Published in final edited form as:

Sens Actuators B Chem. 2009 February 2; 136(1): 186. doi:10.1016/j.snb.2008.11.001.

Free swelling and confined smart hydrogels for applications in chemomechanical sensors for physiological monitoring

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Abstract

We investigate thin films of “smart” polymer hydrogels used to convert miniature pressure sensors into novel chemomechanical sensors. In this versatile sensing approach, a smart hydrogel is confined between a porous membrane and the diaphragm of a piezoresistive pressure transducer. An increase in the environmental analyte concentration, as sensed through the pores of the membrane, is detected by measuring the change in pressure exerted by the hydrogel on the pressure transducer diaphragm. We compare the response of such a sensor with the response of a free-swelling hydrogel identical to the one used within the sensor. The sensor and the free hydrogel are observed to have comparable mean response times. However, the time-dependent response curve of the sensor, unlike that of the free hydrogel, is highly asymmetric between swelling and deswelling, with a smaller time constant for deswelling. We also investigate novel methods for increasing sensor sensitivity, such as use of a two-layer membrane with a nanoporous polymer inner layer, and pre-loading of the hydrogel under pressure. In ionic strength response tests, use of an inner membrane increases sensor sensitivity without increasing mean response time, an effect that varies with membrane water fraction.

Keywords

Chemical sensor; Hydrogel; Piezoresistive sensor; Smart material

1. Introduction

A ‘smart’ or ‘stimuli-responsive’ hydrogel is a cross-linked polymer network that reversibly swells and absorbs water in response to some external stimulus such as change in temperature, pH, or concentration of some analyte [1,2]. Since smart hydrogels are also biocompatible, they are highly suitable for use in implantable biomedical sensors and autonomous drug delivery devices [3], particularly when the hydrogel response time is reduced by miniaturization [4]. Many sensing approaches have been proposed that employ smart hydrogels [5], but perhaps the simplest sensing scheme can be obtained by confining a smart hydrogel between a porous membrane and the diaphragm of a miniature pressure transducer. In such a scheme, a change in the environmental analyte concentration, as sensed through the pores of the membrane, changes the hydrogel osmotic swelling pressure (see definition in Section 2.5), thereby

changing the mechanical pressure measured by the pressure transducer. Sensor selectivity can be enhanced by attaching moieties to the hydrogel that selectively bind the analyte of interest [6,7]. Fig. 1 shows our preliminary version of a “chemomechanical sensor” that embodies this sensing principle. The sensor consists of a piezoresistive pressure transducer with a cylindrical stainless steel sensing area (diameter 3.18 mm) completely covered with a hydrogel film (thickness $\approx 400\text{ }\mu\text{m}$). This hydrogel is held in place with a cap having a top surface that consists of a replaceable porous membrane through which mass transfer occurs. The smart hydrogel was synthesized in our lab and is responsive to both pH and ionic strength [8,9]. In previous work with this sensor, we performed tests with a single type of porous membrane and a single value of the hydrogel loading pressure, and analyzed the results neglecting mechanical compliance [9]. In the current study, we present some of the first results for the effect of variations in membrane pore size, open area, and rigidity on chemomechanical sensor response. This is important because the optimum pore size is not known *a priori*, and a tradeoff is likely to exist in its selection. On one hand, a membrane with larger pores and high porosity will allow rapid mass transport, which should reduce sensor response time. On the other hand, such a membrane may also allow the hydrogel to partially exude through the pores, which should reduce sensor sensitivity. Hence we present the results of empirical tests of the effect of the membrane and of the initial hydrogel loading pressure on sensor performance. We also compare the time-dependent response of the sensor with the time-dependent response of a free-swelling hydrogel identical to the one in the sensor. Outside the sensor, smart hydrogel response to an external stimulus is isotropic and unconstrained. However, when the same hydrogel is placed in the sensor, the swelling response is almost completely constrained in the transverse direction by the sensor sidewalls, and partially constrained in the axial direction by the porous membrane and pressure transducer diaphragm. Furthermore, the hydrogel in the sensor experiences elastic forces exerted by the porous membrane and the piezoresistive diaphragm that are not present outside the sensor. In order to assess the significance of these elastic forces, we compare the asymmetry of the time-dependent response (swelling vs. deswelling) for hydrogels inside and outside the sensor.

Although smart hydrogels have been studied for many years, their use as pressure-generating materials in chemomechanical sensors has been studied in only a few laboratories [6,9-12]. The most relevant previous studies were published by Herber et al. [11] and Trinh et al. [12]. Both of these publications include results for the time-dependent response of a chemomechanical sensor, as well as estimates of the degree of hydrogel constraint within the sensor. Trinh et al. [12] attached a pH-responsive hydrogel ($40\text{ }\mu\text{m}$ thick) to the backside of a piezoresistive silicon diaphragm ($20\text{ }\mu\text{m}$ thick), and used a rigid porous silicon membrane ($320\text{ }\mu\text{m}$ thick, $600\text{ }\mu\text{m}$ pore size) to hold the hydrogel in place. The deflection of the piezoresistive membrane during sensor response to pH was determined via nanofocus microscan measurements. Herber et al. [11] attached a pH-responsive hydrogel ($10\text{ }\mu\text{m}$ thick) to the front side of a silicon piezoresistive diaphragm, with the hydrogel held in place by a rigid microporous silicon membrane ($200\text{ }\mu\text{m}$ thick, $50\text{ }\mu\text{m}$ pore size). The hydrogel volume change was estimated to be less than 7% during sensor response testing. In both of these previous studies, commercial pressure chips were used in the construction of the chemomechanical sensor, which is also true for our prototype chemomechanical sensor (Fig. 1). In the future, we plan to fabricate chemomechanical sensors with custom-designed pressure chips, and the results presented here will guide the design of the porous membranes and piezoresistive diaphragms.

2. Experimental methods

2.1. Materials

The monomers hydroxypropyl methacrylate (HPMA), *N,N*-dimethylaminoethyl methacrylate (DMA), and tetra-ethyleneglycol dimethacrylate (TEGDMA) were obtained from Polysciences, Inc. and used as received. Ammonium peroxydisulfate (APS, Sigma-Aldrich), *N,N,N',N'*-tetra-methylethylenediamine (TEMED, Sigma-Aldrich) and Delbecco's phosphate-buffered saline solution (PBS, Sigma-Aldrich) were also used as received. Market grade wire cloth meshes (type 304 stainless steel) were obtained from Small Parts, Inc., Miramar, FL, USA. Nanoporous polyethylene terephthalate (PET) membranes made by ion bombardment and nonporous cellulosic paper membranes were donated by Andreas Koch of Oxyphen AG, Lachen, Germany.

2.2. Hydrogel synthesis

Polyelectrolyte pH-responsive hydrogels containing HPMA/DMA/TEGDMA at a nominal mole ratio of 70/30/02 were prepared by free radical cross-linking copolymerization as in Refs. [8,9]. In brief, nitrogen gas was bubbled through pregel solutions containing measured amounts of the monomers HPMA and DMA and cross-linker TEGDMA, after which the pregel solution was injected into a cavity (thickness 400 μm) between two square glass plates of surface area 64 cm^2 . Shortly thereafter, free radical polymerization was initiated at room temperature by injection of the initiator APS and the reaction accelerator TEMED. After 4 h at room temperature, the hydrogel slab was removed from the glass mold, cut into square samples (1–2.3 cm in length) and washed in PBS buffer (pH 7.4) for at least 2 days before testing. In order to accelerate the cleaning process, the hydrogels were subjected to several swelling/deswelling cycles induced by variations in bath ionic strength between 0.05 M and 0.15 M.

2.3. Sensor construction and sensor response tests

Fig. 1 contains a sketch of the chemomechanical sensor employed in this study. This is the same sensor employed in a previous investigation from this lab [9], though the porous membrane was varied in the current study as described below. The sensor consists of a piezoresistive pressure transducer (model EPB-501-5P, Entran, Inc., Fairfield, NJ, USA) with a cylindrical stainless steel sensing area (diameter 3.18 mm) completely covered with a hydrogel film of thickness $\approx 400 \mu\text{m}$. The hydrogel is held in place in the sensor by a cap with a top surface that consists of a replaceable porous membrane through which mass transfer can occur. The sensor cap porous membrane is a stainless steel wire cloth mesh (mesh size 40–200, corresponding mesh opening 381–74 μm), used with or without either an Oxyphen nanoporous membrane (pore size 0.1 μm , thickness 20 μm , porosity 15%) or a nonporous paper membrane (thickness 80 μm). The Entran pressure transducer was calibrated using a water column (pressure range 0–14 kPa) and an air manometer (model PCL-200 D from Omega, pressure range 0–65 kPa). A smart hydrogel was synthesized and cleaned as described above, a circular biopsy tool was used to cut a disc-shaped sample of appropriate diameter, and the sample was then transferred while in a deswollen state to the sensing surface of the pressure transducer using tweezers. The sensor cap with chosen wire mesh was attached to the sensor base by tightening three screws that were adjusted to impose an axial compressive stress on the hydrogel in the sensor. The sensor was then inserted into a large covered environmental bath containing PBS buffer at room temperature with known ionic strength (0.05 M or 0.15 M) and pH value (6.8 or 7.4). This bath also contained a magnetic stirrer used to minimize external mass transfer resistance to the sensor. Sensor response tests were performed by either injecting buffered saline solution into the environmental bath, or by rapidly switching the sensor into another environmental bath of differing ionic strength, and then noting the time-dependent response of the pressure transducer. The time-dependent pressure signal was captured with an Agilent data acquisition system.

2.4. Free-swelling tests

Hydrogels from the same synthesis batch were used in both the free-swelling tests and in the sensor response tests. Furthermore, in order to make the external mass transfer resistance as similar as possible, the same environmental bath was used in both types of response tests, with the same degree of stirring. In the free-swelling test procedure, hydrogel samples were pre-conditioned by soaking in PBS buffer until reaching equilibrium, and then transferred into the appropriate environmental bath. Periodically, a hydrogel sample was withdrawn and rapidly weighed after removing excess surface water by light blotting with a laboratory tissue. The time-dependent hydrogel sample weight W was monitored in this way until a steady value was obtained. The time-dependent swelling ratio Q was calculated as W/W_d , where W_d is the weight of the same hydrogel sample when completely dry. Dry weights were determined by weighing samples after several days of drying in a laboratory oven at 55 °C.

2.5. Thermodynamic analysis and predicted effect of initial hydrogel pressure

A simple working equation for the chemomechanical sensor can be derived by combining the standard model for the swelling of polyelectrolyte hydrogels [9,13-16] with the standard model for membrane osmometry [16]. This equation is by no means exact, but it nonetheless useful as qualitative guide to the trends that can be expected. For an unconfined polyelectrolyte hydrogel, the total free energy of swelling ΔF_{tot} contains three contributions: a negative contribution associated with the mixing of water with polymer segments, a negative contribution associated with the mixing of water with counterions, and a positive contribution associated with the stretching of the hydrogel network [13-16]. The osmotic swelling pressure Π is obtained by differentiating ΔF_{tot} with respect to moles of water [13-15]:

$$\Pi = - \left(\frac{\delta \Delta F_{\text{tot}} / \delta n_1}{V_1} \right) = \frac{(\mu_{1,0} - \mu_1)}{V_1} \quad (1)$$

In Eq. (1), V_1 is the molar volume of water, n_1 is the number of moles of water, μ_1 is the chemical potential value for water in the hydrogel *at ambient pressure*, and $\mu_{1,0}$ is the chemical potential value for water in the reference solution that surrounds the hydrogel. Hence $\Pi = 0$ for the unconfined hydrogel at equilibrium. However, Π can be increased above zero by compressing the hydrogel inside the chemomechanical sensor, thereby increasing the thermodynamic pressure of the hydrogel so that it exceeds that in the surrounding solution by an amount P . This is the same principle used in reverse osmosis or in membrane osmometry, and thus the standard thermodynamic equation for a membrane osmometer [16] may be applied here:

$$P = \Pi = \frac{(\mu_{1,0} - \mu_1)}{V_1} \quad (2)$$

The content of Eq. (2) is that the chemical potential of water in the hydrogel may be less than that in the surrounding solution (both calculated at ambient pressure), provided that the pressure in the hydrogel exceeds that in the surrounding solution by an amount $P = \Pi$. In a chemomechanical sensor response test, we must have $\Delta P = \Delta \Pi$, where Π is manipulated by varying environmental pH or ionic strength, and ΔP is measured by the piezoresistive diaphragm. Restricting attention to an ionic strength response test at fixed pH ≈ 7 , Π is a function of environmental ionic strength I and hydrogel swelling ratio Q , $\Pi = \Pi(I, Q)$. For example, osmotic deswelling experiments were performed on hydrogels with the same nominal composition as in the current study [9], and the results for Π from this previous study are well fit by the empirical equation:

$$\Pi = A Q^{-2} - B \quad (3)$$

Here A and B are constants determined empirically for a given choice of reference solution: $A = 5591$ kPa and $B = 93.1$ kPa at $I = 0.15$ M; $A = 5286.7$ kPa and $B = 38.5$ kPa at $I = 0.05$ M. Suppose we perform a sensor response test in which ionic strength I is suddenly reduced from $I_0 = 0.15$ M to $I_f = 0.05$ M. This increases the chemical potential of the surrounding water ($\mu_{1,0}$), or, equivalently, increases Π . In the ideal case, ΔP will increase by an amount $\Delta \Pi_0 = \Pi(I_f, Q_i) - \Pi(I_0, Q_i)$, where Q_i is the initial swelling ratio just before the start of the sensor response test. However, in practice, the piezoresistive sensor will respond to an effective Π change that is less than this, due to mechanical compliance that allows a slight increase in the hydrogel swelling ratio within the sensor. Hence the actual signal ΔP measured by piezoresistive diaphragm in a ionic strength response test is given by:

$$\Delta P = \Delta \Pi_0 - \Delta \Pi_1 = [\Pi(I_f, Q_i) - \Pi(I_0, Q_i)] - [\Pi(I_f, Q_f) - \Pi(I_f, Q_i)], \quad (4)$$

where Q_f is the final swelling ratio of the hydrogel in the sensor, $Q_f > Q_i$. The first term on the right hand side of Eq. (4) is the response of an ideal chemomechanical sensor with no mechanical compliance, and the second term is the correction for hydrogel swelling within the sensor. The postulated path of the hydrogel during the response test for a hydrogel loaded in the sensor at ambient pressure P_0 is shown schematically as A→B→C in Fig. 2. In Fig. 2, $\Delta \Pi_0$ is the vertical distance between points A and B, $\Delta \Pi_1$ is the vertical distance between points B and C, and the signal ΔP is the vertical distance between points A and C. Fig. 2 was constructed using Eq. (3) for Π , and assuming a linear proportionality between pressure and hydrogel swelling ratio:

$$P = H(Q - Q_0), \quad (5)$$

where H is the effective spring constant of the container that confines the hydrogel in the sensor, and Q_0 is the swelling ratio that gives zero gage pressure. It is obvious from Fig. 2 that the signal ΔP increases with increase in H , the slope of the line P vs. Q . However, ΔP becomes independent of H when H is sufficiently large; that is, when the line P vs. Q in Fig. 2 approaches the vertical. Now consider an ionic strength response test in which the hydrogel is loaded into the sensor at an elevated pressure P_{high} , $P_{\text{high}} > P_0$. In this case, the hydrogel may follow the path shown schematically in Fig. 2 as D→E→F. Eq. (4) still applies and may be used to compare the sensor response starting at P_{high} with the sensor response starting at P_0 . In the former case, the initial value of Π is of course higher due to hydrogel compression, but what matters for the signal is $\Delta \Pi_0$, and Eq. (3) predicts that $\Delta \Pi_0$ has essentially the same value at loading pressures of P_{high} and P_0 . The effective spring constant H may be larger for the test performed starting at P_{high} , which would tend to increase the sensor signal. On the other hand, Eq. (3) predicts that the osmotic modulus $\kappa = -Q \partial \Pi / \partial Q$, a measure of the resistance of the hydrogel to the loss of water by squeezing, increases with decreasing Q . If this is the case, then $\Delta \Pi_1$ will be larger for the sensor response test performed starting at P_{high} , which will tend to reduce the sensor signal (see Eq. (4)). As shown in Fig. 2, the predicted sensor signal is expected to be slightly less for sensor response tests performed at elevated loading pressure. However, this analysis is based on Eq. (4), which uses a single parameter H to characterize the effective constraint of the chamber and the piezoresistive diaphragm on the hydrogel, when in reality the elastic properties of the chamber and the diaphragm are anisotropic. We have also assumed that H is independent of loading pressure and hydrogel swelling ratio.

3. Results

3.1. Free-swelling tests

The synthesized HPMA/DMA/TEGDMA hydrogels are pH-responsive because they contain pendant tertiary amines (on DMA) that become protonated at sufficiently low environmental pH value, thereby temporarily increasing the osmotic swelling pressure Π of the hydrogel. The osmotic swelling pressure can also be temporarily increased by reducing the environmental ionic strength at fixed pH, which increases the chemical potential of the surrounding water. In either case, the temporary increase in Π is compensated for by swelling of the unconfined gel, and by some combination of swelling and increase in pressure P for the gel in the sensor (see Eq. (4)). From previous work on hydrogels of the same composition [8], the water content of the unconfined hydrogel varies with pH primarily in the transition pH range between 7.0 and 8.0. Fig. 3 shows the time-dependent change in the swelling ratio Q of the unconfined gel when the external pH value is cycled between 7.4 and 7.15 at fixed ionic strength in PBS buffer. As expected, Q is higher at the lower pH value (by about 25%), and the free-swelling response is both reversible and reproducible, albeit very slow. Fig. 4 shows the time-dependent change in the swelling ratio Q of the unconfined gel when the external ionic strength is cycled between 0.15 M and 0.05 M at fixed pH equal 7.4. As expected, Q is higher at the lower ionic strength value (by about 33%), and the response is once again reversible and reproducible. Comparing Figs. 3 and 4, the most obvious difference is the time scale of the response, which is about 50 times slower for the pH change than for the ionic strength change, even though the initial hydrogel thickness is the same and amount of swelling is similar. Siegel has already reported that hydrogels of similar composition can exhibit very slow pH response kinetics [17]. For our purposes, the key conclusions to be drawn from Fig. 3 are (1) the degree of protonation along the hydrogel backbone increases with decreasing pH and (2) the pH response time is so long for hydrogels of thickness 400 μm that drift of the pressure baseline is likely in the chemomechanical sensor. Thus we exclusively consider ionic strength sensor response in the following. The perceptive reader may also notice that the shape of the time-dependent response curve is different in Figs. 3 and 4. The time-dependent ionic strength response of the unconfined hydrogel accurately obeys the 2nd order kinetic model of Quintana [18-19], whereas the time-dependent pH response does not, nor does the time-dependent sensor response given below. Hence for qualitative comparison of response kinetics, we define τ_{50} as the time at which the change in the swelling ratio or the change in the swelling pressure reaches 50% of its long time value. In Fig. 4, τ_{50} is about 3 min for both swelling and deswelling, whereas τ_{50} is about 2.25 h for swelling and 3.5 h for deswelling in Fig. 3. The free-swelling response times are unaffected by changes in the width of the square samples (1–2.3 cm) at fixed initial thickness (400 μm).

3.2. Sensor response tests

In order to obtain good performance of the chemomechanical sensor (Fig. 1) in response to a reduction in environmental salt concentration (or pH), we must employ a porous membrane that allows rapid diffusive transport, and yet does not allow the gel to fully swell to its unconfined volume or to exude through the pores in the membrane. Since the membrane design parameters needed to achieve this are unknown, we begin by investigating sensor performance with off-the-shelf wire cloth meshes used as membranes. Fig. 5(a) shows an SEM micrograph of one particular stainless steel wire cloth mesh used as the permeable membrane in the sensor. The micrograph confirms that the mesh is highly regular with the parameters expected for 80 mesh wire: size of opening 178 μm , wire diameter 135 μm , open area 31%. The ionic strength response of the sensor used with this mesh is given in Fig. 6. Fig. 6 shows the swelling pressure as a function of time during cyclic variations in environmental ionic strength value I between 0.15M and 0.05M at fixed pH equal 6.8. In this experiment, a hydrogel was first transferred in a deswollen state from a PBS bath at $I=0.15\text{M}$ into the sensor, and then the sensor cap was tightened until the pressure signal increased by 11 kPa above the ambient value. The observed

sensor response in Fig. 6 is rapid and reversible, even for the first swelling cycle, provided that the hydrogel is subjected to several free-swelling cycles before loading into the sensor as recommended by Guenther et al. [20]. However, in some cases (2nd and 3rd cycles in Fig. 6), the sensor exhibits a slight overshoot measured to be of order 5% in response to the decrease in environmental strength. This phenomenon was previously reported by Herber et al. [11], who suggested that once the peak pressure is reached, a small amount of salt transfers out of the hydrogel, thereby reducing hydrogel swelling pressure Π . The response time τ_{50} in Fig. 6 is 6.4 min for swelling, and 2.3 min for deswelling, which may be compared with 3 min for both swelling and deswelling in Fig. 4. Thus confinement of the hydrogel in our chemomechanical sensor both increases the mean response time (at least for ionic strength changes), and produces an asymmetry between the kinetics of swelling and deswelling.

3.3. Influence of initial hydrogel pressure on the magnitude of the sensor response

In Section 2.5, thermodynamic arguments were used to predict the effect on ionic strength response of an increase in the hydrogel loading pressure, defined as the initial value of the gage pressure P prior to a sensor response test. This quantity can be adjusted by tightening or loosening the screws that attach the sensor cap to the sensor base, thereby increasing the pressure exerted by the porous membrane on the gel. The predicted effect of the hydrogel loading pressure was tested by cycling the environmental ionic strength twice between 0.15M and 0.05 M, and measuring the response of the sensor at two different values of the loading pressure. The results obtained are shown in Fig. 7, where the initial pressure values for the two cycles, from left to right in Fig. 7, are 11 kPa and 19 kPa. As a rough approximation, according to Eq. (3), an increase in loading pressure from 11 kPa to 19 kPa compresses the initial hydrogel volume by about 5%. As shown in Fig. 7, the sensor response magnitude increases from 40 kPa to 61 kPa. Thus the sensor sensitivity increases significantly with increasing loading pressure, in disagreement with the predictions put forth in Section 2.5. In between the two cycles in Fig. 7, one also observes that tightening of the sensor screw cap causes a temporary jump in pressure that relaxes to a plateau before the start of the next cycle.

One possible explanation for the discrepancy between theory and the experimental results in Fig. 7 is that the effective spring constant H was assumed to be constant in Section 2.5, independent of hydrogel swelling ratio and hydrogel loading pressure. The value of H characterizes the effective stiffness of the chamber used to confine the hydrogel in the sensor, and as such will be affected by any compliance associated with the membrane or piezoresistive diaphragm, or by the presence of any free space in the chamber. Our calibration measurements show that the stiffness of the piezoresistive diaphragm is independent of pressure over a very wide pressure range as expected for silicon, but this may not be the case for the wire cloth mesh. The initial deflection of the wire cloth membrane is of course larger if the response test is performed at an elevated loading pressure value. If the stiffness of the wire cloth mesh increases with increasing deflection, this could explain the observed increase in sensor response magnitude with increase in initial pressure. In order to test this hypothesis, we repeated the ionic strength response test of Fig. 7 after replacing the 80 mesh wire cloth membrane with a 40 mesh wire cloth, which is much stiffer. The 40 mesh wire cloth is approximately twice as thick as the 80 mesh wire cloth (405 μm vs. 290 μm), has a wire diameter of 265 μm , a mean mesh opening of 381 μm , and an open area of 36%. Fig. 8 shows the results obtained. Even though the 40 mesh wire cloth is stiffer than the 80 mesh wire cloth, sensitivity to ionic strength response is less when the sensor is deployed using the 40 mesh wire cloth membrane. Fig. 8 also confirms that the sensor response magnitude increases with increasing hydrogel loading pressure. Thus the increase in the sensor response magnitude with increasing initial loading pressure cannot be explained by an increase in mesh stiffness with mesh deflection.

3.4. Use of two-layer membranes in the sensor

According to the results in Fig. 8, the chemomechanical sensor is less sensitive when used with the 40 mesh wire cloth membrane than with the 80 mesh wire cloth membrane, even though the 40 mesh wire cloth membrane is stiffer. A possible explanation for this surprising result is that the hole size or open area of the 40 mesh wire cloth is too large, and hence the hydrogel partially exudes through the mesh while swelling, thereby reducing sensor sensitivity. One would like to vary the wire mesh opening while holding the mesh stiffness constant, but this is not possible because mesh opening and mesh stiffness both decrease with increasing mesh number. In order to circumvent this problem, we explore the use of two-layer membranes in the sensor. The function of the outer layer is to provide stiffness, whereas the inner layer has a smaller pore size and thus prevents the hydrogel from exuding through the mesh. The first two-layer membrane explored was obtained by combining 40 mesh stainless steel wire cloth with 200 mesh stainless steel wire cloth (thickness = 100 μm , mean opening = 74 μm , wire diameter = 58 μm , open area = 29%). This combination was a failure. Sensor sensitivity was actually less when the sensor was used with the 40/200 mesh combination than with the 40 mesh wire cloth membrane alone, perhaps because of poor adhesion between the two stainless steel layers. Much better sensor performance was obtained when the 80 mesh stainless steel wire cloth mesh was combined with the nanoporous Oxyphen PET membrane (thickness 20 μm , pore size 0.1 μm , open area 15%, see Fig. 5(b) for SEM image). As shown in Fig. 9, the sensitivity of the sensor to ionic strength change increases dramatically when the nanoporous membrane is added as an inner layer to the 80 mesh stainless steel wire cloth. However, mixed results are obtained when the nanoporous membrane is added to the 40 mesh wire cloth: sensor sensitivity is improved, but sensor reproducibility is worsened. A possible explanation for this is that the Oxyphen PET membrane is so thin and flexible that it can partially exude through the large 40 mesh openings (381 μm), but cannot exude through the smaller 80 mesh openings (178 μm). With the 40 mesh wire cloth, better results are obtained with a cellulosic paper inner layer that is thicker and stiffer than the nanoporous Oxyphen PET membrane. The dry thickness of the paper layer is 80 μm , four times that of the Oxyphen membrane. Unlike the Oxyphen, no nanopores were etched in the paper membrane, but in the SEM images (Fig. 5(c)), one observes an occasional micropore. As shown in Fig. 10, the sensitivity of the sensor to ionic strength change increases dramatically when the paper membrane is added as inner layer to the 40 mesh stainless steel wire cloth. This was not unexpected. The unexpected result in Fig. 10 is the improvement in response time that also occurs, particularly with respect to deswelling kinetics. Fig. 11 shows the effect on sensor performance of adding the nonporous paper membrane to the 80 mesh wire cloth membrane. Fig. 11 confirms that the introduction of the nonporous paper layer improves both sensor ionic strength response kinetics and sensor sensitivity.

The data of Table 1 provides a summary of the response time values τ_{50} observed for both freely swelling hydrogels and for the chemomechanical sensor of Fig. 1 deployed with various combinations of porous membranes and at various loading pressures. The table also includes values for the magnitude of the sensor response. In all cases the results were measured with hydrogels of initial thickness approximately 400 μm subjected to cyclic changes in ionic strength between 0.05M and 0.15M at fixed pH. The batch-to-batch variation in hydrogel swelling pressure response is of order 5 kPa, which is the principle source of sensor experimental uncertainty. When the paper or PET membrane was used as inner layer, it was difficult to adjust the loading pressure to a pre-determined value. Hence sensor tests with different membrane configurations were unfortunately often performed at different loading pressures. Several trends are apparent. The mean response time of the sensor (i.e. average τ_{50} value, swelling and deswelling) is almost always greater than that of the identical free-swelling hydrogel. Undoubtedly the hydrogel in the sensor swells less than a free-swelling hydrogel, because the porous membrane and the piezoresistive diaphragm oppose swelling in

the axial direction. In fact, Toomey et al. [21] showed that a smart hydrogel attached to a surface in such a way that lateral swelling is prevented has a smaller volume response than an unattached hydrogel. This being the case, one might have expected the sensor response time to be smaller than that of a free-swelling hydrogel. A possible explanation for this is that the hydrogel in the sensor has only one exposed surface through which diffusion can occur, unlike the freely swelling hydrogel. The swelling response time of the sensor is always larger than the deswelling response time. An increase in the hydrogel loading pressure invariably increases the sensitivity of the sensor used with any type of porous membrane, and also reduces the mean response time. The sensor response time for the swelling half-cycle is reduced to a much greater extent by an increase in loading pressure than the sensor response time for the deswelling half-cycle. Introduction of either the nanoporous Oxyphen (Fig. 9) or the nonporous paper (Fig. 10) as an inner membrane layer substantially increases sensor sensitivity. However, the effect on the sensor response kinetics is less certain, and analysis of the data is complicated by the necessity of comparing results at different loading pressures. Introduction of the nanoporous Oxyphen PET membrane or the nonporous paper to the 80 mesh wire cloth improves sensor sensitivity without substantially changing the mean response time. The Oxyphen PET membrane could not be used with the 40 mesh wire cloth, as noted previously. Introduction of the nonporous paper to the 40 mesh wire cloth substantially decreases the mean response time, primarily by reducing the time constant for the deswelling half-cycle (Fig. 10, Table 1). In fact, the smallest average response time (swelling plus deswelling) is obtained when the sensor is deployed with a two-layer membrane consisting of a 40 mesh stainless steel wire cloth and the nonporous paper membrane. This is the only sensor configuration that gives response kinetics as fast or faster than that of a freely swelling hydrogel.

4. Discussion

For a fixed change in ionic strength, our simple model (Section 2.5, Fig. 2) predicts that the change in osmotic swelling pressure $\Delta\pi_0$ is largely independent of the initial state of compression of the hydrogel. Hence it is very surprising that the sensor response signal is observed to increase with loading pressure under all conditions (Figs. 7 and 8, Table 1). The two most likely sources of error in the model are (1) the use of Eq. (3) to calculate $\Delta\pi_0$ and (2) the assumption that the spring constant H in Eq. (5) is independent of Q and loading pressure. Eq. (3) is based on osmotic deswelling measurements performed several years ago on hydrogels of similar composition [9], and thus we do not expect it to be quantitatively accurate here for hydrogels synthesized much more recently under slightly different reaction conditions. Nonetheless, the prediction that $\Delta\pi_0$ is a weak function of loading pressure in the range of loading pressures studied (5–30 kPa) is probably qualitatively accurate, given that theoretical analysis based on the Donnan model [13] leads to the same prediction. The assumption that H is independent of loading pressure is much more suspect. The value of H characterizes the effective stiffness of the chamber used to confine the sensor, $H=dP/dQ$. If there is free space available in the sensor chamber at low values of the loading pressure, then the hydrogel can expand laterally into the free volume without increasing P , and H is correspondingly low at low swelling ratios. However, when the hydrogel swells enough to fill all the free space, the value of H will increase to a much higher value reflecting the true stiffness of the membrane and the piezoresistive diaphragm. Thus the true plot of P vs. Q in Fig. 2 should probably be a curve with a slope that increases dramatically above a critical swelling ratio. An increase in loading pressure will reduce this critical swelling ratio by reducing the amount of free space initially available, thereby reducing the compliance correction $\Delta\pi_1$ and increasing the sensor signal ΔP (see Eq. (4)). This likely explains the observed increase in sensor sensitivity with increasing loading pressure. Furthermore, if the true stiffness of the stainless steel mesh greatly exceeds the osmotic modulus (Section 2.5) of the gel, then the signal becomes insensitive to the mesh stiffness. Apparently the initial compression of the hydrogel was never sufficient to completely remove all the free space initially available, because the

sensor response signal increases with loading pressure over the entire range of loading pressures studied (5–50 kPa).

If the hydrogel can expand laterally into free space without deflecting the piezoresistive diaphragm, then the response time τ_{50} derived from the P signal may not reflect the true response time of the hydrogel. This may explain why an increase in loading pressure also improves the response time of the sensor. To some extent, this improvement may be attributable to the reduction in gel thickness with initial gel compression, which reduces the diffusion path length. However, using Eq. (3), one predicts that the reduction in thickness is only of order 10% for a loading pressure range increase of 20 kPa. Furthermore, one would expect the reduction in diffusion path length to affect the swelling and deswelling response times similarly. In practice, sensor response time for the swelling half-cycle is reduced to a much greater extent by an increase in loading pressure. For example, with hydrogel loading at a pressure of 11.5 kPa in the sensor with the 80 mesh wire cloth (Table 1), the τ_{50} value for swelling greatly exceeds that for deswelling (9.5 min vs. 3.5 min), whereas the two τ_{50} values become more nearly equal at a loading pressure of 21 kPa (6.5 min vs. 3.3 min). This implies that the presence of free space in the sensor chamber at low loading pressures is partly responsible for the asymmetry in the time-dependent response curve between swelling and deswelling. This can be explained as follows. The membrane and the piezoresistive diaphragm exhibit mechanical forces that oppose swelling and accelerate deswelling. During the swelling half-cycle, the hydrogel expands laterally to fill all available free space in the sensor before the outward deflection of the piezoresistive diaphragm is complete. On the other hand, during deswelling the piezoresistive diaphragm completes its return to its equilibrium position before the hydrogel finishes contracting laterally within the sensor. Hence the apparent time constant τ_{50} derived from the pressure signal is larger for swelling than for deswelling. An increase in the hydrogel loading pressure increases sensor sensitivity and decreases the apparent asymmetry between swelling and deswelling kinetics by reducing the amount of lateral swelling within the sensor.

If the membrane pores are too large, then the hydrogel can swell by exuding through the pores without deflecting the piezoresistive diaphragm. The effect of this will be similar to that of lateral swelling within the sensor chamber: a reduction in $H=dP/dQ$, an increase in the compliance correction ΔI_1 , and a decrease in the sensor signal ΔP (see Eq. (4)). We have indirect evidence that this is the case: introduction of a nanoporous or nonporous inner layer substantially increases the sensitivity of the sensor used with the 80 mesh wire cloth (Fig. 9) and with the 40 mesh wire cloth (Fig. 10). We believe that the inner membrane layer increases sensitivity by preventing the hydrogel from exuding through the holes in the stainless steel mesh. Unfortunately, we cannot image the interface between a steel mesh and the hydrogel in a meaningful way, because the interface rearranges and the contact pressure changes when the sensor is transferred from the aqueous solution to the vacuum chamber of the SEM. The 80 mesh wire cloth has a square pore opening of 178 μm with 31% open area. While this may seem like a very coarse mesh, it is not out of line with the porous membranes used in previous studies of chemomechanical sensors: 600 μm pore size and 24% open area by Trinh et al. [12], 50 μm pore size and 31% open area by Herber et al. [11]. Of course the optimum pore size will vary to some extent with hydrogel mechanical properties, and different hydrogels have been used in all studies of chemomechanical sensors from different laboratories published to date.

The PET Oxyphen nanoporous membrane and the nonporous paper membrane are both too flexible to be used in the sensor without a stainless steel mesh to provide rigidity. Thus a two-layer membrane is best for optimizing the sensitivity of our sensor. Surprisingly, it may also be best for optimizing the sensor response time, at least for ionic strength changes. The diffusive permeability of a two-layer membrane with a nanoporous inner layer is surely much less than

that of a single stainless steel 80 mesh cloth with a pore opening of 178 μm , and yet the average sensor response time is approximately the same (Fig. 9 and Table 1). Perhaps introduction of the Oxyphen PET layer eliminates the time required for the hydrogel to exude through and retract from the holes in the steel mesh, and this is more important to the response kinetics than the decrease in diffusive permeability. The most puzzling results pertain to the use of the nonporous paper (Fig. 5(c)) as an inner membrane layer on the stainless steel wire cloths. Introduction of the paper layer improves sensor sensitivity by preventing the hydrogel from exuding through the openings in the steel mesh. Not surprisingly, the effect is more pronounced with the 40 mesh (Fig. 10) than with the 80 mesh (Fig. 11), because the 40 mesh is coarser. However, the paper layer is fairly thick, and hence its use in the sensor increases the diffusion path length by over 25%, assuming that the water-swollen paper does not penetrate into the hydrogel. Nonetheless, use of the paper layer with the 80-mesh wire does not substantially change sensor response time, and its use with the 40-mesh wire actually reduces sensor response time, primarily by reducing the time constant for deswelling (Fig. 10). It is puzzling that the nonporous paper seems to offer so little resistance to mass transfer. However, this is another indication that we are studying a kinetic regime in which the time-dependent mechanical properties of the membrane are far more important than its mass transfer resistance. Furthermore, membrane mass transfer resistance is governed by the product of the membrane thickness and the permeability, where the latter is the product of the diffusivity and the solubility of the diffusing species [22]. Water is the principal diffusant in our experiments, and the solubility of water is much lower in PET than in paper (see below). Hence even though the paper layer is at least four times thicker than the Oxyphen PET layer, the difference in mass transfer resistance may be much less. The hydrophilicity of the paper layer probably also explains the observation that use of the paper layer enhances the asymmetry of the time-dependent sensor response curve, whereas use of the PET layer does not. The Oxyphen PET membrane is hydrophobic and absorbs little water when immersed in PBS buffer. On the other, the weight of the dry nonporous paper membrane doubles when placed in PBS buffer, with little dependence on ionic strength between 0.15M and 0.05 M. Hence, when subjected to squeezing mechanical forces within the chemomechanical sensor, the paper membrane can reduce its volume by expelling water, whereas the PET membrane cannot. Thus the paper membrane is slightly compressible and contributes an elastic (osmotic) force that oppose hydrogel swelling and accelerates hydrogel deswelling, thereby enhancing the asymmetry of the sensor response curve.

5. Conclusions

The chemomechanical sensor exhibits a reversible and reproducible response to environmental ionic strength change with all of the membranes studied, and at all values of the hydrogel loading pressure. However, the choice of the membrane and the value of the loading pressure strongly affect sensor sensitivity and sensor response kinetics. If the hydrogel is loaded at pressures close to ambient, then sensor sensitivity is relatively low, and the time-dependent response is highly asymmetric between swelling and deswelling. This occurs because the membrane and the piezoresistive diaphragm exhibit mechanical forces that oppose swelling and accelerate deswelling, and also because the gel can swell laterally into a small amount of free space within the sensor. An increase in the hydrogel loading pressure increases sensor sensitivity and decreases the apparent asymmetry between swelling and deswelling kinetics by reducing the amount of lateral swelling within the sensor. The stiffness of a stainless steel mesh used as a porous membrane is of little importance to sensor response, probably because this stiffness greatly exceeds the osmotic modulus of the hydrogel. On the other hand, the steel mesh pore size is very important, and this pore size is too large for almost all of the stainless steel wire cloth meshes commonly available. This can be rectified by introducing an inner membrane layer (nanoporous PET or nonporous paper) to prevent the hydrogel from exuding through the stainless steel mesh, thereby increasing sensor sensitivity. Surprisingly, the average

sensor response time is not increased by the introduction of either type of inner membrane layer, a result that indicates that the response time is more sensitive to the membrane's time-dependent mechanical properties than to its diffusive permeability. The permeability of the nonporous paper membrane appears to be larger than expected due to its high affinity for water. In addition, because the hydrophilic paper layer absorbs a large quantity of water, it can be compressed by squeezing. Hence when the paper membrane is used as an inner layer on the stainless steel mesh, this introduces an additional elastic force that affects sensor response kinetics by opposing swelling and accelerating deswelling.

Acknowledgments

The authors thank Prashant Tathireddy, Loren Rieth, Michael Orthner, Box Cox, Seok Lew, and Mike Knutson for their assistance on this project, Ferenc Horkay of NIH for useful discussions, and Andreas Koch of Oxyphen AG for the donation of nanoporous membranes. This project was supported by the National Institutes of Health NHLBI/NIBIB Grant # 5R21EB008571-02.

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Fig. 1. Preliminary version of the chemomechanical sensor used in this study. A piezoresistive pressure transducer with a cylindrical sensing area (A) is completely covered with a disc-shaped hydrogel film (B) of approximate thickness 400 μm . The hydrogel is held in place by a cap (C) that has a top surface which is a replaceable wire mesh/porous membrane (D).

Fig. 2.

Schematic diagram showing postulated path of hydrogel thermodynamic state during two sensor response tests, both tests involving the same reduction in environmental ionic strength, but with differing values of the initial pressure on the hydrogel. The two solid curves summarize the measured results from Ref. [9] for hydrogel swelling pressure vs. swelling ratio Q , and the two dashed-dotted lines are hypothetical curves for piezoresistive sensor pressure P vs. Q . The sensor response signal is the vertical distance between points A and C (zero loading pressure) or D and F (high loading pressure).

Fig. 3. Time-dependent pH response of free-swelling hydrogel (initial thickness $\approx 400\ \mu\text{m}$) in PBS buffer at fixed ionic strength (0.15 M). Initial environmental pH value was 7.4, pH was suddenly decreased to 7.15 at time = 0, suddenly increased to 7.4 at time=7h, and then the cycle was repeated.

Fig. 4. Time-dependent ionic strength response of free-swelling hydrogel (initial thickness $\approx 400\ \mu\text{m}$) in PBS buffer at fixed pH 7.4. Initial environmental ionic strength value (I) was 0.15 M, I was suddenly decreased to 0.05M at time = 0, suddenly increased to 0.15M at time = 24 min, and then the cycle was repeated.

Fig. 5. (a) SEM image of stainless steel 80 mesh wire cloth inside of chemomechanical sensor; (b) SEM image of nanoporous polyester membrane (Oxyphen AG) prior to its use in sensor with wire cloth membrane in some of the sensor tests (field of view = 35 μm in width); (c) SEM image of nonporous cellulosic paper membrane (Oxyphen AG) prior to its use in sensor with wire cloth membrane in some of the sensor tests (field of view = 35 μm in width).

Fig. 6.

Time-dependent change in pressure (relative to baseline pressure) measured by chemomechanical sensor of Fig. 1 in response to change in ionic strength I at fixed pH 6.8 in PBS buffer. The initial environmental ionic strength value was 0.15M, I was suddenly decreased to 0.05M at time = 17 min, suddenly increased to 0.15M at time = 45 min, and then the cycle was repeated three times (single layer 80 mesh wire, baseline = initial, loading pressure = 11,000 Pa).

Fig. 7.

The effect of hydrogel loading pressure on the sensor response to ionic strength changes at fixed pH 6.8 in PBS buffer. The ionic strength was cycled between 0.15 M and 0.05 M, and the change in pressure (relative to baseline) was measured with the initial pressure on the hydrogel adjusted to 11 kPa for the first cycle, and 19 kPa for the second cycle (single layer 80 mesh wire, baseline pressure = 11,000 Pa).

Fig. 8.

Influence of wire mesh and initial hydrogel loading pressure on sensor response to ionic strength change at fixed pH 7.4 in PBS buffer. The ionic strength was cycled between 0.15 M and 0.05 M, and the pressure (relative to baseline) was measured with the hydrogel constrained by: single layer 40 mesh wire ($\diamond$); single layer 80 mesh wire (filled diamonds). The initial pressures on the hydrogel were: 9500 Pa (first cycle with 40 mesh); 23,000 Pa (2nd cycle with 40 mesh); 11,500 Pa (first cycle with 80 mesh), 24,000 Pa (second cycle with the 80 mesh), baseline pressure = 9500 Pa for experiments with 40 mesh, 11,500 Pa for experiments with 80 mesh.

Fig. 9.

The effect of adding a nanoporous polymer layer on sensor response to ionic strength change at fixed pH 7.4 in PBS buffer. The ionic strength was cycled between 0.15M and 0.05 M, and the pressure change (relative to baseline) was measured with the hydrogel constrained by: single layer 80 mesh wire ($\diamond$); single layer 80 mesh wire plus nanoporous polymer (filled diamonds). The initial pressures on the hydrogel were: 10,500 Pa (single layer 80 mesh); 10,500 Pa (80 mesh + polymer), baseline pressure = 10,500 Pa.

Fig. 10.

The effect of adding a nonporous paper layer on sensor response to ionic strength change at fixed pH 7.4 in PBS buffer. The ionic strength was cycled between 0.15M and 0.05 M, and the pressure change (relative to baseline) was measured with the hydrogel constrained by: single layer 40 mesh wire ($\diamond$); single layer 40 mesh wire plus paper (filled diamonds). The initial pressures on the hydrogel were: 9500 Pa (single layer 40 mesh); 7500 Pa (40 mesh + paper), baseline = initial loading pressure for both cycles.

Fig. 11.

The effect of adding a nonporous paper layer on sensor response to ionic strength change at fixed pH 7.4 in PBS buffer. The ionic strength was cycled between 0.15M and 0.05 M, and the pressure change (relative to baseline) was measured with the hydrogel constrained by: single layer 80 mesh wire ($\diamond$); single layer 80 mesh wire plus paper (filled diamonds). The initial pressures on the hydrogel were: 24 kPa (single layer 80 mesh); 19 kPa (80 mesh + paper membrane), baseline = initial loading pressure for both cycles.

Table 1

Ionic strength response times and response magnitudes of sensor with various membrane configurations.

Porous membrane	pH	Loading pressure (kPa)	Response pressure (kPa)	Mean response time (min)	Swelling half time (min)	De-swelling half time (min)
Free-swelling gel	7.4	N/A	N/A	3.1	3.25	3.0
Free-swelling gel	6.8	N/A	N/A	2.8	2.9	2.6
80 mesh wire	7.4	10	55	6	8	4
80 mesh wire	7.4	23	69	5.6	7.1	4.1
80 mesh plus nonporous paper	7.4	7	54	5.5	8.5	2.5
80 mesh plus nonporous paper	7.4	18	83	5.1	7.5	2.7
40 mesh wire	7.4	9	38	5.7	7.8	3.5
40 mesh wire	7.4	16	47	5.2	6.3	4.1
40 mesh wire	7.4	22	52	5.1	5.8	4.4
40 mesh plus nonporous paper	7.4	8	51	3	4.6	1.4
40 mesh plus nonporous paper	7.4	10	69	2.7	3.9	1.4
80 mesh wire	7.4	11.5	57	6.5	9.5	3.5
80 mesh wire	7.4	21	65	4.9	6.5	3.3
80 mesh plus nanoporous polymer	7.4	13.5	92.5	5.15	6.1	4.2
80 mesh plus nanoporous polymer	7.4	24	112	4.9	4.6	5.2