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HYDROGEL-BASED CHEMICAL AND BIOCHEMICAL SENSORS

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Summary: Hydrogels are cross-linked polymer networks able to absorb or to release large amounts of water. The water uptake is associated with a considerable volume change but also with changes of optical properties like the refractive index. The swelling can be excited by a large spectrum of different physical (e.g. temperature, electrical voltage, magnetic field) and chemical factors (e.g. pH value, concentrations of chemical or biochemical species). The particular sensitivity can be adjusted by tayloring the composition of the hydrogel or via its functionalization. If the interaction between hydrogel and analyte to be measured is reversible then such hydrogels are becoming a promising candidate for miniaturized, cost-effective and inline-capable sensors.

Keywords: Hydrogels, swelling pressure, chemical sensors.

1. HYDROGELS IN MICROSYSTEM TECHNOLOGY

Hydrogels are cross-linked polymer networks able to absorb or to release large amounts of water [1]. This ability is caused by hydophilic functional groups attached to the polymer backbone. At the same time, due to the cross-links between the polymer`s network chains, hydrogels show an extremely high resistance to dissolution. Hydrogels exhibit a half liquid-like and half solid-like behavior.

The mechanical properties of hydrogels are characterized by a pronounced elastic modulus accompanied by a considerably smaller viscous modulus. The latter part can significantly influence repeatability and long-term behavior since it might cause creep [3].

The water uptake is associated with a considerable volume change. In doing so, hydrogels show remarkable properties:

- The strong volume change can be excited by a large spectrum of different physical (e.g. temperature, electrical voltage, magnetic field) and chemical factors (e.g. pH value, solvent concentration) [4].
- This swelling process is reversible.
- The energy density of hydrogels is very high what easily enables miniaturization.

All these properties make hydrogels a promising candidate for being used in sensors and actuators and allow their integration into microsystems. Hence, hydrogel-based microsystems enable novel sensor solutions in microsystem technology with a high potential for miniaturization and cost-effective fabrication, in particulur by using silicon-based MEMS technologies [5].

2. APPLICATION POTENTIAL OF HYDROGEL-BASED SENSORS

The property of hydrogels that the volume or other material parameters change depending on external measured variables can be easily exploited for chemical or biochemical sensors. This can be done simply by coupling the hydrogel to a corresponding transducer, which converts the change in hydrogel properties into an electrical signal. Hydrogels can be specially tailored so that they are sensitive to a particular measurand. The transducer can then be exploited as a platform technology serving as a family of sensors for a variety of (bio-)chemical species. Examples are the measurement of the swelling pressure by means of pressure or optical sensors.

In addition to this advantage, there are a number of further advantages:

- Unlike electrochemical sensors, no counter and reference electrodes are required, which are often the source of long-term instabilities.
- When measuring the swelling pressure, the separation between electronic components and the chemical part can easily be achieved (see Section 5).
- MEMS-based sensors are miniaturized and cost-efficient.

However, in addition to good sensitivity, chemical sensors should also exhibit high selectivity, good long-term stability and short response times. These are the issues on which the current research activities are concentrated and on which the following Sections are focused.

3. COOPERATIVE DIFFUSION AND SENSOR RESPONSE

The response of a hydrogel on changes of environmental properties is usually governed by a two-step mechanism [1]. In the first step, the stimulus triggering the swelling/shrinking must permeate the gel. The rate of this first step is determined either by heat transfer (for temperature-sensitive polymers) or mass transfer of ions or solvents wherein the first process is faster [6]. For that reason, thermo-sensitive gels can respond faster than chemo-responsive ones.

The second step is characterized by the change of the degree of swelling which is determined by the motion of the net chains of the polymer, the so-called cooperative diffusion. The response time depends on the square of the characteristic dimension (e.g. length, thickness) and is inversionally proportional to the cooperative diffusion coefficient.

To make hydrogel-based devices (e.g. sensors) fast, the cooperative difusion as well as the diffusion of the anylyte to be measured into and out of the hydrogel has to be as fast as possible. This can be achieved in two ways:

- The size of the hydrogel element should be small (e.g. thin). This requires miniaturisation what is in agreement with the MEMS technologies often used.
- The hydrogels should have an optimum porosity with respect to fast diffusion and mechanical stability at the same time [7, 8]. Therefore, hydrogels with a homogeneous pore distribution and simultaneously narrow size distribution are targeted [9].

4. OPERATIONAL PRINCIPLES OF HYDROGEL BASED SENSORS

The application of stimuli-responsive hydrogels in chemical sensors is based on their ability to undergo a volume phase transition under the influence of external stimuli (temperature, pH value, concentration of chemical and biochemical species). The stimulus lowers or increases an energy barrier between two possible states of the gel, a stable state (deswollen gel) and a metastable state (swallen gel). It has to be mentioned that a difference in the energy barrier hight between the forward and backward transitions leads to a hysteresis of the gel charactersitics and might influence both the reproducability and the signal response of the sensor [3].

- Hydrogel swelling is connected to a swelling pressure that can be determined via well-known MEMS-based piezoresistive pressure sensors (see Section 5) [10].
- Hydrogel swelling will cause bending when hydrogel layers are deposited on (e.g. micromechanical) bilayer cantilevers [11, 12].
- Hydrogel swelling in conjunction with the liquid absorbed by the gel influences the refractive index of the gel so that it can be evaluated by optical methods. For instance, reflective index changes can be evaluated advantageously by means of plasmonic sensor substrates with gold nanostructures (see Section 7) [13].
- In [14] a glucose-indicating hydrogel is demonstrated where binding of glucose leads to a change of fluorescence. Signal evaluation is carried out fluorescence-optically.

Sensitivity to a certain chemical species can be achieved by chemically tailoring the hydrogel, whereas responsivity to biochemical species, e.g. biomolecules, is reached via functionalization with appropriate enzymes. This enables a large variety of possible measurands like humidity, pH value, concentration of certain ions, ethanol content, glucose, and many more.

5. PIEZORESISTIVE HYDROGEL-BASED SENSORS

Figure 1 shows the operational principle of a hydrogel-based piezoresistive chemical sensor. The aqueous solution to be measured is pumped through the inlet channel into the cavity of the silicon chip. The corresponding ions cause the hydrogel (2) to swell or shrink, resulting in a swelling pressure that deflects the thin bending plate (3). This leads to mechanical stresses in the plate and, hence, via the piezoresistive effect in the piezoresistors (4), to an electrical output voltage.

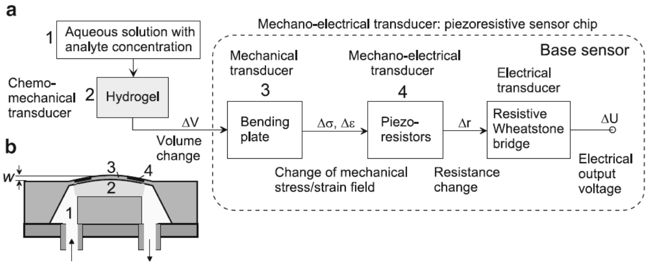

Fig. 1 (a) Operational principle and (b) cross-section of a hydrogel-based chemical sensor. 1 measuring solution; 2 hydrogel; 3 Si bending plate; 4 piezoresistors (from [1])

This principle has a number of advantages:

- The electrical components at the upper side of the bending plate is strictly separatet from the solution to be measured.
- Piezoresistive Si sensor elements are cost-effective and show –with respect to chemical sensors– an excellent long-term behavior.
- Signal processing is simple and robust.

The set-up of Fig. 1 can be used as an universal sensor paltform where sensitivity, selectivity and long-term stability as decisive sensor properties must be adapted for the particular measurement by choice of the appropriate type of hydrogel. Current research is working intensively to find and study appropriate hydrogels for a large number of possible analytes, including thermally, chemically and UV-cross-linkable hydrogels (Table 1).

Table 1**:** Hydrogels for the measurement of chemical analytes

Measurand, analyte	Hydogel	Ref.
pH-value	poly(vinyl alcohol)/poly(acrylic acid) (PVA/PAAc)	[1, 3]
	HPMA/DMAEMA/TEGDMA/EG	[12, 14]
Temperature	N-isopropylacrylamide (NIPAAm)	[1, 3]
Ethanol	PNIPAAm (MBAAm 4)	[15]
	poly(acrylamide-bisacrylamide) (Aam/Bis)	[16, 17]
NaCl, NaI	P2VPblock-P(NIPAAm-co-DMIAAm), PNIPAAm (MBAAm 4), PNIPAAm-DMAAm-DMIAAm	[18]
Transition metal ions	P2VP-block-P (NIPAAm-co-DMIAAm), PDMAEMA-DMIMA	[19]
Ammonia	poly(acrylic acid/2-(dimethylamino)ethyl methacrylate) (AAc/DMAEMA)[1])	[20]

[1]) Ammonia leads via the reaction $NH_3 + H_2 \rightarrow NH_4^+ + OH^-$ to a change of the pH value.

Table 2: Functionalised hydrogels for the measurement of biochemical species. The biochemical reactions lead to a change in pH value and, hence, swelling of the pH-sensitive hydrogels.

Measurand, analyte	Hydogel, functionalised with	Ref.
Glucose	HPMA/DMAEMA/TEGDMA/EG, glucose oxudase	[21]
Urea	Poly(Acrylic acid-co-Dimethylaminoethylmethacrylate)	[22]

6. SENSORS WITH FORCE COMPENSATION

A very efficient way to reduce response time and to enhance long-term stability is the usage of the force-compensation principle (Fig. 2) [23, 24]. Here the swelling due to the measurand is compensated by applying a counter force due to a second sensitivity. This leads to the situation that the hydrogel always stays in its initial state with a constant volume. The measurement signal is then taken from the micro-actuator applying the counterforce. Due to the almost constant volume no diffusion of analyte solution into and out of the hydrogel occurs what –regarding to Sections 1 and 2– avoids creep effects and shortens decisively the sensor response time (Fig.3).

Miniaturised force-compensation sensors can be realised by using a second (e.g. temperature-sensotive) hydrogel as actuator and control the volume constancy via a corresponding temperature change [25], e.g. by a Peltier element.

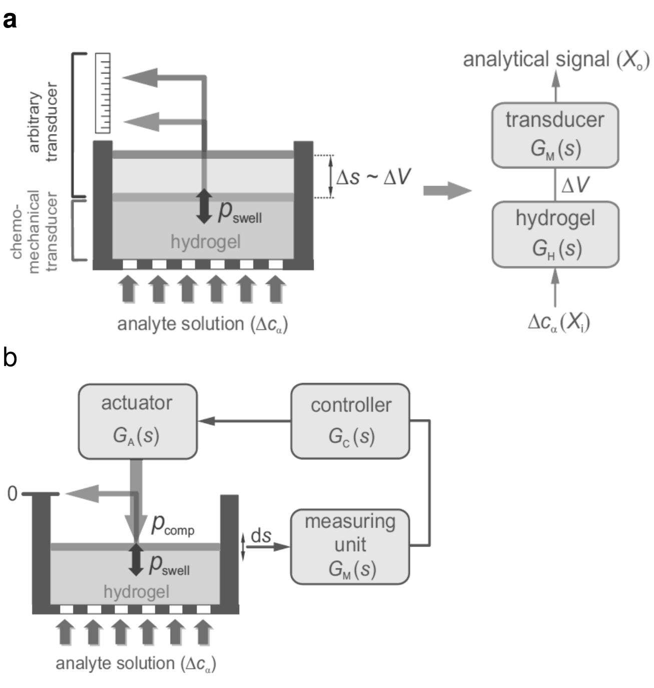

Fig. 2 (a) Open-loop and (b) closed-loop hydrogel-based chemical sensor, comprising the hydrogel as chemomechanical transducer and an chemo-mechano-electrical transducer, which converts the volume change ΔV of the hydrogel into an electrical output signal. As force-compensation sensor, the output signal is given by the compensation pressure (force) p_{comp} instead of the deflection-proportional output voltage (from [24]). p_{swell} swelling pressure; ds deflection; G_i transfer functions of hydrogel, measuring unit/transducer, controller and actuator, respectively

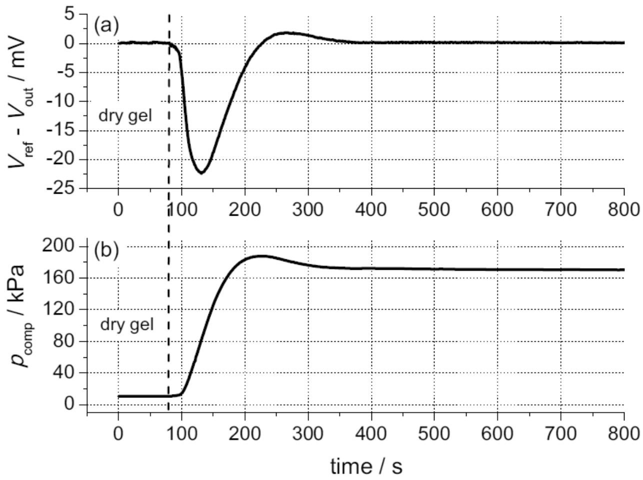

Fig. 3 Response of (a) the voltage difference $V = V_{ref} - V_{out}$ and (b) the sensor output signal p_{comp} for the initial swelling process in water

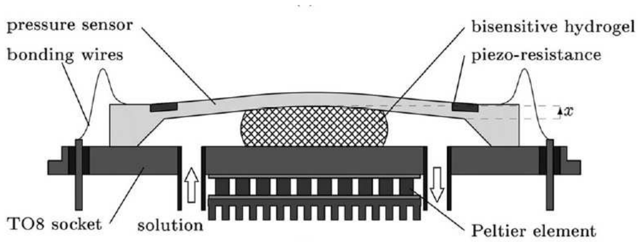

Fig. 4 Chemical sensor with force compensation using a bisensitive hydrogel that swells with respect to the measurand and where the volume can also be controlled via temperature (from [])

A novel way towards a simpler set-up is to integrate the sensor and the actuator hydrogels in one single hydrogel, so-called bi-sensitive hydrogels (Fig.4) [26]. It was shown that in particular interpenetrating networks show superior properties both with respect to sensitivity and mechanical stability [27].

7. HYDROGEL-BASED PLASMONIC SENSORS

Hydrogel-based plasmonic sensors consist of an optically active nanostructured gold substrate and a pH-sensitive hydrogel layer for the analyte-specific detection of refractive index changes. Gold nanostructures as often used are well-known to support localized surface plasmon polaritons, which induce a refractive index-sensitive optical transmittance behavior [28, 29]. Such structures can therefore be used as signal transducers for corresponding hydrogels [13]. The substrates are placed on an optical holder and are irradiated with a LED (875 nm central wavelength) in the spectral window between 750 and 1000 nm (Fig. 5). The light transmitted through the sensor substrate is collected with an optical fiber and directed to a spectrometer. The sensor signal originates from the superposition of the incident LED light spectrum and the extinction spectrum of the sensor substrate. From this superposition, a transmittance spectrum with a characteristic dip around 870 nm results. This dip, which represents the plasmon resonance wavelength, shifts upon refractive index changes occurring during the pH-induced swelling of the hydrogel.

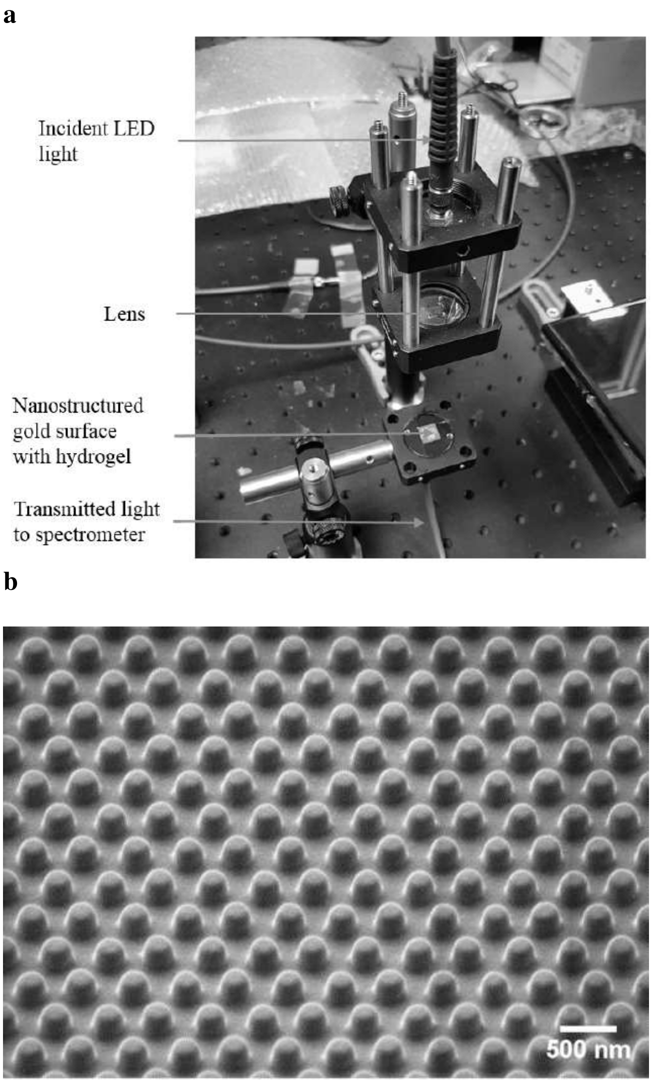

Fig. 5 (a) Set-up for analyzing the transmittance spectrum of plasmonic sensor substrates, (b) REM micrograph of the nanostructured gold surface (from [30])

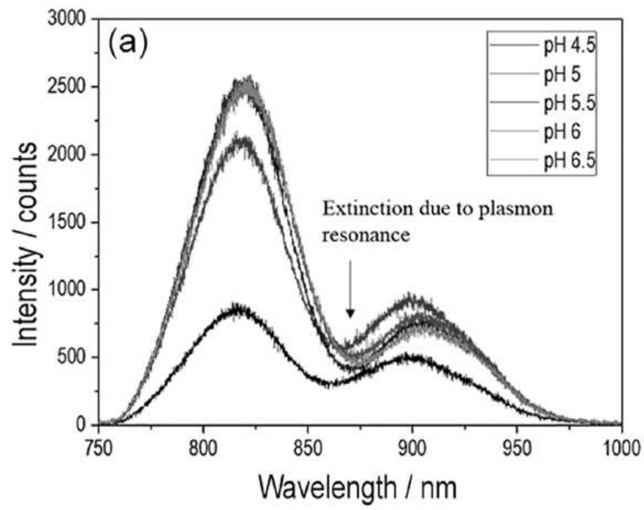

Fig. 6. (a) Transmittance spectra and (b) plasmon resonance wavelengths for swelling states of the pH-sensitive hydrogel for pH values between 4.5 and 6.5 (from [13])

The quality of the plasmonic sensor substrates, in particular the particle size distribution, is decisive for the measurement uncertainty. However, the manufacturing process has to be cost-effective and should allow the mass production. In [30] a nanopillar array was fabricated using nanoimprint lithography according to [31]. A silicon master fabricated by means of UV lithography is used to transfer a negative of the nanostructure into a PDMS mould. The PDMS is imprinted in an UV-curable SU-8 photoresist which is uniformly spread on the substrate carrier [30]. Finally, the substrates are coated with a 2 nm thick chromium adhesive layer and a 40 nm gold layer as the surface plasmon-active elements.

The resulting nanopillars have a diameter of 230 nm, a center-to-center distance of 450 nm and a height of 150 nm with a very narrow size distribution of only a few nm (Fig. 5b).

In [32] the plasmon resonance signal was evaluated with an advanced set-up comprising a double-layered photodiode, which is both the spectrally selective element and the detector at the same time due to its stack structure. Instead of extracting the spectral information from the spectrum itself, the centroid of the overall spectral distribution is evaluated in real time on the basis of the measured ratio of the two stacked, wavelength-dependent photocurrents. This cancels out the negative effects of aging of the light source and of temperature changes.

It was shown that with such a readout electronics a measuring accuracy for the centroid wavelength of 0.1 nm can be achieved, which corresponds to 10^{-3} RIU (refractive index units) for a refractive index sensor. The refractive index sensitivity amounted to 118 nm/RIU.

8. CONCLUSIONS

Hydrogels are a fascinating material which properties (e.g. swelling, refrective index) can be taylored with respect to a particular sensitivity to certain (bio-) chemical species and measurands, respectively. Their combination with a mechano-elctrical or optical transducer enbles the creation of sensor platforms for a large variety of variables. Besides sensitivity, also selectivity, long-term-stability and fast sensor response are crucial points which are in the focus of current research. The paper has shown different approaches to advance the properties of current hydrogel-based sensors, e.g., by force-compensation, porous hydrogels, and novel interrogation techniques. Most recent progress in research has already lead to first commercial products [14].

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CHEMICZNE I BIOCHEMICZNE CZUJNIKI HYDROŻELOWE

Hydrożele są usieciowanymi sieciami polimerowymi zdolnymi do absorbowania lub uwalniania dużych ilości wody. Pobór wody wiąże się ze znaczną zmianą objętości, ale także ze zmianami właściwości optycznych, takich jak współczynnik załamania światła. Pęcznienie może być wzbudzane przez różne czynniki (np. temperaturę, napięcie elektryczne, pole magnetyczne) i czynniki chemiczne (np. pH, stężenie substancji chemicznych lub biochemicznych). Pożądaną czułość można uzyskać przez odpowiedni skład hydrożelu lub poprzez jego funkcjonalizację. Jeśli oddziaływanie między hydrożelem a analitem, który ma być zmierzony, jest odwracalne, wówczas takie hydrożele stają się obiecującym materiałem do budowy miniaturowych, ekonomicznie opłacalnych czujników.

Słowa kluczowe: Hydrożele, ciśnienie pęcznienia, czujniki chemiczne.