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Catheter-mounted smart hydrogel ultrasound resonators for intravenous analyte monitoring

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***Abstract*— Continuous monitoring of drug concentrations in blood plasma can be beneficial to guide individualized drug administration. High interpatient variability in required dosage and a small therapeutic window of certain drugs, such as anesthetic medications, can cause risks and challenges in accurate dosing during administration. In this work, we present a sensing platform concept using a smart hydrogel micro resonator sheet with medical ultrasound readout that is integrated on the top of a catheter. This concept is validated *in-vitro* using glucose as an easy to access and handle target analyte. In the case of continuous glucose measurement, our novel catheter-mounted sensing platform allows the detection of glucose concentrations in the range of 0 mM to 12 mM. While these experiments use a well-known glucose-sensitive smart hydrogel for proof-of-principle experiments, this new sensing platform is intended to provide the basis for continuous monitoring of various intravenously applied medications. Selectivity to different drugs, e.g., fentanyl, can be accomplished by developing a corresponding smart hydrogel composition.**

***Clinical Relevance*— Many intravenous medications, especially anesthetics, show considerable pharmacokinetic inter-subject variability. Continuous monitoring of intravenous analyte concentrations would enable individualizing the administration of these drugs to the specific patient.**

I. Introduction

Sedative and analgesic drugs are administered perioperatively to facilitate medical procedures, e.g., surgery, and to manage postoperative pain. In clinical anesthesia, determining the right dose is critically important and challenging at the same time because the window that represents drug concentrations that are safe, effective, and efficient is very small [1]. Additionally, the pharmacokinetics and -dynamics are highly nonlinear, time-variant, and have a large interpatient variability. Conventional drug monitoring methods such as liquid chromatography-tandem mass spectrometry (LC-MS) and enzyme-linked immunosorbent assays (ELISAs) provide the advantages of high selectivity and sensitivity. However, their dependence on larger lab settings, use of multi-step techniques, and slow processing times do not lend themselves to clinical anesthesia [2]. Instead, anesthesiologists currently rely on estimating hypnosis from the processed EEG signals or using surrogate measures indicating anesthetic drug side effects or autonomic nervous system activity, such as respiration, blood pressure, or heart rate. These measures are combined with information on the patients' comorbidities, demographics, and type of surgery, to dose anesthetic drugs [3]–[5].

The continuous monitoring of drug concentrations in blood plasma would be an important tool to help setting the right dose. Such feedback on drug levels in near real-time would decrease the mental workload of experienced anesthesiologists and might in the future allow for automated closed-loop systems for drug administration [6]. A smart hydrogel-based sensor system can be a promising tool in this regard. A smart or stimulus-responsive hydrogel is designed to undergo a volume phase transition in response to an analyte concentration. It obtains the energy for this volume phase transition from its aqueous environment [7]. Also, smart hydrogels can be designed to be biocompatible, implantable, and biodegradable [8], [9]. Smart hydrogel-based intravenous analyte concentration monitoring systems have the possibility of fulfilling most of the continuous drug sensing requirements such as; biocompatibility, selectivity, sensitivity (within an analyte's physiological range), and reversibility [10]–[12].

The employed sensing principle is based on the swelling-state-dependent oscillation response of a smart hydrogel resonator sheet [13]. Ultrasound (US) can be used to read out the hydrogel's analyte-dependent swelling state (Fig. 1). If the hydrogel layer is excited by ultrasonic waves of fixed frequency, the ultrasound response changes depending on the concentration-dependent hydrogel swelling state. This change is reflected as a change in Mean Pixel Intensity (MPI) of an area of the image that corresponds to the approximate location of the smart hydrogel structure. Evaluation of these MPI changes allows tracking the analyte concentration. In the experiments described below, this resonance absorption of ultrasound waves in catheter tip-mounted smart hydrogel structures is used for continuous monitoring of analyte concentrations. In the employed design, a thin strip of smart hydrogel resonator sheet is fixed on the tip of a catheter intended to be eventually used in the intravenous space (Fig. 2). A commercial medical ultrasound probe is used to track the smart hydrogel's swelling state. Since glucose is an accessible and easy to handle analyte, we use a glucose sensitive smart hydrogel in which the volume decreases with

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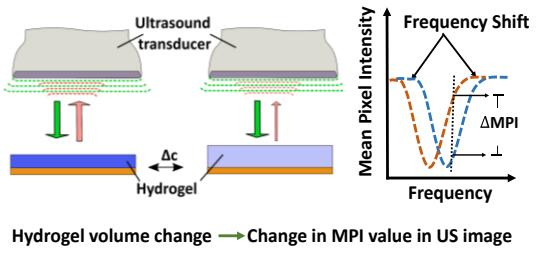

Figure 1. Illustrative representation of the sensing and readout principle, which is based on a change in the intensity of the reflected ultrasonic waves as a result of an analyte concentration-induced change in the hydrogel's volume. In the ultrasound image, the intensity change is expressed as changes in mean pixel intensity (MPI).

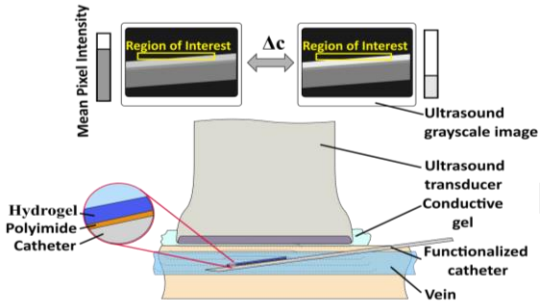

Figure 2. Illustrative figure showing the hydrogel as a part of the catheter for the intravenous drug monitoring as well as the measurement principle.

increasing glucose concentration in this study to demonstrate an *in vitro* proof-of-principle study [14]. The system can be modified to detect the concentration of drugs by developing a smart hydrogel with corresponding drug sensitivity [15]–[17] and integrating it with the catheter.

II. Materials and Methods

A. Sensor Fabrication

The pre-gel monomer solution for the smart hydrogel was prepared as discussed by Leu et al. [18] with modifications as described by Farhoudi et al. [13]. Polyimide (PI) polymer films of 25 µm thickness were used as substrates. They were surface-modified to increase hydrogel adhesion with a process as described by S. Van Vlierberghe et al. [19]. The functionalized PI films were used as the base layer where the pre-gel solution is crosslinked into the smart hydrogel by means of collimated UV light at 0.15 mW/cm^2 intensity for 3.5 mins (Fig 3). Two hydrogel sheets of 140 µm and 280 µm thickness, respectively, were fabricated by means of varying the thickness of the PTFE spacer that is used in between the polyimide and the glass cover. The hydrogel sheet and the underlying PI film were then cut into thin strips (length: 1 cm, width: 500 µm) using a tool made from two razor blades and a spacer. These strips were attached to a catheter tip (18G, BD Insyte) with cyanoacrylate-based adhesive. Finally, the assembly was subjected to a conditioning process to ensure the measurement results' reproducibility [20].

B. Measurement Process

To image the sensor at 4 MHz when immersed in 1x phosphate buffer saline (1xPBS) solutions containing various concentrations of glucose, a medical ultrasound imaging equipment (ACUSON S2000, Siemens Medical Solutions USA) with an ultrasound probe (9L4, Siemens Medical

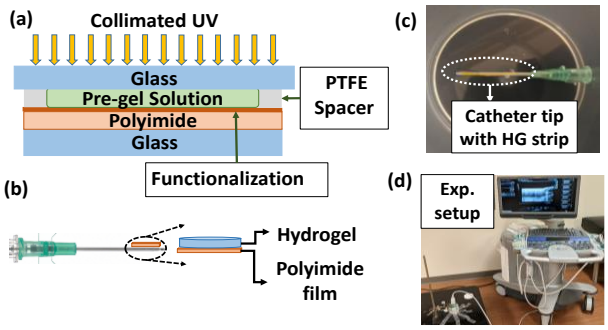

Figure 3. (a) Fabrication of the sheet resonator using a PTFE spacer, (b) illustrative figure showing the hydrogel strip on the tip of the catheter, (c) actual sensor fabricated and fixed in a 50 ml bath for the proof-of-principle measurements, and (d) measurement setup.

Solutions, USA) was used. This commercial medical device only allows image acquisition at fixed frequencies. The effect of frequency selection on MPI values and the resonance conditions have been discussed previously [13]. The catheter was fixed inside a container containing the analyte solution, and the probe was fixed on top of the sensors at a focal distance of 3 cm. The imaging axis was perpendicular to the length of the strip. The dynamic range was set to maximum as described previously [13]. The container and the probe were first rinsed three times with the new solution during solution change. Solutions and sensors were kept at room temperature for 12 h before any experiments to avoid temperature drift effects.

C. Preparation of glucose solutions

The glucose solutions used in this study were prepared by adding an appropriate amount of 1x phosphate buffer solution (PBS) to 500 mM of glucose stock solution. For the stock solution, 18.1 g of D-(+)-Glucose (Sigma-Aldrich) was dissolved in 170 mL of 1x PBS, and then the volume was increased to 200 mL by the addition of PBS. The PBS solution was prepared by dissolving 8 g of NaCl (Sigma- Aldrich), 0.2 g of KCl (Avantor - Macron Fine Chemicals), 0.24 g of KH_2PO_4 (Avantor - Macron Fine Chemicals), and 1.44 g of Na_2HPO_4 (Fisher Scientific) in 800 mL of deionized (DI) water, and then the pH was adjusted to 7.40 at 22˚C. Finally, the volume was brought to 1 L by adding DI water.

D. Data Analysis

For evaluation, the grayscale images were analyzed for their mean pixel intensity values in the hydrogel area as described in a previous publication [13]. Fig. 2 shows an illustrative example of such an area of interest. First, the images underwent a stabilization step. Next, a region of interest (ROI) was selected around the gel area with an area of 400 pixels (length: 40 pixels, width: 10 pixels). All the images were evaluated with the same ROI within one experiment. In the last step, all of the individual images' MPI were calculated and plotted with respect to time.

III. Results

Two catheter tips with a hydrogel strip thickness of 280 µm and 140 µm, respectively, were exposed to glucose concentrations of 3 mM to show the influence of the hydrogel resonator thickness as exhibited in Fig. 4 and Fig. 5. For a 280 µm thick gel, the sensor was imaged in 1x PBS for one hour, and then, 3 mM of glucose solution was introduced,

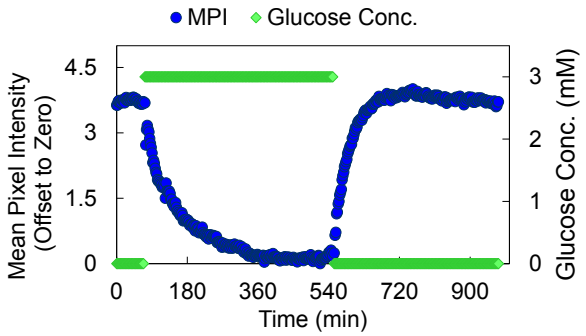

Figure 4. The response of the catheter functionalized with a hydrogel strip of 280 µm thickness at 4 MHz when exposed to 0 mM and 3 mM of glucose concentration. The time between each of the data points is 2 min.

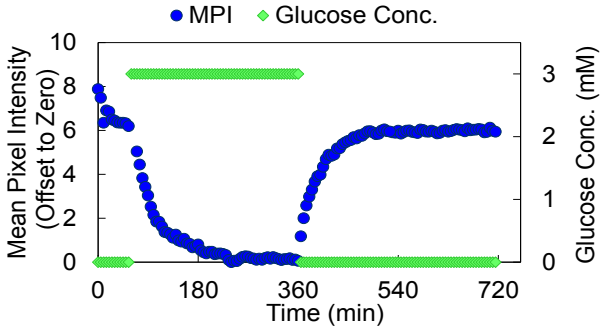

Figure 5. The response of the catheter functionalized with a hydrogel strip of 140 µm thickness at 4 MHz when exposed to 0 mM and 3 mM of glucose concentration. The time between each of the data points is 5 min.

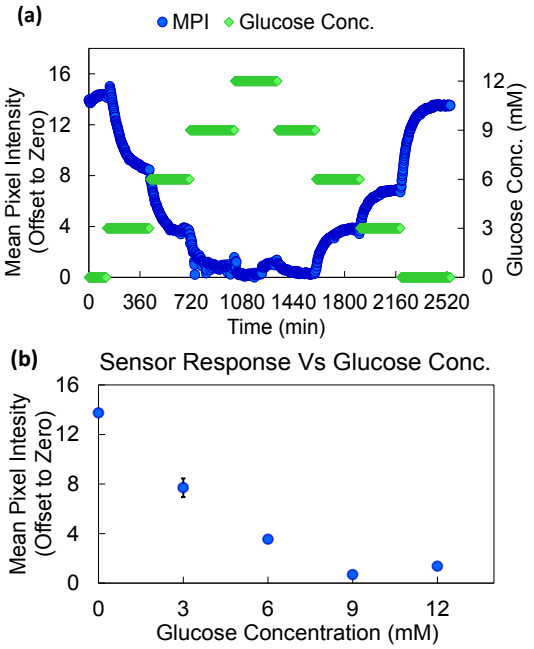

Figure 6. (a) The response of the catheter functionalized with hydrogel strip of 140 µm thickness at 4 MHz when exposed from 0 mM to 12 mM concentration of glucose in 3 mM incremental steps. The time between each of the data points is 2 min. (b) The steady-state MPI values of each step averaged over the increasing and decreasing concentration. The error bars exhibit the standard deviations.

followed by continual imaging over 7 h. Finally, the sensor was exposed again to 1x PBS, and imaging continued for another 7 h. From Fig. 4, the T90 values are 104 min for swelling (3 mM to 0 mM of glucose) and 190 min for shrinking (0 mM to 3 mM of glucose). The T90 value represents the time span until 90% of the steady-state value is reached. A hydrogel sheet with similar thickness (279 µm) was also used in setups of previous works [13]. For the catheter with a 140 µm thick gel, at first, the sensor was in 1x PBS for one hour, imaged, and subsequently, 3 mM of glucose was added, followed by continual imaging over 5 h. Finally, the sensor was exposed again to 1x PBS, and imaging continued for another 6 h. Fig. 5 shows the sensor's response at 4 MHz frequency. The T90 values are 80 min for swelling (3 to 0 mM glucose) and 110 min for shrinking (0 to 3 mM of glucose).

For the second experiment, the sensor was introduced to glucose concentrations starting from 0 mM up to 12 mM in incremental steps of 3 mM. The concentration of glucose was then decreased from 12 mM glucose to 0 mM in the same steps. The time interval between glucose concentration changes was 5 h. The catheter was continuously imaged at 4 MHz. Fig. 6a shows the response of the sensor structure against time to these glucose concentrations. Fig. 6b shows the responses resulted from averaging the values obtained for each concentration, and the error bars show the standard deviation of those values.

IV. Discussion

This study investigated the response of this new sensor platform to glucose to demonstrate its proof-of principle. This sensing system can easily be adapted for various other drugs in the bloodstream by replacing the glucose-sensitive hydrogel with another smart hydrogel. In comparison to previously published results on the ultrasound sensing principle [13], we were able to miniaturize the hydrogel sheet into a strip (length: 10 mm, width: 500 µm) successfully so that it fits on the tip of a catheter (18G, BD Insyte). In addition, by reducing the thickness to 140 µm from 280 µm, we reduced the T90 response time by almost 1/3 for glucose. The reduction in T90 occurs because the response of the hydrogel structures, with identical composition and a relatively similar test setup, speed up when the critical dimensions are scaled down [21]. The response time of the smart hydrogel to glucose is comparable to previous studies that reported T90 values ranging from 60 min to 175 min [14], [22]. However, it may be different for anesthetic drugs due to different diffusion properties and binding mechanisms in the hydrogel. For example, glucose sensitivity is based on the complex formation of glucose molecules with the boronic acid groups of the polymer network. In contrast, in the case of an anesthesia drug such as fentanyl, the interaction with the polymer network can occur differently, e.g., by aptamer binding. From Fig. 4 and Fig. 5, it can be seen that the sensors' sensitivity for glucose response is 1.2 MPI/mM (for 280 µm) and 2.2 MPI/mM (for 140 µm). Reasons for the smaller response magnitude of the thicker gel might be the difference in its resonance condition when excited with 4 MHz frequency of the ultrasound wave. Fig. 6 shows that MPI values decrease for incrementing concentrations of glucose. However, for 12 mM glucose, the steady-state MPI is higher than 9 mM. This phenomenon has been observed before in the previous studies of glucose-sensitive hydrogels [13], [23].

Since high amounts of glucose in the solution lead to higher amounts of diols, each boronic acid group binds with more diols forming 1:1 complex bond, causing the gel to swell. This is different from regular 2:1 complex bonds that occur with a lower amount of glucose in a solution, increasing the crosslink density and thus causing the gel to shrink [23]. The sensor has a nearly linear range from 0 mM to 9 mM as exhibited in Fig. 6b. The similar response magnitude between the start and the end of each experiment suggests that the sensor has low hysteresis and is capable of reproducible measurements.

V. Conclusion

In this study, we fabricated catheter-mounted smart hydrogel resonators to be used as a sensing component with remote readout via medical ultrasound. The obtained preliminary proof-of-principle results validate the potential of the sensing system. Future work includes improvements to the hydrogel component to improve both the response time and analyte sensitivity as well as experimental verification in tissue phantoms and *in-vivo*. While a glucose-sensitive smart hydrogel has been used as a well-known sensing component, it can be easily replaced by a smart hydrogel that is responsive to other analytes. Therefore, this catheter-mounted smart hydrogel-based system can become a tool to provide intravenous monitoring of clinically relevant analytes, for example, anesthesia medication.

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Conflict of Interest

The authors declare the following competing financial interests that are managed through the University of Utah conflict of interest management: F. Solzbacher declares a financial interest in Sentiomed, Inc. and Blackrock Microsystems, LLC and J. J. Magda declares a financial interest in Applied Biosensors, LLC.

The fundamental intellectual property of the novel sensing mechanism is protected by the following patent application: Ultrasound imaging of biomarker sensitive hydrogels, US20190192113A1 with N. Farhoudi, F. Solzbacher, J. J. Magda, and C. F. Reiche listed as inventors.

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