Fast-Reacting Smart Hydrogel-Based Sensor Platform for Biomedical Applications

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ABSTRACT

Biomedical sensors based on smart hydrogels that change their swelling state in the presence of an analyte, are a very promising concept due to the inherent biocompatibility of these polymers. However, a widespread use requires the development of reliable, robust and biocompatibile transduction methods for the hydrogel's volume change. Here we report on a novel bending sensor platform whose most outstanding features are the high geometric flexibility, the compatibility with any type of smart hydrogel and the potential for wireless readout.

Keywords: smart hydrogel, biomedical sensor, mechanical bending

1 INTRODUCTION

Smart hydrogels are inherently biocompatible hydrophilic three-dimensional polymer networks. The biocompatibility stems from a very high water content ($\geq$ 90%) and mechanical properties very similar to tissue [1, 2, 3].
A smart hydrogel can undergo a volume phase transition (change in volume and stiffness) induced by an external parameter such as a change in temperature, pH or ion (charge) concentration [4]. Furthermore, they can be tailored to react to specific analytes by molecular imprinting and / or attachment of additional groups to the polymer network that chemically bind the desired analyte [5].
These properties make hydrogels ideal candidates for the development of biomedical sensors [6]. In that context, desired analytes include metabolites like glucose, small molecules (e.g. drugs like fentanyl) and small proteins like thrombin [7].
However, to date smart hydrogels are rarely used for that purpose as the reliable detection of their swelling state remains a challenge. It requires the development of reliable, robust and highly sensitive detection methods for minutest changes in the hydrogel's swelling state. Many different approaches have been employed (see [8] for an overview), e.g. miniaturized silicon pressure sensor chips [9], cantilever sensors [10], magnetic particles [11] and fluorescence-based methods [12].
All of these approaches have their advantages (e.g. high sensitivity for a specific analyte in case of fluorescence) and drawbacks (e.g. biocompatibility issues for silicon pressure sensors; fluorescence only works for certain analytes) and in most cases they are suitable for certain, well-defined applications.

We have recently developed a universal mechanical bending platform for a hydrogel-based biomedical sensor which employs a cantilever principle for read-out. It can be equipped with different types of hydrogel and can be tailored for the target application in terms of dimension and form factor, giving it a high flexibility.

2 SENSOR CONCEPT

The sensor consists of two parts: a polyimide sensing structure with embedded metallic leads and a smart hydrogel attached to one side of the polyimide strip. Any volume change of the hydrogel influences the bending of the sensing structure, resulting in an electrically detectable impedance change of the embedded leads. Through calibration measurements, the impedance can be related to a corresponding analyte concentration and changes thereof. The basic principle is illustrated in figure 1a.

The advantages of the proposed concept are: universality (sensor is compatibly with any smart hydrogel depending on the target analyte), short reaction-time (hydrogels can be made very thin), biocompatibility (only hydrogel and polyimide are in contact with biological environment, all other components are encapsulated in the polyimide), ease of incorporation in clinical procedures (due to flexibility in design) and potential for wireless read out.

3 SENSOR FABRICATION

Sensors are fabricated in two steps: first the creation of the sensing structure with standard microfabrication techniques including sputter deposition of metallic leads and contacts, and deep reactive ion etching to create the outline of the sensing structure. The outcome is a wafer with polyimide-metal sandwich structures which can be removed individually and processed further.
The second step is the attachment of the hydrogel on one

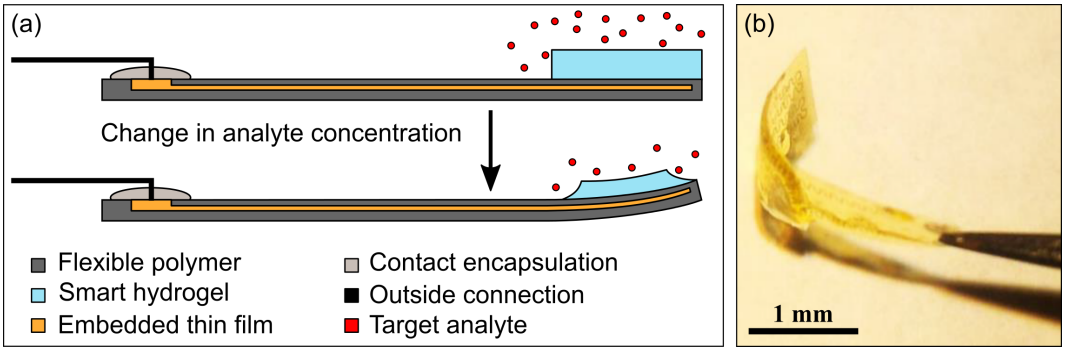

Figure 1: (a) Sketch of the basic sensor principle with marked key components and (b) example for a fabricated sensor device (without cables).

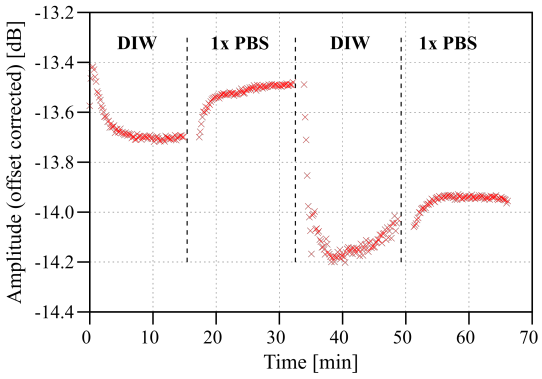

Figure 2: Ionic strength response measured as reflected impedance amplitude with a network analyzer at a frequency of 163.5 MHz. The solution was exchanged between de-ionized water (DIW) and phosphate buffered saline (1xPBS). A slight offset was induced for each liquid exchange which has been subtracted.

side of the sensing structure. Therefore, the polyimide undergoes a chemical surface treatment to increase hydrogel adhesion [13]. By use of molding techniques and either thermal or UV polymerization, a desired hydrogel pattern is fabricated and subsequently conditioned [14]. Figure 1b depicts a polyimide structure with attached hydrogel.

4 PRELIMINARY DATA

In first proof-of-principle experiments, sensors of different dimensions have been fabricated, equipped with acrylamide-based hydrogels [13] and tested with different salt concentrations (ionic strength response of the hydrogel). Thereby, the change of the electric impedance of the embedded lead structure was measured as an amplitude change of a reflected wave signal (S11 parameter) at one of the sensor's resonance frequencies. Results indicate a very fast and strong response as shown in figure 2.

5 OUTLOOK

With the basic sensor principle demonstrated, next steps include the optimization of the embedded metallic lead structure to increase signal strength and SNR as well as testing of different hydrogels tailored for various biomedical analytes.
Our target application at this point is the real-time monitoring of biomarker and medication levels which are critical during surgeries and stationary patient care. Our suggested polyimide-based sensor platform would be an ideal candidate for incorporation into catheters used for drug administration without requiring a change in clinical routine or increasing the patient's discomfort.

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Conflict of interest statement

Florian Solzbacher declares financial interest in Blackrock Microsystems LLC and Sentiomed, Inc.

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