SENSITIVITY CONSIDERATIONS FOR A SMART HYDROGEL-BASED MICROSENSOR FOR CATHETER APPLICATIONS

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ABSTRACT

Equipping catheters with sensing capabilities is a very promising perspective for in-situ monitoring of blood biomarkers. This requires suitable sensor concepts that ideally are biocompatible, adjustable for different target analytes and small enough to fit inside the catheter without obstructing its normal use. We are presenting a novel sensor concept utilizing a stimulus responsive hydrogel as sensing element and power transfer-based transduction, that has the potential to fulfil the above requirements. The work presented here is focused on evaluating sensitivity and limit of detection of the power transfer transduction approach.

KEYWORDS

Stimulus-responsive hydrogel, power transfer transduction principle, flexible microsensor, smart catheter

INTRODUCTION

Catheters are increasingly enhanced with additional functionalities. Most developments target improvements in handling and precise control to minimize tissue damage, by integration of pressure sensors, magnetic actuators and microgrippers [1,2]. Far fewer concepts aim for in-situ tracking of blood-based parameters and analytes. So far, only sensors for monitoring of blood oxygen and fentanyl/propofol have been reported, despite a clearly stated need for such sensing capabilities [3-5]. The main challenge for these concepts is that almost each biomarker requires a specialized sensing approach.

With our work, we aim at addressing this current lack by developing a microsensor platform that fits into a catheter without impacting its normal use and offers the versatility of adjusting it to different target analytes. For that purpose, we employ stimulus-responsive (smart) hydrogels as sensing elements. These polymers exhibit a reversible, reproducible and adjustable volume change in response to external stimuli, compositional versatility and easily achievable biocompatibility [6]. For the proposed sensor platform, the smart hydrogels are combined with a novel power transfer-based concept for transduction of their swelling state. In the following, the underlying sensing principle is introduced, followed by a discussion of sensitivity considerations based on proof-of-concept studies.

EXPERIMENTAL PART

The basic functional principle is depicted in fig. 1. The sensor comprises the smart hydrogel sensing element that is sandwiched between two thin film transducers made from polyimide (PI) and with an embedded metal strip line. One of the transducers (sender) is driven with a sinusoidal current and the induced voltage in the other one (receiver) is measured as the sensor output signal. The hydrogel's swelling state affects the spacing and orientation between the two transducer parts and hence, the amount of transferred power by the electromagnetic field between sender and receiver, and the magnitude of the receiver's output voltage.

The transducers used in the proof-of-concept studies have been fabricated by standard microfabrication techniques, with dimensions of 15 mm x 480 µm x 6 µm (length, width and thickness, respectively) to fit inside a microcatheter (fig. 1c). The embedded platinum meander has a thickness of 800 nm, line width and interline spacing of 230 µm and 10 µm. The transducers are assembled back to back with an electromagnetic shield in between except at the tip region (5 mm) where the smart hydrogel is polymerized (thickness 400 µm). Details about sensor fabrication can be found in [7]

To characterize the feasibility of the transduction principle for smart hydrogel volume detection and evaluate the potential as a sensor platform for blood analyte monitoring, two different exemplary and well-know glucose- and pH-sensitive hydrogels (denoted as GSH and PSH in the following) are employed. Additionally, a reference sensor was fabricated where the hydrogel is replaced by a non-responsive piece of medical grade epoxy of the same dimensions. The assembled sensor is placed inside a flow cell for automated immersion in and exchange of the respective stimulus solutions. Different tests are conducted where the stimulus is either repeatedly alternated between two different concentrations (*functionality test*), or increased and decreased in a stepwise fashion either without (*step test*) or with (*reset test*) immersion in the base of pure 1x phosphate buffered saline (PBS) solution (pH = 7.4). Each condition is applied for 6 hours.

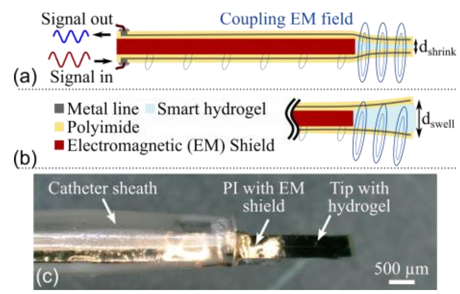

Figure 1: Schematic of power-transfer concept for two different swelling states of the hydrogel (a,b). (c) Tip of a microcatheter with integrated sensor.

RESULTS AND DISCUSSION

Fig. 2 depicts the measured sensor output voltages from the different tests exemplarily for the PSH. These results provide the basis for the sensitivity analysis. As a first characteristic, the sensor base line is determined by calculating the saturation voltages as an average of the last two hours of each condition without stimulus (pure 1x PBS @ pH 7.4). This results in $V_{0,\mathrm{GSH}}$ = 0.171 mV ± 0.44% and $V_{0,\mathrm{PSH}}$ = 1.257 mV ± 0.76% for GSH and PSH, respectively. The reference sensor shows no dependence on any stimulus change and therefore, the base line is calculated by averaging over the complete measurement time, resulting in $V_{0,\mathrm{ref}}$ = 0.271 mV ± 0.50%. While all sensors show different base line voltages that can be attributed to fabrication- and setup-related variations, the standard deviations are all in the same range below 1% of the respective base voltage. This provides a fundamental noise limit for the sensor. The absence of a stimulus-dependent output signal of the reference sensor furthermore indicates that the transducer itself does not contribute to the analyte response of the sensor.

Fig. 3 depicts the sensitivities obtained from step and reset test of the GSH and PSH sensors. Thereby, the sensitivity S has been defined as the ratio between change of sensor output voltage ΔV and change of stimulus (ΔSt), either glucose concentration ΔC or pH

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value ΔpH, i.e. $S = \Delta V/ \Delta St$. Both target stimuli are varied in the relevant range of human blood levels [8]. In both cases, the sensitivity of the reset test is higher compared to that of the step test. This can be attributed to the immersion in pure 1xPBS after each stimulus exposure in the reset test, which removes all analyte molecules from the hydrogel. In contrast, the stimulus can accumulate within the material in the step test. These results clearly indicate the importance of considering the sensing material's specific properties, such as hysteresis and potential asymmetries in swelling and deswelling. This is specifically important with regard to real-time analyte monitoring.

Furthermore, it is evident from fig. 3 that the sensitivity for both sensors decreases with increasing stimulus concentration. This is again attributed to the behavior of the hydrogel [9].

The described sensitivities are specific for the respective hydrogel and stimulus. A more general sensitivity for the transduction concept should be based on the relation between the hydrogel swelling change (irrespective of the stimulus causing it) and the sensor output voltage. Therefore, we have used an optical microscope to determine the steady state swelling of the hydrogel and hence, spacing between the transducers. It needs to be noted that this is a very rough approach since hydrogel can only be viewed from the side. When considering the linear ranges of the GSH (0 – 9) mM and PSH (7.4 – 8.0) pH, an estimate of the sensitivities results in 0.0013 mV/µm and 0.0021 mV/µm, respectively.

Following the procedures outlined in [10], an estimate for the limit of detection (LOD) can be deduced. By using the standard deviations of the base line voltages and the slope of the linear regression fit for change of voltage plotted over change of spacing between the transducers, the LOD amounts to 0.43% and 3.43% hydrogel thickness change for the GSH and PSH sensor, respectively. As stated above, the optical determination of the distance between the transducers is a rather rough estimate but the LOD values still give an indication of the sensing potential of the power transfer transduction concept and its platform capabilities.

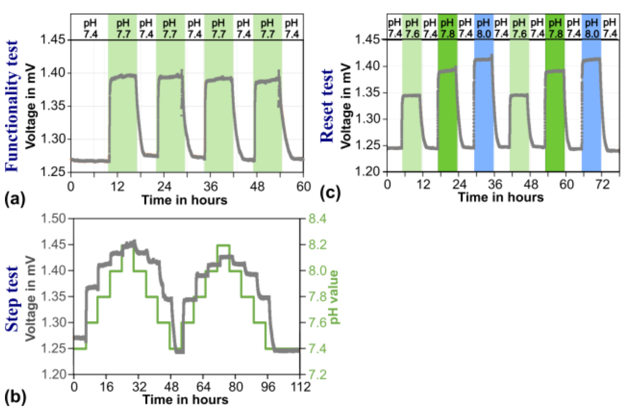

Figure 2: Measured sensor output voltages for PSH proof-of-concept sensor in (a) functionality, (b) step and (c) reset test.

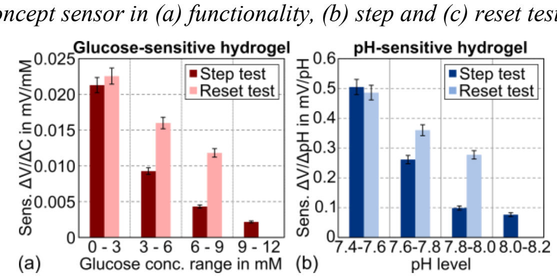

Figure 3: Sensitivity determined from step and reset test of power transfer-based sensor with (a) glucose- and (b) pH-sensitive hydrogels.

CONCLUSION AND OUTLOOK

Within this work, we have presented a novel sensor platform approach for catheter-based blood analyte monitoring. It features a stimulus-responsive hydrogel as sensing element and a novel power transfer-based transduction principle. Studies with exemplary glucose- and pH-sensitive hydrogels were conducted to evaluate the potential of the sensor concept and specifically sensitivity and limit of detection. It is found that hydrogel swelling changes of single figure percentages can be detected.

CONFLICT OF INTEREST STATEMENT

Florian Solzbacher declares a financial interest in Blackrock Neurotech and Sentiomed, Inc. These competing financial interests are overseen by the University of Utah's Conflict of Interest Management.

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