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Ratiometric analysis of sensor recovery time for organ health monitoring

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***Abstract*—Real-time pH and oxygen concentration sensing is critical for monitoring tissue damage and organ health; however, there is no report to date in such context of a single device that can simultaneously detect both pH and oxygen changes. This paper presents the development of a single optical sensor device that can simultaneously and reversibly respond to changes in both pH and oxygen concentration. The proposed optical sensor integrates both pH- and oxygen-sensitive probes, and is optimized to achieve minimal cross-sensitivity during simultaneous measurements. This approach enables high accuracy in early detection of chemical correlates of tissue or organ damage, improving screening and efficacy in organ transplants.**

Keywords—Organ health monitoring, tissue damage, pH sensing, oxygen sensing, recovery time

I. Introduction

During organ transplants, surgeons often find it difficult to differentiate between healthy and damaged organs. As the number of organs available for transplant is far smaller than the demand, discarding organs due to insufficient information on organ health is highly inefficient. Therefore, it is critical to monitor the organ during transplantation to avoid any post-surgical issues. Moreover, through organ health monitoring, partially-ill organs can be treated with anti-rejection therapies and the functionalities of the organs can be restored.

The primary biomarkers for organ monitoring are pH and oxygen. When the tissue of the organ gets damaged, insufficient blood flow leads to a pathological condition called ischaemia, wherein lack of oxygen supply to tissues further leads to anaerobic glycolysis of the cells. During this phase, lactic acid is produced, decreasing the pH of the damaged tissue. Hence, a damaged tissue/organ exhibits insufficient oxygen supply and decreased pH levels.

Previous reports already proposed the fabrication of dedicated pH and oxygen sensors based on fluorescent probes similar to those adopted here, namely ruthenium and pyranine [1-3]. However, a single bi-functional sensor substrate comprising both sensing probes (Fig. 1), and optimized to minimize cross-sensitivity during simultaneous measurements, is shown here for the first time. Ruthenium and pyranine are usually utilized as fluorescent probes through encapsulation in polymers [3-4]. Oxygen-sensitive ruthenium incurs fluorescence quenching in presence of oxygen, with fast recovery. The pH probes undergo higher absorption at higher pH values, leading to higher fluorescence and recovery time. Here, a ratio-metric optical measurement approach is additionally carried out, whereby the sensor's responses towards pH and oxygen are opposite. This eliminates random fluctuations in the sensor matrix due to internal and external factors.

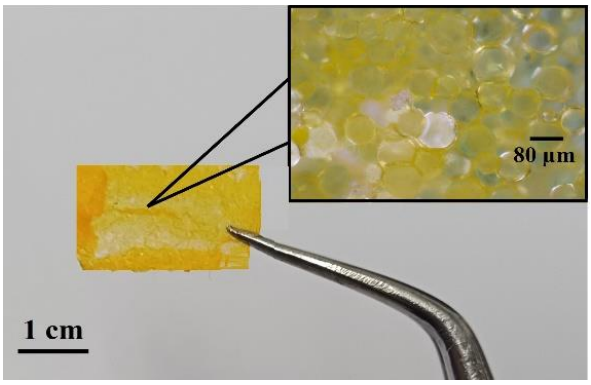

Figure 1: Microscopic image of the hydrogel-based sensor comprising of oxygen-sensitive ruthenium complex and pH-sensitive microbeads.

II. Sensor Fabrication And Experimental Methods

A. Fabrication of the bi-functional sensor

Fabrication of a single bi-functional sensor with both pH- and oxygen-sensitive probes were targeted (Fig. 2). Initially, 10 g of AmberChrom microbeads were soaked in 10 ml of demineralized (DM) water. 35 mg of 8-Hydroxypyrene-1,3,6-trisulfonic acid trisodium salt (HPTS) was dissolved in 100 ml of DM water and the microbead solution was added to it. The resulting solution was stirred for 15 hours at 400 rpm. The microbeads with HPTS were collected through filtration. 200 mg of the ruthenium complex was dissolved in 5 ml solution of methanol and toluene (4:1). The solution was stirred for 1 hour at 100 rpm to obtain Ru40 solution. The hydrogel matrix was prepared by dissolving 1 g of HydroMed D4 precursor to 10 ml of 90% ethanol. The solution was stirred for about 6 hours to get a uniform hydrogel solution. 3.5 g of the HPTS-functionalized microbeads along with 1 ml of Ru40 was added to 10 ml of hydrogel solution. The mixture was stirred for 6 hours to get a well-dispersed mixture of ruthenium and microbeads in the hydrogel. All stirrings were performed at room temperature. The solution was finally drop-casted over a glass slide, followed by drying at room temperature to prepare the bi-functional sensing layer.

Concentration of the ruthenium complex was optimized keeping the HPTS concentration fixed. For other concentrations of ruthenium, *i.e.,* 5 mg/ml, 10 mg/ml, 25 mg/ml and 50

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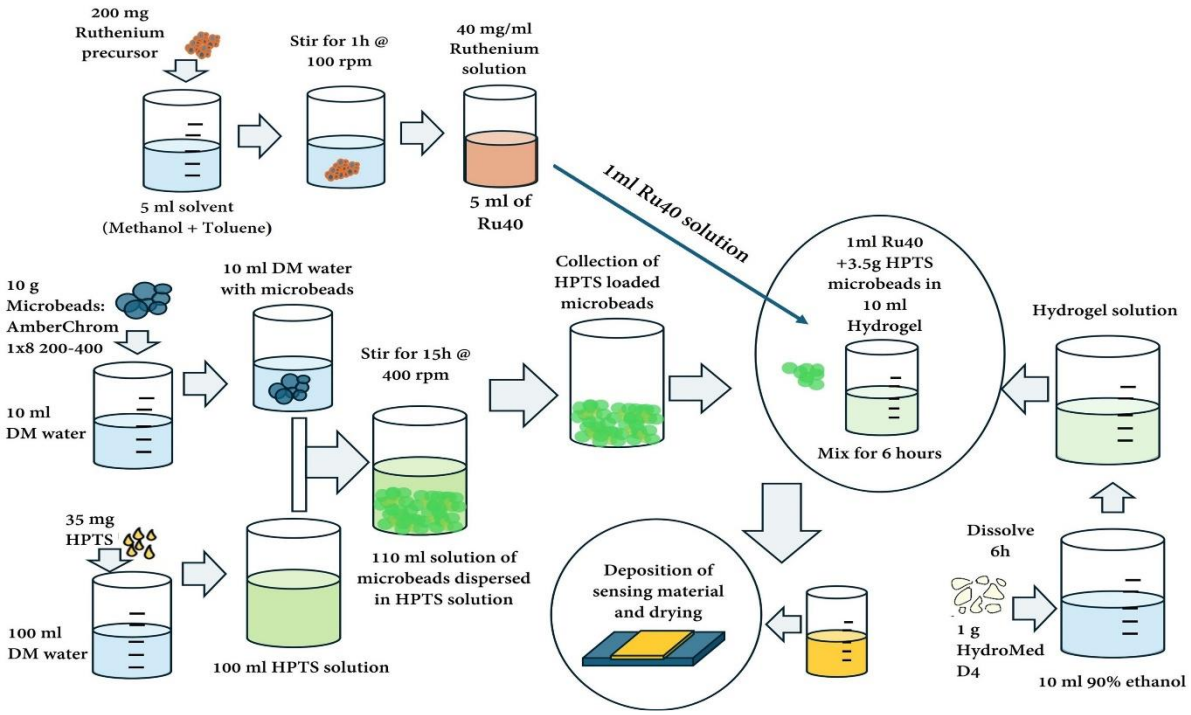

Figure 2: Fabrication steps for developing the bi-functional pH- and oxygen-sensitive hydrogel-based sensor substrate.

mg/ml, severe cross-sensitivity issues were observed. This means that, while measuring the pH of the solution at fixed oxygen levels, the oxygen-sensitive peak (600 nm, see Section II.B) undergoes intensity variations. Conversely, while measuring the oxygen levels in the solution at a fixed pH value, the pH-sensitive peak (520 nm) undergoes severe variations in intensity. The effect of cross-sensitivity is highly minimized at the optimized ruthenium concentration of 40 mg/ml in the hydrogel precursor. The effective optimized ratio of ruthenium to HPTS in the sensor is 1:88 by weight ($HPTS_{88}Ru$).

B. *Experimental setup*

The hydrogel-based sensor substrate comprising both pH- and oxygen-sensitive probes was illuminated with a 405 nm LED source, and the reflected light was recorded using a spectrophotometer (Fig. 3 and Fig. 4).

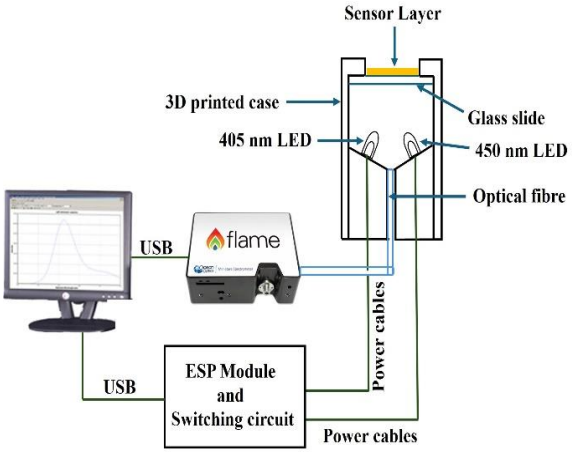

Figure 3: The single-sensor setup for simultaneous optical monitoring of both pH and oxygen changes.

The ESP module controlled the switching of the LED, which was further controlled by custom MATLAB® scripts. The sensor was tested for oxygen at a wavelength of 600 nm and for pH at 520 nm, respectively. The sensor was illuminated initially in the presence of oxygen. After removing the illumination, the sensor recovered to zero fluorescence after a short recovery time (T_{rec}). The same experiment was carried out in the absence of oxygen and for different pH values using calibrated solutions. Fig. 4 illustrates the detailed setup used for experiments.

Fig. 5 depicts the envisioned application of the device to monitor organ health in real-time. The single-wavelength excitation to achieve dual-wavelength sensitive emission, independently for pH and oxygen, contributes towards higher accuracy in organ health monitoring.

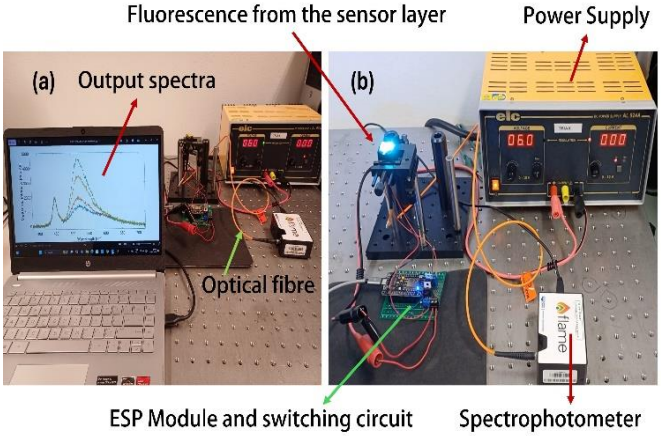

Figure 4: The measurement setup comprising power supply, spectrophotometer, microcontroller-based IoT module ESPDUINO ESP32, LEDs and laptop. The MATLAB® script drives the ESP module to control the switching of the LEDs during measurements. The spectrophotometer collects the reflected fluorescence from the sensor for analysis.

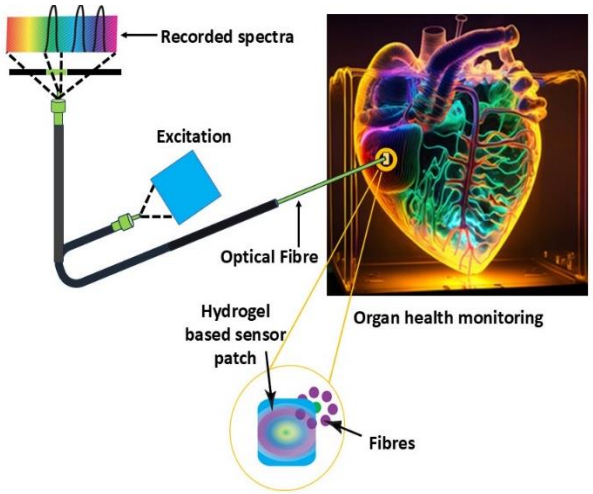

Figure 5: The proposed single-sensor system for monitoring both pH and oxygen concentration as correlates to tissue damage during organ transplants.

III. Results And Discussion

At high oxygen levels, the fluorescence at 600 nm quenched at a higher rate, and shorter recovery time for the sensor was recorded (*i.e.*, 1.38 s for 21% oxygen), as depicted in Fig. 6. At 0% oxygen, the sensor exhibited higher fluorescence and higher recovery time (~2.78 s). The same sensor was tested for pH detection. The substrate was illuminated with the same 405 nm LED source, but detection was carried out at 520 nm. At higher pH values (~7.6), after the illumination source was removed, the sensor showed higher fluorescence [5, 6]. At pH value of 7.6, the sensor recovered to its baseline (zero fluorescence) in 2.82 s, whereas at a lower pH value (~6.6), the recovery time was 1.41 s, as shown in Fig. 7.

The ratio of recovery time for oxygen and pH provides accurate indication for tissue damage. For healthy tissue, $T_{rec}(pH)$ is high and $T_{rec}(O_2)$ is low, leading to a lower ratio. For damaged tissues, $T_{rec}(pH)$ is low and $T_{rec}(O_2)$ is high. For the experiments carried out at 0% and 21% oxygen levels along with pH values of 6.6 and 7.6, the measured ratios were as follows: T_{rec} (pH 7.6)/ T_{rec}(21% O_2) = 2.04, corresponding to the condition of a healthy tissue; T_{rec} (pH 6.6)/ T_{rec}(0% O_2) = 0.50, corresponding to the condition of damaged tissues. The proposed single-wavelength optical excitation and measurement at two different wavelengths for simultaneous pH and O_2 monitoring enable a miniaturized, robust and reproducible sensor system.

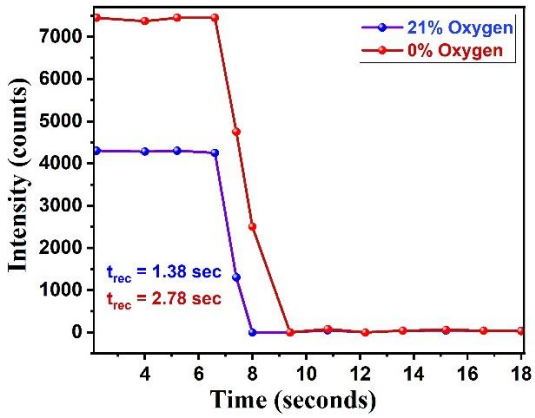

Figure 6: Recovery time of the sensor at pH 7.0 in presence of 0% and 21% oxygen, respectively.

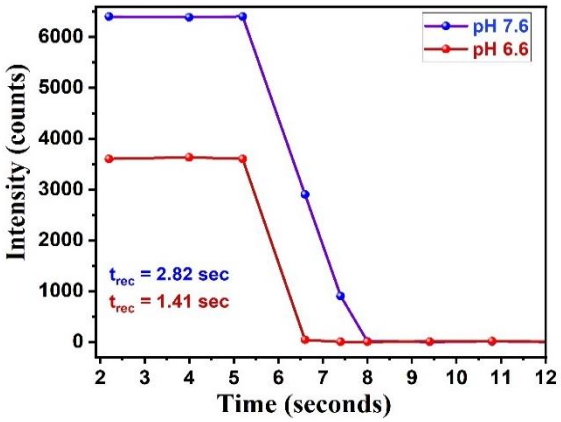

Figure 7: Recovery time of the sensor in presence of solutions of pH 6.6 and 7.6 at 21% oxygen. The higher the pH, the higher the intensity and the longer is the recovery time.

Fig. 8 shows the transient real-time response of the $HPTS_{88}Ru$ sensor towards change in pH levels of the solution from 6.6 to 7.4. The sensor was initially exposed to a solution of pH value 6.6 for 10 minutes. The sensor was then withdrawn from the 6.6 pH solution and exposed to a solution of pH 7.0. When the sensor is illuminated with 405 nm light, the phenolic groups in the HPTS absorb more light at higher pH. This results in higher fluorescence intensity as shown in Fig. 8. The sensor exhibits an extremely-fast response time of 12 s, making it appropriate for medical applications.

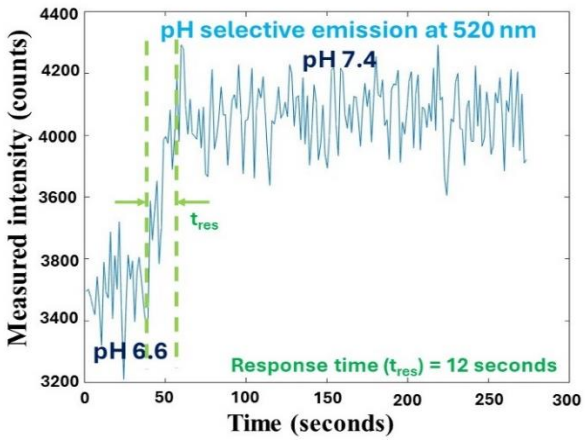

Figure 8: Transient response of the hydrogel-based sensor with HPTS-loaded microbeads.

IV. Conclusion

This paper presented the successful fabrication of a single sensor device capable of detecting pH and oxygen changes independently. The ratios of the ruthenium particles and HPTS-loaded microbeads were optimized to incur almost zero cross-sensitivity. The single-wavelength excitation of both probes and the selective emission at two different wavelengths make the proposed sensor substrate ideal for detecting tissue damage during organ transplant surgeries. The ratio of the recovery times of the sensor for pH and oxygen could provide a clear distinction between physiological conditions of healthy and damaged tissues. By further developing optical filtering techniques, this research can directly be applied to detect damaged tissues during organ transplant surgeries.

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