Development of Stimulus-Sensitive Hydrogels Suitable for Actuators and Sensors in Microanalytical Devices

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Stimulus-sensitive hydrogels are polymeric materials which have a number of properties that make them interesting as materials for fabricating microsensors and microactuators, especially with respect to their swelling and shrinking behavior in response to a stimulus like pH or temperature. These properties include: low power consumption, good elasticity, simple hydrogel fabrication using cleanroom compatible UV-photolithography techniques and the fact that stimulus-sensitive hydrogels are powerful materials. In combination with pressure transducers, sensors can be made for gasses such as NH_3 and CO_2. The advantage of this type of sensor is the absence of a reference electrode that is used with electrochemical sensors. By using hydrogels as actuators, it should be possible to fabricate microactuators for valves and pumps that have superior closing properties and dust tolerance over conventional actuators. To overcome the issue of long response time constants we give a number of possible solutions such as the use of microspheres made of a stimulus-sensitive hydrogel.

1.   Introduction

   Stimulus-sensitive hydrogels, which are types of water swellable polymers that shrink and swell as a function of parameters (so-called stimuli) such as pH and temperature, have been investigated for a considerable amount of time for applications such as advanced drug dosing and polymer artificial muscles.[1,6] Recently, research has been initiated to see if the same hydrogels can be exploited for the fabrication of microactuators and microsensors in

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microanalytical devices.

It is the aim of this paper to give an introduction to this new field and show some of the approaches used by our group and the results obtained. This is to give an idea of potential applications of stimulus-sensitive hydrogels in microanalytical devices.

An example of the work done recently on the use of stimulus-sensitive hydrogels in the microanalytical field is the work done on hydrogel microvalves[2,3] which has been published by Beebe et al. showing that hydrogels can be used with good results to seal microchannels in a reversible manner. Another example is the work done by our group which shows that a pH-sensitive hydrogel in combination with a pressure sensor can be used to fabricate a CO_2 sensor (as explained below).

The main reasons why research is being performed on the development of hydrogels for microactuators and microsensors are: powerful actuator performance, good elastic properties, low power consumption, low actuation voltage, pH-sensitivity and simple fabrication using cleanroom compatible UV-photolithography.

In our group, there are two main hydrogel research interests. The first is the development of micro fluidic actuators that are based on hydrogels for micro flow control applications such as microvalves and micropumps. The second is the development of a microsensor based on a hydrogel in combination with a pressure transducer to fabricate a CO_2 sensor.

In this paper, first a short overview of the theory behind stimulus-sensitive hydrogels will be given which will explain why these hydrogels swell and shrink as a function of pH or temperature. After this it will be explained why hydrogels are interesting materials for microsensor and microactuator applications and in the experimental section, the details of the fabrication of the hydrogel devices will be given. Finally obtained research results will be reported.

2. Theory

A stimulus-sensitive hydrogel consists of a polymer matrix that contains a large amount of water. The amount of water in the hydrogel, which can be up to 95%,[4] is a function of several parameters such as the pH and the temperature of the aqueous environment the hydrogel is kept in. The variation in the amount of water inside the polymer as a function of one of these parameters results in volume changes of the polymer which are on the order of several tens of percents between the "swollen" and the "shrunken" state.

A stimulus-sensitive hydrogel is generally made up of the following components (see Fig. 1):
- backbone monomers (*e.g.*, acrylamide) which form the major part of the polymer network
- comonomers which can be weak acids (e.g. acrylic acid) and weak basic comonomers (*e.g.*, 4-vinyl pyridine) or comonomers which can form hydrogen bonds that are labile above a certain critical temperature (*e.g.*, N-isopropylacrylamide).
- crosslinkers which keep the polymer chains attached to each other and which are used to control the elastic as well as the swelling properties of the hydrogel (*e.g.*, ethylene glycol dimethacrylate)

The swelling and shrinking of a stimulus-sensitive hydrogel is the result of two

Fig. 1.   Simplified view of the composition of a stimulus-sensitive hydrogel.

opposing forces that are present in the hydrogel. The first force is the result of the attractive interactions between the comonomers and water and the repulsive interaction between charged comonomers with equal sign of charge. This force will result in an outward movement of the hydrogel and causes the hydrogel to swell by promoting an influx of water and hydrated ions into the hydrogel matrix. The force originates from electrostatic and hydrogen bond interactions between comonomers and water and repulsive electro-static interactions between comonomers.

The second force, which opposes the first one, tends to pull the polymer chains together to minimize their exposure to the water and promotes an efflux of water. This shrinking force is a result of van der Waals and hydrophobic interactions between the hydrogel backbone molecules.

When the two opposing forces in a hydrogel are in equilibrium, the hydrogel will have a constant volume. When the forces are not in equilibrium, the volume of the hydrogel will change. When the swelling force is dominant, the hydrogel will swell until a new equilibrium has been reached and when the shrinking force is dominant, the hydrogel will shrink until a new equilibrium has been reached.

In the case of a pH-sensitive hydrogel, a hydrogel containing groups with pH-depen-dent ionization, the swelling force increases dramatically when the acid or basic comono-mers are ionized. This is because the ionized comonomers have a larger interaction with water molecules than the unionized comonomers.

In thermosensitive hydrogels, the swelling force will decrease above a certain critical temperature (lower critical solution temperature, LCST). This is a result of the fact that the hydrogen bonds between the monomer groups and the water molecules, which are thermo-labile, will be disrupted by thermal agitation around the critical temperature. This means that the interaction energy between the polymer network and the water will decrease, resulting in a smaller swelling energy.

The swelling and shrinking of a hydrogel as a function of a certain stimulus can be visualized in a so-called swell curve which plots a particular dimension of the hydrogel such as the diameter of a hydrogel disc as function of a stimulus. Figure 2 shows the swell curve of a temperature-sensitive hydrogel.

It should be mentioned here that the flux of water through a hydrogel is a very slow process. Thus for actuators to be fast, the hydrogels need to be in the micrometer range.
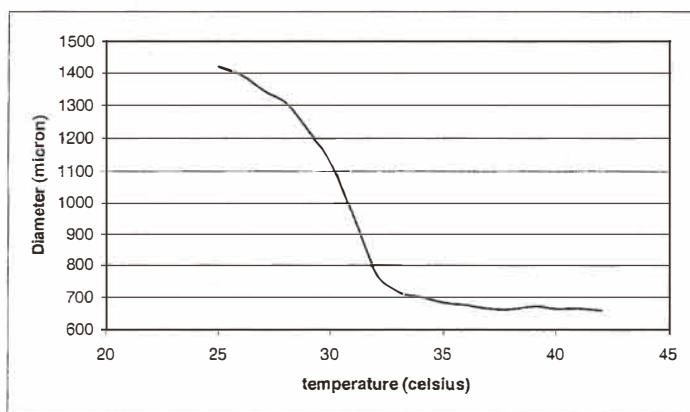
Fig. 2.   Swell curve of a temperature sensitive hydrogel. The diameter of a 1000 μm hydrogel disc was measured as function of temperature. Gel: poly-NIPAAm with 4% crosslinker (see description in experimental).

For instance the swelling of a 1 mm hydrogel sphere takes approximately 0.6 h while the swelling of a 1 μm hydrogel sphere takes about 2 ms.[5]

3.   Hydrogel Applications

The main applications for hydrogels in the past have been the manufacture of contact lenses and absorbents. This has been because of the biocompatibility of certain hydrogels and the property of some hydrogels to absorb large amounts of water. In the research field, there has been a large research effort to explore the use of hydrogels for drug dosing applications.

Only since recently, research has been conducted to explore the use of hydrogels in microsystem technology. This research is mainly focused on the use of hydrogels for microsensors and microactuators.

Below, the use of hydrogels for microactuation and microsensing purposes is discussed in two separate sections.

3.1   *Actuator applications*

Because a hydrogel contains a large amount of water, hydrogel structures tend to be soft and flexible. This gives a hydrogel actuator a certain advantage over hard actuators such as metal or silicon actuators because the actuator shapes itself after objects it encounters during expansion such as channel walls or dust particles. This property results in superior closing properties and dust tolerance of hydrogel-based microvalves.

Hydrogels are powerful materials. The power of these actuators is on the same order as a human muscle. Experiments to manufacture artificial muscles with hydrogels have

revealed that powers in the range of 100 N/cm^2 can be reached.[6]

Furthermore, an interesting feature of hydrogel microactuators is that they do not need high actuation voltages such as is the case with PZT actuators or use high currents like electro-magnetic actuators. Instead, a hydrogel microactuator can be controlled by using a low-power heater resistor to generate temperatures above the critical temperature of a temperature sensitive hydrogel (LCST) or by using local electrolysis to change the pH of the environment surrounding a pH-sensitive hydrogel. This last scheme uses two electrodes in an aqueous solution between which a small voltage is present (2V) to either generate acid or base particles according to the following electrolysis equations:

$$\text{Cathode:} \quad 2\,H_2O + 2\,e\text{-} \rightarrow H_2 + 2\,OH^-$$
$$\text{Anode:} \quad \ 2\,H_2O - 4\,e\text{-} \rightarrow O_2 + 4\,H^+$$
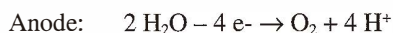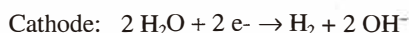
Depending on whether the electrode near the hydrogel is the anode or the cathode, the hydrogel will swell or shrink in response to the current applied through the electrode. When this current is reversed, the swelling or shrinking is reversed.

The application of hydrogels for microactuators is made easy because the actuators can be made very easily using a technique called photopatterning. This technique results in hydrogels with accurate dimensions and arbitrary 2D shape. The photopatterning technique is explained below in more detail.

3.2 *Sensor applications*

Hydrogels can be used to make sensors in a number of ways. One way is to deposit a pH-sensitive hydrogel on top of a conductivity sensor and measure the conductivity of the hydrogel as a function of the pH. In this way, it is possible to fabricate a pH sensor. This principle was reported by Sheppard *et al.*[7]

Another method, being developed by our group, is to use a pH-sensitive hydrogel in combination with a pressure sensor and to measure the pressure that the pH-sensitive hydrogel generates inside the pressure sensor by swelling due to pH changes. In this way a pH sensor can be fabricated which can measure the pH of a solution in the range of 2 pH units around the pKa of the pH-sensitive comonomer. An advantage of this approach is that no reference electrode is needed as is necessary with electrochemical measurement techniques.

Using the pH-sensitive hydrogel/pressure sensor combination, it is also possible to measure dissolved gasses that alter the pH of water by either acidifying the water like CO_2 or by alkalizing the water like NH_3. Because the pH of the water is dependent on the gas concentration, the pressure signal will be a measure of the concentration. For this application, it is necessary for the pH sensitive comonomers to have a pKa value near the pKa of the dissolved gas, which for instance is the case for the comonomer acrylic acid (pKa=4.6) and carbon dioxide (pKa=6.4). See below for results of a CO_2 sensor fabricated using this approach.

4.   Experimental

Chemicals: N-isopropylacrylamide (NIPAAm), 2-hydroxyethyl methacrylate (HEMA), ethylene glycoldimethacrylate (EGDMA), 2,2-dimethoxy-2-phenylacetophenone (DMPAP), dimethylsulphoxide (DMSO), acrylic acid (AAc), 4-vinylpyridine (4-VP), ethanol and N,N-methylene ethylene bisacrylamide (bis) were used without further purification.

Preparation of the hydrogel photopatterning solutions:

pH-sensitive hydrogel with weak acid comonomer:
1. HEMA   7.8 mL
2. AAc   1.1 mL
3. EGDMA   111 μL
4. DMPAP   400 mg

All components were mixed and dissolved in a plastic container that was shielded against light with aluminum foil to prevent unwanted photopolymerisation of the solution. After all the components were dissolved, the container was stored at 4°C in a refrigerator until use.

pH-sensitive hydrogel with weak basic comonomer:
1. HEMA   7.8 mL
2. 4-VP   1.7 mL
3. EGDMA   111 μL
4. DMPAP   400mg

All components were treated in the same way as the solution above.

Temperature sensitive hydrogel (4% crosslinker):
1. NIPAAm 5.7 g
2. bis   301 mg
3. DMPAP   387 mg
4. DMSO   10 mL

All components were treated in the same way as the first solution.

The photopolymerisation was carried out in a silicon microchannel using a low-power 365 nm light source for thin-layer chromatography. The microchannel was fabricated in silicon by etching to a depth of 50 μm using deep reactive ion etching (DRIE). The microchannel can be seen in Fig. 3 showing patterning results with a mask with a round aperture.

A research pipette was used to fill the channel with the photopolymerisation solution and a teflon cover sheet (30 μm thickness, DuPont) was applied over the filled microchannel to avoid evaporation of the photopatterning solution. After aligning the mask with the channel, the solution was exposed to a 365 nm light source to polymerize the hydrogel. For the weak acid and basic comonomer hydrogels, the exposure time was 3 minutes. For the temperature-sensitive hydrogel, the exposure time was 30 s. After UV exposure, the cover sheet was taken off of the microchannel and unexposed parts of the hydrogel photopatterning mixture were washed away with analytical grade ethanol.
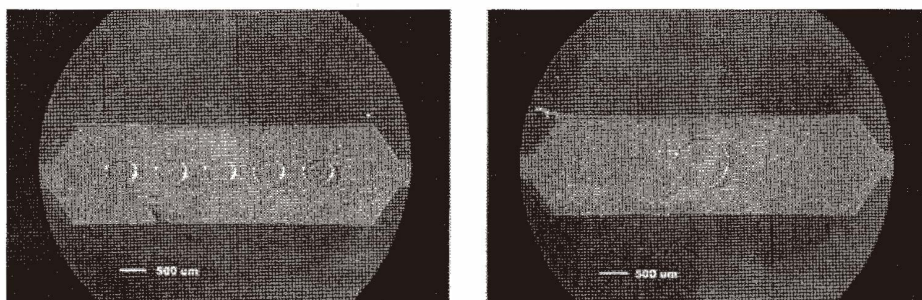
Fig. 3.   Thermosensitive hydrogel patterning results obtained using 365 nm UV photolithography. The disc in the left figure is 500 μm in diameter and the disc in the right figure is 1000 μm in diameter. Exposure time is 30 s, developer is ethanol p.a.

5.   Results

5.1   *Photopatterning of hydrogels*

The standard way to fabricate hydrogels is to make a monomer solution and add a so-called initiator. This is a compound that starts the polymerisation reaction which results in the formation of the hydrogel network. Normally, the initiator will be a thermal initiator which is a nonselective compound i.e., the reaction proceeds in the whole monomer solution and no local control of the polymerisation is possible. Fabrication of a hydrogel microactuator using such an initiator is difficult and requires additional fabrication steps such as the incorporation of hydrophobic patches on the chip surface to keep the polymerizing solution in a confined region of the chip where the actuator needs to be formed.[8] Also the application of the monomer solution is difficult and polymerisation times can be long (on the order of minutes for thermosensitive hydrogels).

On the other hand, the use of a special kind of initiator called a photoinitiator overcomes the problem of additional processing steps, which is much easier because the monomer solution does not need to be applied locally and the polymerisation time is fast (30 s for thermosensitive hydrogels). A photoinitiator is a compound that can start the polymerisation reaction in response to irradiation by UV light. By using a photomask, the UV light can be applied locally and thus hydrogels can be made locally [2] in, for instance, a microchannel.

The photopatterning of hydrogels is very easy and compatible with standard 365 nm UV photolithography techniques used in most cleanrooms. It is possible to photopattern hydrogels in almost every shape desired. The results of this are shown in Fig. 3.

5.2   *Tailoring of hydrogel swelling*

The properties of hydrogels can be tailored easily by altering the chemical composition of the hydrogel. For instance the swelling of a pH-sensitive hydrogel can be increased by incorporating more of the ionizable comonomer into the hydrogel matrix. Also the

maximum displacement of a hydrogel can be altered by adjusting the amount of crosslinker in the polymer. With the last method it is possible to accurately make hydrogels with a predefined displacement. To design hydrogels using this technique, a graph showing the amount of swelling of a hydrogel as a function of the amount of crosslinker has to be plotted (see Fig. 4).

Using the graph in Fig. 4 we have been able to design a chip-based actuator for a pinch valve with accurate swelling properties that opened and closed a fluid channel comprising a 350 μm silicone fiber in response to changes in pH.

Initial tests of the closing pressure of this pinch valve are very promising. The valve could withstand the maximum pressure that can be applied by hand on a water filled syringe connected to the silicone fiber.

5.3 *Coulometric actuation*

In Fig. 5, the principle of coulometric hydrogel actuation is shown. By electrolyzing water, H^+ and OH^- ions are generated that induce volume changes in a pH-sensitive hydrogel that is close to one of the electrodes. In Fig. 5, the response of a hydrogel containing acid groups is shown in response to OH^- ions generated by the cathode.
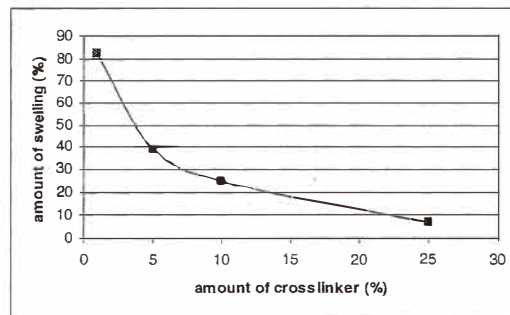

Fig. 4.   The amount of swelling of a pHEMA-co-AAc hydrogel as a function of the amount of crosslinker.
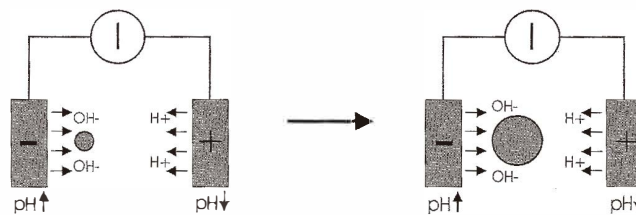

Fig. 5.   Response of a hydrogel containing acid groups to hydroxyl ions generated by local electrolysis of water.

In an experiment we have used photopatterned discs of hydrogels with basic groups (4-VP) on a gold electrode. This electrode was used in an electrolysis setup. Before electrolysis, the discs had a 1000 μm diameter and after electrolysis the discs had a 1350 μm diameter. The experiment was performed in a solution of 10 mM KNO_3 and the electrolysis was carried out using a current of 100–500 μm for 1–5 min.

5.4 CO_2 sensor

A CO_2 sensor has been developed by our group using a pH-sensitive hydrogel that contained the monomer acrylamide and the comonomer acrylic acid. This sensor consisted of a standard blood pressure sensor for infusion purposes (Truwave sensor, Baxter healthcare corporation) which was filled with the pH-sensitive hydrogel and closed by a metal membrane that allowed gas and water to pass through but kept the hydrogel in the pressure sensor.

The sensor was placed in a water bath which contained a buffer solution. This buffer solution was used to bias the sensor close to the pKa of the acrylic acid monomer present in the hydrogel. This was done because the sensitivity of the sensor to a pH change caused by CO_2 will be highest when the pH is close to the pKa of the acrylic acid monomers.

Two gasses were used in our setup. The first gas was carbon dioxide which was the gas to be measured. The second gas was nitrogen which was used to flush the carbon dioxide gas out of the water after the measurement. During the experiment, the pH was monitored using a glass electrode.

In Fig. 6 results are shown of the influence of the CO_2- induced pH changes on the pressure sensor signal showing that these pH changes due to CO_2 can be measured using this setup.
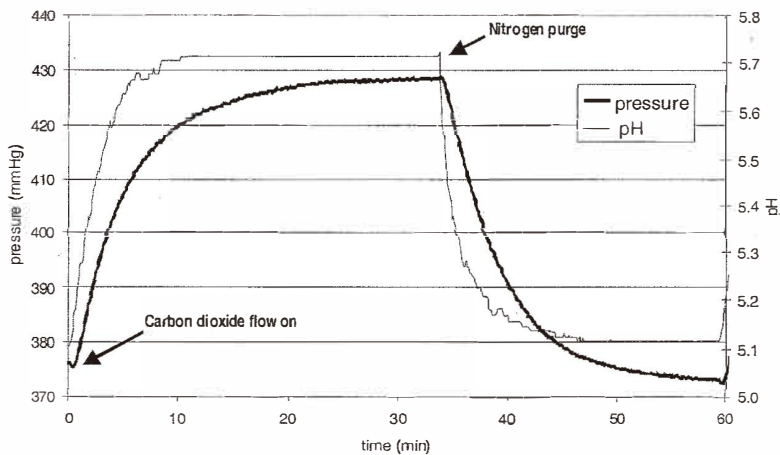

Fig. 6.   Results of CO_2 measurement using a pH-sensitive hydrogel in conjunction with a pressure sensor. The thick curve is the pressure curve and the thin curve shows the pH of the bathing solution surrounding the sensor. The pH was measured with a normal glass electrode.

5.5 *Hydrogel microspheres*

Because hydrogel swelling and shrinking is a slow process, hydrogel sensors and actuators are also slow. To overcome this problem, hydrogel microspheres can be used. Hydrogel microspheres are very small spherical hydrogel particles which, due to their small size, will have a much faster response to a pH change than a large hydrogel. By replacing a large hydrogel with the same volume of microspheres, the response time of, for instance, a hydrogel sensor can be made much faster. This is because the swelling and shrinking of a hydrogel is a diffusion process and the diffusion distance in a small sphere is much smaller than in a large hydrogel. Effectively, the diffusion process is converted from a slow serial process to a fast parallel process.

Recently, the use of hydrogel microspheres has been investigated for application in the CO_2 sensor mentioned above. Instead of filling the sensor with a large hydrogel, the sensor was filled with microspheres synthesized by a method published by Eichenbaum *et al.*[9] The response time of the sensor to a pH change was much faster than that of a sensor fabricated earlier that used a single large hydrogel as can be seen in Fig. 7.

The sensor using microspheres still has a time constant in the minutes range instead of in the seconds range. This is almost certainly due to the use of the filter membrane which covers the sensor to keep the microspheres from being released in the bathing solution. By using a better membrane that has appropriate characteristics such as higher water permeability, the time constant of the sensor should be shifted towards the seconds regime.

6. Discussion

Because the process responsible for the swelling and shrinking of the hydrogels is a slow process, the time constants of hydrogel microsensors and microactuators are very large compared to those of other microsensors and microactuators. To solve this problem, a number of solutions are available by keeping the size of the sensor or actuator as small as
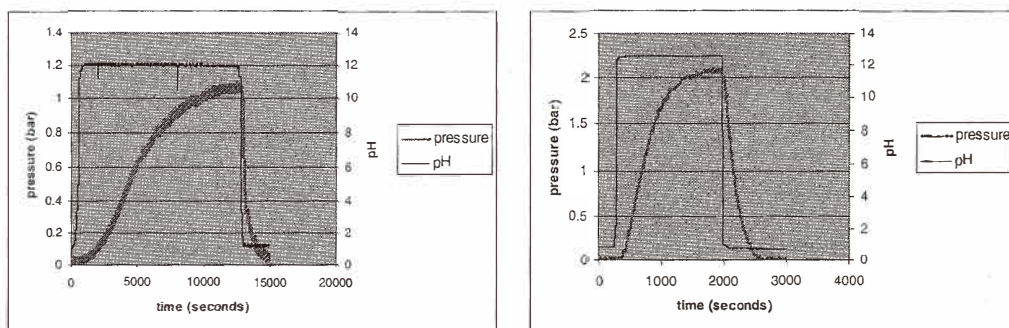

Fig. 7. Left: the pressure build up in response to a large step in pH of a hydrogel/pressure transducer combination with one large hydrogel. Right: the pressure build up when hydrogel microspheres are used. Note the different scales on the x-axes.

possible, thus minimizing the hydrogel volume, the time constant associated with the swelling and shrinking will decrease. Another solution is to use porous hydrogels.[10,11] These hydrogels have a porous structure which gives rise to higher water permeability and thus a decrease in the time necessary for the swelling and shrinking process to complete. Another approach to accelerate this process is the use of so-called hydrogel microspheres. These are micrometer size spheres made of stimulus-sensitive hydrogel which have response times on the order of milliseconds. By replacing a hydrogel block with the same volume of hydrogel microspheres, the time constant is reduced significantly because the swelling and shrinking process then consists of the parallel swelling and shrinking of a large number of fast microspheres instead of a single large and slow hydrogel block.

7.   Conclusions

Hydrogels are interesting for use in sensors and actuators in microanalytical systems because they have a number of interesting features such as: high flexibility, the need for only small operation voltages and currents, ease of fabrication and the fact that they are powerful actuators. As an illustration, a pH-stimulated microvalve and a CO_2 sensor, based on a hydrogel/pressure sensor combination, are described.

At the moment, hydrogel sensors and actuators are still in the developmental phase and several problems need to be overcome. One of these problems, the large time constant, can be overcome by using so-called microspheres to shorten the time needed for the movement of water in and out of the polymer matrix.

By continuing the research on hydrogels, it should be possible to develop a new family of microsensors and microactuators that can be of importance in microanalytical devices of the future.

References

1   O. Pillai and R. Panchagnula: Current Opinion in Chemical Biology **5** (2001) 447.
2   D. J. Beebe, J. S. Moore, J. M. Bauer, Q. Yu, R. H. Liu, C. Devadoss and B-H Jo: Nature **404** (2000) 588.
3   D. J. Beebe, J. S. Moore, Q. Yu, R. H. Liu, M. L. Kraft, B-H Jo and C. Devadoss: PNAS **97** (2000) 13488.
4   J. Varshosaz and M. Falamarzian: Eur. J. Pharm. Biopharm. **51** (2001) 235.
5   T. Tanaka, E. Sato, Y. Hirokawa, S. Hirotsu and J. Peetermans: Phys. Rev. Lett. **55** (1985)2455.
6   D. L. Brock: A. I. memo no 1330, Available at: http://www.ai.mit.edu/projects/muscle/papers/memo1330/memo1330.html
7   N. F. Sheppard, M. J. Lesho, P. McNally and A. S. Francomacaro: Sensors and Actuators B **28** (1995) 95.
8   K. Kobayashi and H. Suzuki: Sensors and Actuators B **80** (2001) 1.
9   G. M. Eichenbaum, P. F. Kiser, S. A. Simon and D. Needham: Macromolecules **31** (1998)5084.
10 H. Tamagawa, S. Popovic and M. Taya: Polymer **41** (2000) 7201.
11 B. Zhao and J. S. Moore: Langmuir **17** (2001) 4758.