Dissolvable membranes as sensing elements for microfluidics based biological/chemical sensors

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We demonstrate a chemical and biological sensing mechanism in microfluidics that transduces chemical and biological signals to electrical signals with large intrinsic amplification without need for complex electronics. The sensing mechanism involves a dissolvable membrane separating a liquid sample chamber from an interdigitated electrode. Dissolution of the membrane (here, a disulfide cross-linked poly(acrylamide) hydrogel) in the presence of a specific target (here, a reducing agent—dithiothreitol) allows the target solution to flow into contact with the electrode. The liquid movement displaces the air dielectric with a liquid, leading to a change (open circuit to ~1 kΩ) in the resistance between the electrodes. Thus, a biochemical event is transduced into an electrical signal *via* fluid movement. The concentration of the target is estimated by monitoring the difference in dissolution times of two juxtaposed sensing membranes having different dissolution characteristics. No dc power is consumed by the sensor until detection of the target. A range of targets could be sensed by defining membranes specific to the target. This sensing mechanism might find applications in sensing targets such as toxins, which exhibit enzymatic activity.

The importance of sensing biological and chemical agents is well recognized and there has been considerable effort in this direction.[1,2] Currently there are many sensing methods, examples include: enzyme-linked chemiluminescence assays,[3,4] electrochemiluminescence,[5] surface plasmon resonance,[6,7] ellipsometry,[8] reflectometry,[9] interferometry,[10] mass-spectrometry,[11] and nano-scale devices.[12,13] Although these methods have high specificity and sensitivity, they generally require specialized and often expensive instrumentation consuming relatively high power and/or need trained personnel for their operation and hence are not conducive to autonomous microsensors.

In this communication, we present an autonomous microfluidic sensing mechanism (Fig. 1) based on dissolvable membranes which provides *high intrinsic* transduction of a bio/chemical signal to an electrical signal. Target-recognition membranes separate a liquid sample chamber and on-chip interdigitated electrodes (initially in air). The presence of the target in the sample makes the membrane porous and dissolves it, allowing the liquid sample to flow into contact with the electrodes leading to a sudden change in the resistance between the electrodes. A large dc output voltage (several volts) can be generated without complex electronics, which can directly drive digital electronic circuits. Thus, the sensor's output is significantly less susceptible to noise, parasitics, temperature variation and requires minimal signal conditioning. Dc power is consumed only after detecting the target. The fabrication process is compatible with microelectronics and microelectromechanical systems (MEMS) technology. These features make the sensing mechanism applicable to low cost, autonomous and unattended microsensors.

In this preliminary study, we use the example of dissolution of poly(acrylamide) (PAAm)-based disulfide-crosslinked hydrogel membranes[14] by a reducing agent, dithiothreitol (DTT), as a model system to demonstrate the sensing mechanism. A method to estimate the target concentration (here, the concentration of DTT, C_{DTT}) is also demonstrated.

The microfluidics-based sensor is fabricated on a glass substrate using a merger of MEMS technology and liquid-phase photopolymerization (LP^3).[15] The interdigitated electrodes are fabricated on the glass substrate through nickel (Ni) electroforming and have been discussed in detail elsewhere.[16,17] After formation of the

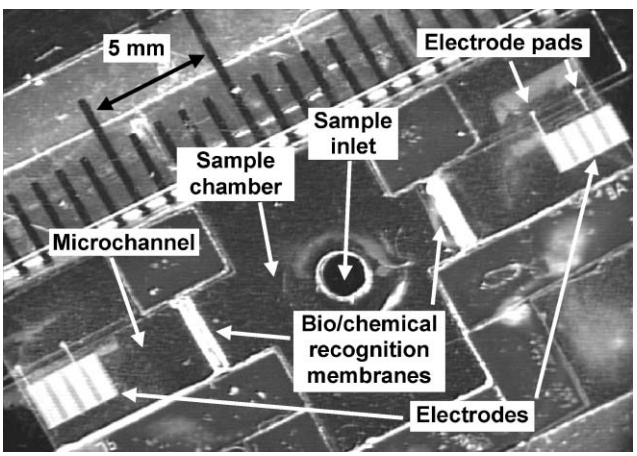

Fig. 1 The device used to demonstrate the scheme to sense the target, as well as estimate its concentration using two juxtaposed hydrogel membranes. Biological/chemical recognition membranes (here, dissolvable poly(acrylamide)-based hydrogels) separate the sampling microfluidics and interdigitated electrodes. The electrodes are initially in air. The membranes become porous and dissolve in the presence of the target (here, dithiothreitol-DTT), allowing fluid to flow into the electrodes. Presence of the fluid drastically changes the resistance between the electrodes, which is transduced to a large output voltage with the circuit shown in Fig. 3. The dissolution time of the membrane depends on target concentration (Fig. 4(B)) and hence can be used to estimate target concentration.

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electrodes, polymer microfluidic infrastructures and the dissolvable hydrogel membranes are photopatterned by LP[3], respectively.[18]

During the experiments, the target solution (containing DTT) was introduced into the fabricated device. The sensor's response to 5 different concentrations (0.1 M, 0.25 M, 0.5 M, 0.75 M, 1 M) of the target were studied. The target concentration (C_{DTT}) was estimated based on the dissolution time-difference of two sensing membranes.

Following the dissolution of the hydrogel membrane in the presence of the target (see Fig. 2), the resistance between the electrodes changed from an open circuit to roughly 1 kΩ (dc) due to the large number of interdigitated electrodes (which constitute parallel resistances), as well as the conductivity of the fluid. Using the circuit in Fig. 3, a dc input voltage of 4.8 V generated a dc output voltage almost equal to the supply voltage (4.79 V) since the output resistor R_0 = 470 kΩ was far greater than the resistance (R_C) of the liquid-filled electrodes. Until detection of the target, no dc power was consumed. Power consumption after detection is determined by the number and physical dimensions of the interdigitated electrodes and the external resistor.

From the previous discussion, the output voltage is nearly independent of C_{DTT}, *i.e.*, the differential transduction, defined as $\frac{\Delta V_{out}}{\Delta C_{DTT}}$, equals 0. Consequently, C_{DTT} cannot be determined based on V_{out} alone. The characteristic response of membranes to C_{DTT}, however, can be used to determine C_{DTT} (Fig. 4). Referring to

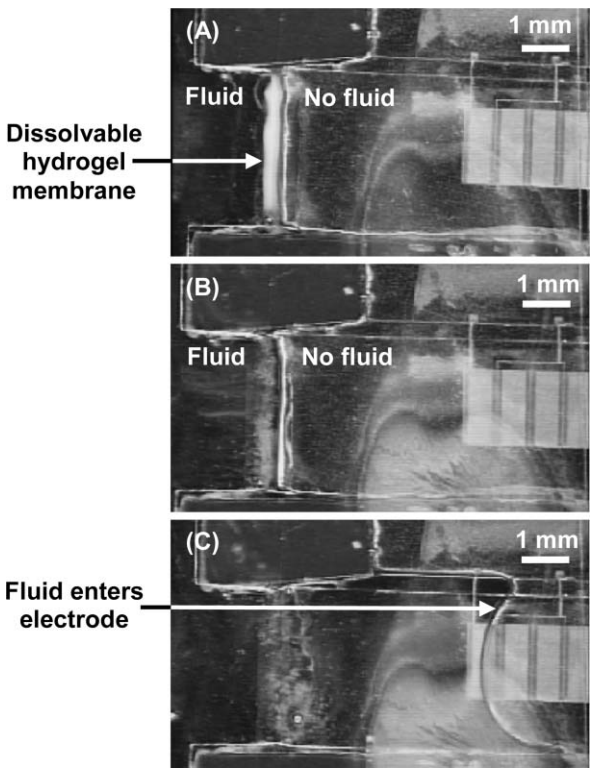

Fig. 2 Images showing the dissolution of a PAAm based hydrogel membrane in the presence of the target (DTT) at various instants of time. The hydrogel thickness is 600 μm and DTT concentration is 1 M. (A) At t = 61 s after flowing in DTT, there is no visible change in the hydrogel. (B) At t = 1200 s the hydrogel becomes more transparent due to the dissolution process. (C) At t = 1802 s the hydrogel is completely dissolved and the fluid flows into the electrode.

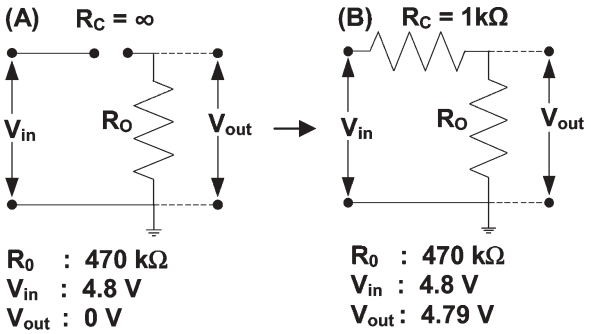

Fig. 3 Transduction of the bio/chemical event (dissolution of the hydrogel membrane) into an output voltage. (A) The circuit before membrane dissolution. The resistance between the electrodes (R_C) is initially ∞ since they are separated by an air gap. R_0 is an external resistor. (B) The circuit after membrane dissolution. The resistance R_C becomes ~1 kΩ due to flow of the water-based target into the electrodes upon membrane dissolution. R_C attains a low value in the presence of the fluid due to the large number of interdigitated electrodes which constitute resistances in parallel. With a dc supply voltage of 4.8 V, the output is 4.79 V dc. This output voltage shows negligible change with input concentration since the external voltage dividing resistor R_0 shown in (B) is far greater than R_C in the presence of fluid.

Fig. 4(A), suppose we use a single membrane of thickness 200 μm, the dissolution time is given by $t_{200\mu m} - t_{init}$, where t_{init} is the instant at which the target enters the sample chamber and $t_{200\mu m}$ is the instant at which the 200 μm wide hydrogel membrane becomes porous and allows fluid into the electrodes. For autonomous sensing, the instant t_{init} at which the target enters the system is random (unknown). Therefore, it is not possible to estimate the target concentration based on the dissolution time of a single membrane. To overcome this issue, multiple (here, two) juxtaposed hydrogel membranes of different thicknesses (200 μm and 600 μm) are used (Fig. 1). The dissolution time increases when the concentration of the target (DTT) decreases *or* when the hydrogel membrane thickness increases (fixing other physical dimensions). Hence, these two membranes have different dissolution times although exposed to the same concentration of the target. The concentration of the target is thus a function of Δt (Fig. 4(B)), where Δt is the difference between the dissolution times of the two membranes.

For example, referring to Fig. 4(B), a 200 μm wide membrane becomes porous in 1320 s, indicating the presence of the target. A 600 μm wide membrane becomes porous in 3214 s. Hence two output signals separated by a lapse of 3214 − 1320 = 1894 s are obtained. From the same figure, it can be seen that based on this time difference, the concentration of the target is 0.25 M.

Membrane dissolution-based transduction takes advantage of molecular level chemical reactions and can be applied to the detection of many chemical/biological agents where dissolution/cleavage of materials is involved. For instance, it was shown that photopolymerizable bio-functionalized hydrogels incorporating a peptide cleavable by a protease can be fabricated.[19] Inherent target recognition and signal amplification associated with enzymatic activity allows protease sensing to be highly specific and sensitive. Using the proposed sensing mechanism, bio-recognition membranes can be integrated with electrodes to realize a biosensor with large voltage output. A single sensor structure can serve to sense

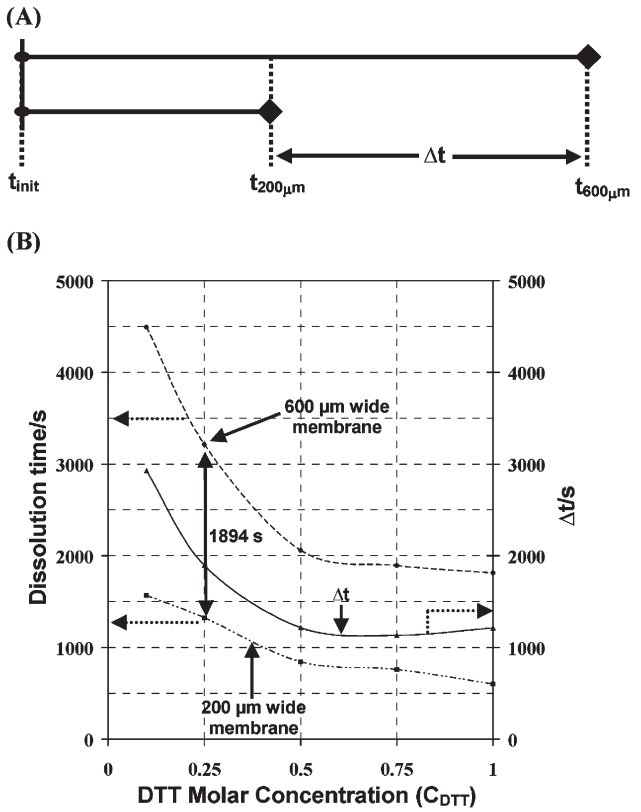

Fig. 4 (A) Estimation of target concentration (C_{DTT}), t_{init}: The instant at which the target enters the system. In autonomous sensing, this instant is unknown. $t_{200\mu m}$ and $t_{600\mu m}$ are instants at which the 200 μm and 600 μm wide membranes dissolve, respectively. These instants are detected by electrical outputs. (B) The dissolution characteristics of the bio/chemical recognition membranes. The time difference of dissolution (Δt) of two juxtaposed membranes of different thicknesses (here 200 μm and 600 μm) is used to estimate the concentration of the target. For example, if the time difference of dissolution is 1894 s (*i.e.*, when two electrical signals generated due to membrane dissolution are separated in time by 1894 s), the estimated target concentration is 0.25 M.

different targets, with one programming step to define multiple membranes, each specific to a target, lending itself to combinatorial sensing arrays.

We have demonstrated a microfluidic chemical and biological sensor based on dissolvable membranes, which provides large electrical outputs (several volts) without complicated on-chip or off-chip electronics. The membrane (sensing element) dissolves in the presence of the target and allows the target containing fluid to flow into interdigitated electrodes (transduction element). The resulting change in the resistance between the electrodes transduces the chemical event into an electrical signal. A scheme to estimate target concentration based on the dissolution time difference of two membranes having different dissolution characteristics, has been demonstrated. The fabrication process is a merger of conventional microsystem technology and liquid-phase photopolymerization. It enables the fabrication of systems combining microfluidic and biological micro-structures with traditional MEMS and electronics. Future work will extend the sensing mechanism to other biologically significant targets. Improvement of the specificity, sensitivity and response time without sacrificing mechanical robustness, optimization of membrane chemistry and photopolymerization parameters will be investigated.

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