane) (PDMS) [10]. Bonding was achieved by using different mixing ratios of PDMS kit components A and B as described in [11]. For the elastic membrane, a ratio of 3:1 (A:B) was used, fabrication was done by spin coating. Structured process layer, actuator layer and swelling agent supply (see Fig. 2(a)) were manufactured by casting of PDMS in a ratio of 30:1 (A:B).



(a) Design and principle of the micropumps

(b) Generated flow of pump chambers with different thickness of actuator chamber

Fig. 2: Micropumps with separate swelling agent supply layer [12].

The master moulds were made by a modified dry photoresist technology originally used in the printed circuit-board fabrication [8]. This technology does not require microfabrication facilities and is rapid and inexpensive.

The hydrogel actuators were synthesised in two different ways, either in situ by photopatterning or ex situ by thermally initiated simultaneous radical polymerisation and milling.

The temperature was set by an electrothermic interface. The conversion of electrical power to heat was done by resistors on a conventional printed circuit board (PCB).

Microvalves and Micropumps

Standard components of microfluidic systems are micropumps and microvalves. Pumps transport fluids by generating a flow or a pressure, valves are able to open and close channels and thus control the flow inside a microfluidic device.

Micropumps. Here, displacement pumps were realised based on PNIPAAm actuators [12]. The design is shown in Fig. 2(a). The main parts are the process and the actuator layer, that are separated by a tensioned elastic membrane. In the process layer the pump chamber is located, were the liquid is processed. The hydrogel is placed inside an actuator chamber within the actuator layer. In normal, cool state (temperature below LCST), the hydrogel actuator is swollen and the elastic membrane deflected. By heating over the LCST, the hydrogel shrinks and the membrane relaxes, thus the chamber is filled. After cooling down again, the membrane is deflected by the hydrogel and the fluid is pushed out of the pump chamber.

To pump in a defined direction, additional measures like check valves or controlled valves are required, the latter are shown in Fig. 2(a).

Diffusion ways for the pump actuator have to be kept as short as possible in order to achieve fast pumping, therefore the dedicated layer for swelling agent supply was introduced. The use of milled particles instead of bulk gels increases the pumping speed further. Drawback of the approach of a separate swelling agent supply layer is the increased complexity of the design and increased manufacturing effort. If only very small pumps are needed or a slow speed is sufficient, this layer can be omitted and SAS integrated into the actuator layer.

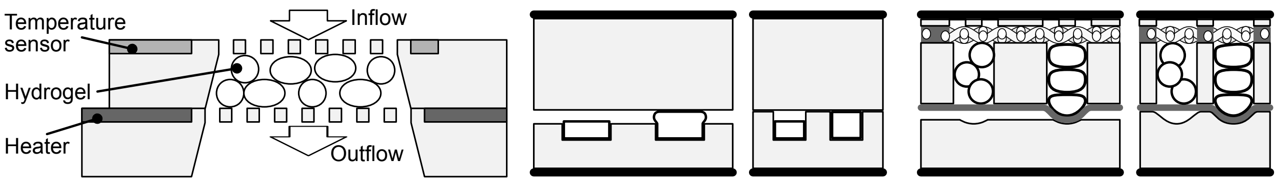
Fig. 2(b) shows the performance of the micropumps.

Metering can be done by simply filling and emptying the pump chamber completely, so a defined volume will be pumped in one cycle.

Microvalves. Hydrogel based valves fabricated in silicon reached opening times of 300 ms and closing times of about 2 s [13].

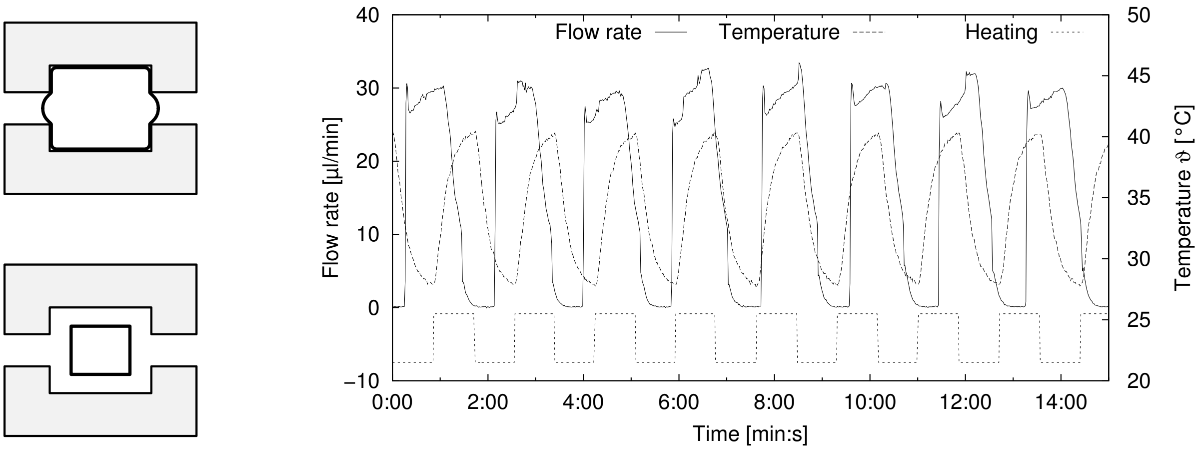
The hydrogel actuators of the valves can be located directly in the process channel (Fig. 3(b)) or can be placed in a separate layer (Fig. 3(c)). In the first case, the process fluid acts as swelling agent, in the second case a extra swelling agent supply is necessary. While this supply means an increased complexity of the design, it avoids any influence of the properties of the process fluid on the actuation characteristics of the hydrogel and vice versa. The location of the valves can also be chosen depending on the Swelling agent supply of the pumps so a consistent technology is used.

The electrothermic control provides full flexibility when changing the states of the valves.



(a) Actuator in process layer (silicon based technology) (b) Actuator in process layer (c) Separated actuator layer

Fig. 3: Different types of microvalves (side view).



(a) Design (top view); top: closed, bottom: open (b) Performance

Fig. 4: Microvalve in polymeric integrable channel structure. Heating power 245 mW, 52 s on, 52 off.

Fig. 4(b) shows the switching behaviour of a valve placed directly in the process layer (Fig. 4(a)). The hydrogel actuator (450 µm x 550 µm x 200 µm in dry state) is located in a slightly bigger chamber (50 µm x 550 µm x 200 µm). It opens in about 1 s and closes within about 20 s.

Chemostats and chemical transistors

As hydrogels like PNPAAm respond to small alterations of the environment and thus combine both sensor and actuator properties, they allow their usage as sensors for these physical or chemical properties [4]. By combining the sensing and actuating abilities, new functionalities, for example inexpensive and simple closed loop control systems, can be realised. Hydrogel-based chemostats are able to adjust different properties (e.g. ph-value or concentrations) in a liquid mixture and mechanically tunable. Both normally open and normally closed chemostats automatically regulating the concentration of a chemical substance by changing the volume of the actuator chamber were realised [14]. Changes in

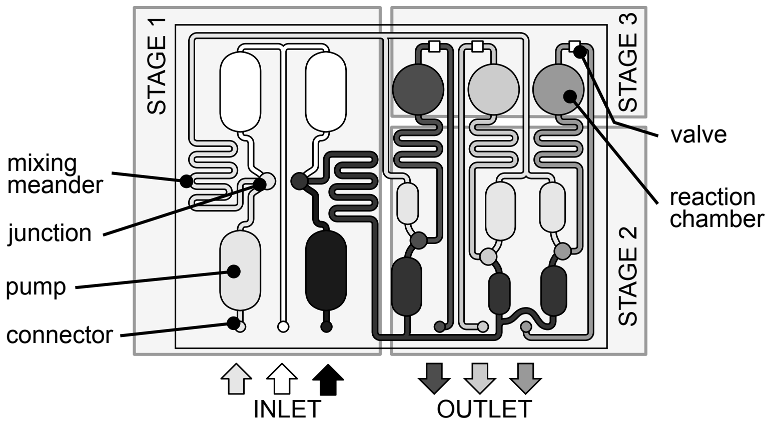


Fig. 5: Schematic of a microfluidic processor.

the swelling agent of PNIPAAm-based hydrogels, e.g. changes in its concentration, can lead to a shift of the gels LCST (fig. 1(b)). Therefore, by setting the temperature by an electrothermic interface, a so-called chemical transistor can be realised. That was done in the design shown in Fig. 3(a) [5].

Integrated microfluidic systems

By combining a number of the described basic elements to a system, microfluidic processors such as µTAS (Miniaturized Total Chemical Analysis System [15]) can be built. The possibility to electronically control each element separately allows to run complex programs, which can be changed and adjusted easily as they are not ”hard-coded” into the fluidic processor.

For proper functionality of the system it is necessary to ensure a correctly set temperature for each element. This becomes more challenging with higher integration degree. A possible solution is the use of an optoelectrothermic control as described in [8].

The microfluidic systems can be simplified by omitting elements, that are not necessary for the correct operation. For example, not every pump needs an inlet and an outlet valve, if pumps are connected in series. Valves can even be omitted completely, if the pumps are controlled in a way, that a pump chamber is be emptied at the same time when the posterior is being filled.

Simple mixing processes in microfluidic devices can be accomplished with meander-shaped channels. If a sufficient mixing is not achievable with these, a Staggered Herringbone Mixer (SHM) can be used [16]. These mixers work passively, thus they can simply replace the proposed meanders.

Fig. 5 shows the schematic of an exemplary microfluidic processor, which is able to mix fluids in different, defined ratios and store the mixture in reaction/monitoring chambers in order to perform enzyme-kinetic assays. It performs its tasks in three stages. In the first stage, it sets a defined environment by mixing both, enzyme probe and substrate, with a buffer solution. In the second stage, enzyme probe and substrate are mixed in different ratios and finally, in the third stage, these mixtures are stored in a reaction chamber, which is transparent and thus can be monitored externally. There the reaction of the substrate to the product catalysed by the enzyme can be analysed photometrically. After rinsing the whole processor with the buffer solution, it is prepared for new assays, thus it is reusable.

Summary

With the help of the proposed fabrication technology and the thereby realised microfluidic elements, low-cost, complex microfluidic systems can be created. The electronic control ensures full flexibility regarding the program sequence.

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