Ultrasound-Mediated Chemical Sensing Using Titanium Dioxide (TiO_2) Nanoparticles-Embedded Hydrogel with Possibilities of Performance Enhancement Using Machine Learning

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Introduction: *In situ* chemical sensing, such as temperature, pH, or a specific molecule, is important in healthcare and environmental monitoring [1]. The principle of chemical sensing usually involves multiple elements, including receptor, transducer, and a complex readout circuit. The receptor selectively detects chemical information, which is then translated into electrical signals by the transducer. However, the receptor is usually consumable, and the transducer requires frequent calibration due to the accumulation of chemical species (e.g., protein, biofilm). More recently, hydrogel-based sensing mechanisms based on the incorporation of micro/nanoparticles onto the polymeric network of hydrogels have been reported [2]. For instance, Holtz et al. demonstrated crystalline colloidal particles polymerized within a hydrogel allowed the change of color in response to glucose [3]. Another effort by our group was embedding silica bead in a pH-sensitive hydrogel, which can be interrogated by ultrasound imaging [4].

In this paper, we present a new wireless pH sensing technique using the ultrasound transmission through titanium dioxide (TiO_2) nanoparticle-embedded hydrogels. Fig. 1 illustrates the principle of the proposed chemical sensing system. The sensing system consists of an ultrasonic transmitter/receiver pair and TiO_2-embedded hydrogel that is implanted under the skin (or any other body area that requires pH monitoring). Filling hydrogel with TiO_2 nanoparticles enhances the ultrasonic wave backscattering, hence eliminates the complicated readout systems, such as the ultrasound imaging system. As the ultrasonic waves pass through the hydrogel, its physical behavior is changed depending on the thickness of the hydrogel. The ultrasonic receiver, placed on the other side of the body, captures the ultrasonic wave that has been altered due to the hydrogel. We analyze the volumetric transition of hydrogel wirelessly by investigating ultrasound behaviors. The transmitted ultrasonic signals are collected, with consideration of feature extraction for machine learning implementation. We expect to interpret pH information from ultrasonic waves with minimal effects due to reflection and noise using this method. Regardless of having many scopes, machine learning enabled direct pH measurement schemes were not reported in the past. The current state of the art pH sensors (with analyte) has measurement errors within 0.1 to 0.01 pH, therefore, our aim in this study is to reach an even lower error rate using machine learning.

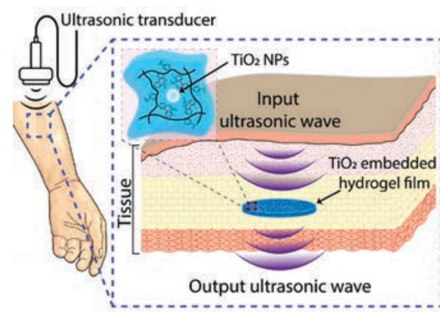

Fig. 1: Schematic view of the wireless chemical sensing

Method: In order to verify the effectiveness of the concept, we prepared a hydrogel that absorbs water molecules depending on pH levels of the medium; it swells at higher pH and shrinks at a lower pH [5]. We created a disc-shaped hydrogel, whose initial size was 20 mm in diameter and 3 mm in thickness. During hydrogel synthesis, TiO_2 nanoparticles (21 nm; Sigma-Aldrich) were mixed into the pre-gel solution. The prepared hydrogel was then tested in media at different pH levels (pH = 3.4, 4.4, 5.7, 6.2, 7.4). For a complete swelling (or shrinking), the hydrogel was kept in the medium for each pH levels at least 40 min before data is taken. Fig. 2 shows an experimental setup. We used a piezoelectric transducer ($36 \times 36 \times 1$ mm^3; PZT-5H, Piezo Inc.) to apply ultrasonic waves into the medium. The hydrogel was placed approximately 6 cm away from the ultrasonic transducer. A short burst wave (10 pulses at 7.0

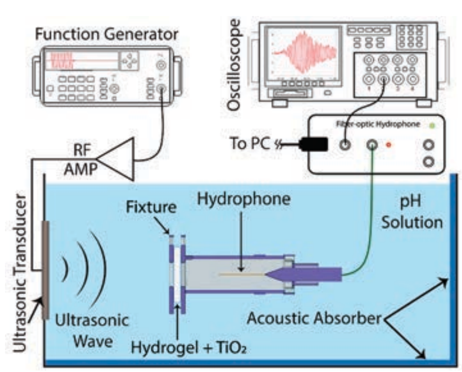

Fig. 2. Experiment setup to capture acoustic signals transmitted through TiO_2 embedded hydrogel swelled at different pH environments

MHz with 1 kHz interval) was transmitted through the body to reach the TiO_2-hydrogel. A fiber-optic hydrophone (FOH64, Precision Acoustics) was used as an ultrasonic receiver. It captured the ultrasonic wave at 10 cm distance from the ultrasonic transducer (or 4 cm from the hydrogel). The data acquisition was done using an oscilloscope (MSOX3024T, Keysight) connected to the hydrophone. The signal was captured for an average of 4.6 µs time duration at a 5 GHz sampling rate.

Results and Discussion: The results presented in this paper were collected and structured for a future machine learning interrogation. The received ultrasonic waveform was a one-dimensional discrete-time signal that had a different wave characteristic depending on the thickness of the hydrogel. A representative example of the transmitted and received waveform is shown in Fig. 3(a) and Fig. 3(b) respectively. The received signal showed a rising and then falling trend in its amplitude. A minimum of 10 input burst pulses was required to induce the characteristic ultrasonic waves due to the change in hydrogel thickness within the environmental pH. More than 10 pulses were not required as it would only induce repetitive waveforms which do not carry any significance in terms of amplitude variation or frequency change. After 10 burst pulses, the ultrasonic waves gradually decayed out until the supplied energy was consumed completely. The received signal cannot be segmented visually indicating more information other than the change in amplitude. The change in frequency was analyzed during the feature extraction phase of the machine learning process, however, they are not visually noticeable and only can be detected using a precision measurement method (such as an oscilloscope).

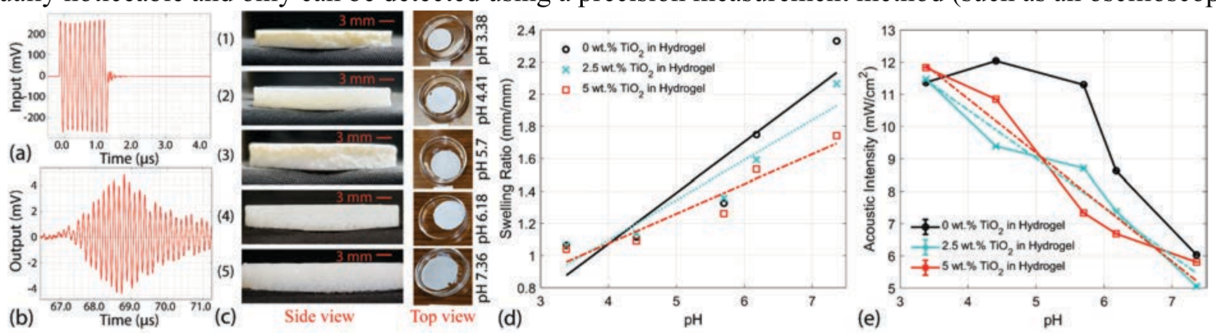

Fig. 3. (a) Transmitted waveform, (b) Received waveform, (c) pH sensitive hydrogel with 2.5 wt.% TiO_2, swelled at different pH levels, (d) Swelling ratio vs. pH of the medium, (e) Transmitted acoustic intensity vs. pH of the medium

For comparison purposes, we used three different concentrations of TiO_2 nanoparticles (0, 2.5, and 5 wt.%) in the experiment. The changes in ultrasonic waves due to these hydrogels in different pH levels were captured. First, the volume transition of the TiO_2 embedded hydrogel was characterized; Fig. 3(c) shows the pictures of swelled hydrogels at different pH environments. Fig. 3(d) shows the swelling ratio at different pH levels. The maximum swelling ratio of hydrogel was 2.3, 2.1, and 1.7 for 0, 2.5, and 5 wt.% TiO_2 concentration, respectively. Filling the TiO_2 nanoparticles impeded the hydrogel swelling by 26%. Although the swelling ratio was sacrificed, TiO_2 nanoparticles improved the ultrasound interrogation in terms of sensing linearity and higher sensitivity, as shown in Fig. 3(e). Due to the close acoustic impedance of the hydrogel (1.5 MRayls) [6] and the water (1.48 MRayls), there were not sufficient ultrasonic reflections; except for at the boundary where random reflections occurred. This led to unpredictable responses when the pristine hydrogel (without TiO_2) was in the pathway of the ultrasonic waves. This was improved when TiO_2 nanoparticles were loaded in the hydrogel; the overall acoustic impedance becomes 6.61 MRayls (@ 5 wt.%, pH = 7), which could reflect ultrasonic waves uniformly and thus linearly attenuated the ultrasound transmission intensity as the hydrogel swells or shrinks ($R^2 = 0.94$). The rates of change in ultrasonic intensities were 1.38, 1.50, and 1.68 $mW/cm^2/pH$ for 0, 2.5 and, 5 wt.% of TiO_2 in the hydrogel, respectively (Fig. 3(e)).

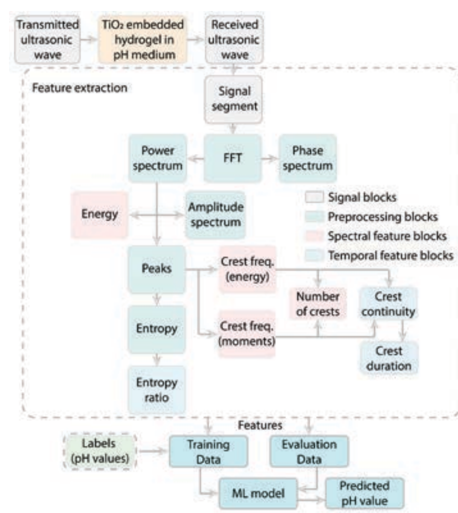

Fig. 4. Block diagram of the machine learning enabled pH sensing system

While the amplitude-based physical analysis was demonstrated in the hydrogel-based pH sensing, other acoustic features can be extracted from the received signals. Thus, we plan to build a machine learning-enabled pH sensing model. Inspired from the speech recognition, we envision our model will extract frequency, phase, energy, and entropy features, as shown in the block diagram in Fig. 4. First, the received signals will be segmented by small moving time frames. Each signal segment will be sequentially analyzed by a fast Fourier transformation. Then, power and phase spectra can be obtained from the processed signal. From the power spectra, several features can be computed, including energy, amplitude spectrum, and peaks. Notably, we can further process peaks and compute a more localized view, such as entropy and its ratio; and crest frequency, continuity, and duration [7]. Once all the features are extracted, we can implement simple machine learning algorithms such as linear regression, support vector machine, or random forest to train on the respective pH values. In the future, more complex and advanced models such as a convolutional neural network (CNN), deep neural networks will be explored to enhance accuracy performance [7], [8]. The size of the training dataset can be determined by looking at the validation accuracy after the training and evaluation of the ML network. Typically, pH measurement devices have measurement error within 0.1 to 0.01 pH, depending on the quality of the device and the measurement procedure. Therefore, we plan to provide sufficient training data for which the accuracy will be on par with the commercial devices. After the training, the machine learning model can be tested using untagged ultrasonic waves (i.e., unknown pH). The model can be validated for different pH ranges, for example, 7.35 to 7.45 is the typical blood pH range [9], but it can be lower (e.g. pH of 1.5−4.0 in the stomach) or higher (e.g. pH of 7.0−8.5 in the intestine) depending on the region in the body [10]. Each result will be compared with measurements from a digital pH meter (AI311, Apera Instruments). We plan to evaluate the prediction capability using different performance indicators, such as mean absolute error (MAE), mean square error (MSE), Pearson correlation coefficient (Pearson's R), and coefficient of determination (R^2).

In summary, we reported a new wireless chemical sensing technique using a smart hydrogel material. While we analyzed the proposed sensing scheme using a traditional method, we acknowledge the need for machine learning to reveal features that could be hidden within the ultrasonic waves.

ACKNOWLEDGMENTS

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Ultrasound-Mediated Chemical Sensing Using Titanium Dioxide (TiO_2) Nanoparticles-Embedded Hydrogel With Possibilities of Performance Enhancement Using Machine Learning

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I. Introduction

- In-situ chemical sensing, such as temperature, pH, or a specific molecule, is important in healthcare and environmental monitoring.
- The principle of chemical sensing usually involves receptor, transducer, and a complex readout circuit.
- The receptor is usually consumable, and the transducer requires frequent calibration due to the accumulation of chemical species.
- We propose a wireless ultrasonic sensing mechanism that minimizes above mentioned shortcomings (Figure 1).
  - Non-consumable hydrogel with titanium dioxide (TiO_2)
  - Ultrasound reads the volume change; thus, recalibration is not necessary.

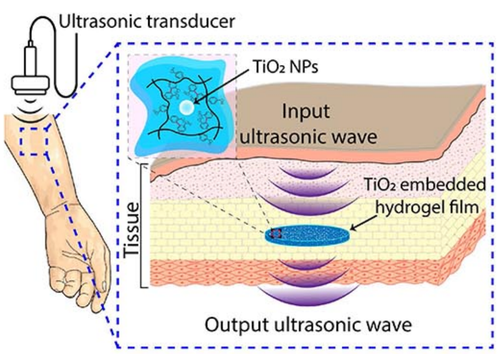

Figure 1. Schematic view of the wireless chemical sensing

II. Methodology

- **Sensing elements:** An ultrasonic transducer, TiO_2-embedded hydrogel, an ultrasonic receiver.
- **Sensing mechanism:** Hydrogel swells at high pH and shrinks at low pH medium. By transmitting ultrasonic waves through the hydrogel, the temporal and spectral feature changes.
- **Data processing:** Ultrasound waves are captured and analyzed to extract the pH information of the medium.

III. Fabrication

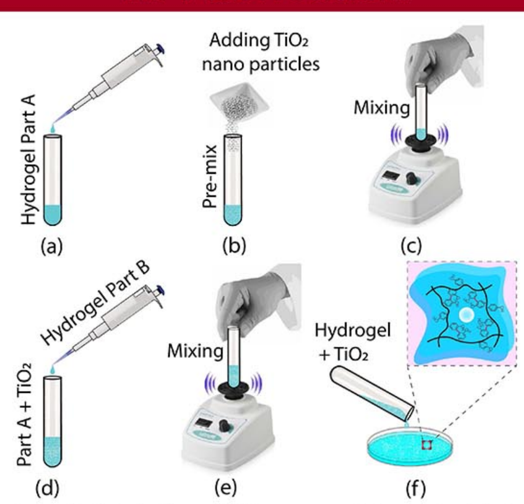

Figure 2. Fabrication of TiO_2 nanoparticles-embedded hydrogel for chemical sensing

IV. Experiment Setup

- Different pH solutions (pH = 3.4, 4.4, 5.7, 6.2, 7.4) were prepared in water tank (Figure 3).
- TiO_2 nanoparticle-embedded hydrogels were soaked for 40 minutes to ensure baseline for each pH level.
- A 36 mm × 36 mm × 1 mm piezoelectric transducer (PZT-5H) was used as an ultrasonic transmitter.
- A fiber-optic hydrophone (FOH64, Precision Acoustics) was placed on the other side to capture the ultrasound waves.
- A short burst wave (10 pulses at 7.0 MHz with 1 kHz interval) was transmitted through the hydrogel.

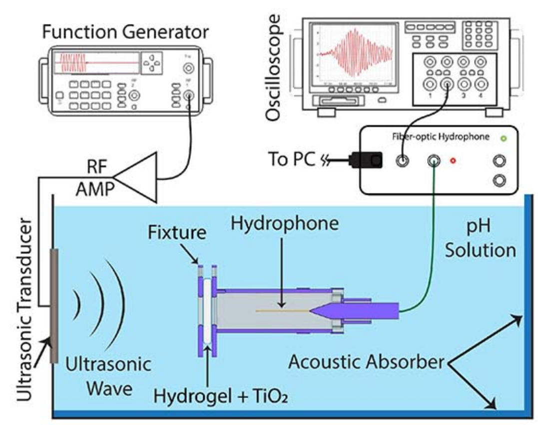

Figure 3. Experiment setup to capture acoustic signals transmitted through TiO_2 embedded hydrogel swelled at different pH environments

V. Data Processing

- We primarily investigated the acoustic intensity in terms of amplitude change.
- Features such as peak-to-peak amplitude, FFT, power and phase spectrum, entropy, etc. can be used to train machine learning algorithms for future machine learning integration (Figure 4).

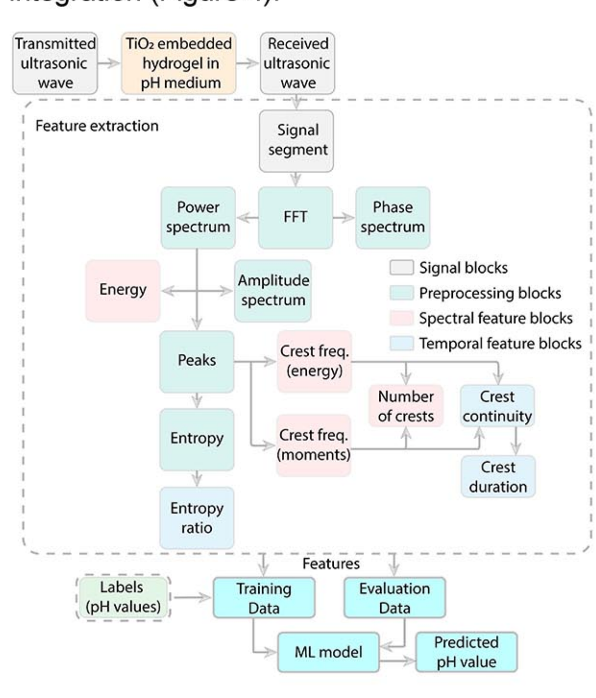

Figure 4. Block diagram of the machine learning enabled pH sensing system

VI. Results

I. Swelling Test Results

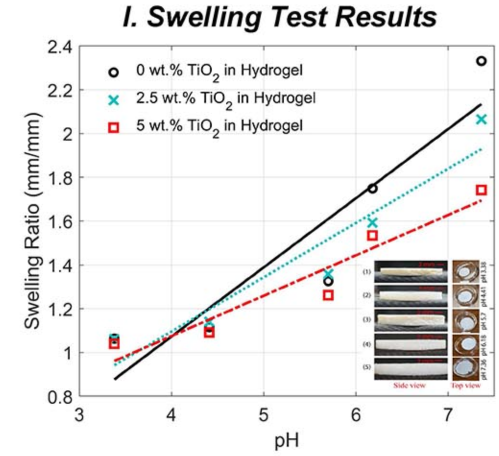

Figure 5. Swelling ratio vs. pH of the medium

- For 0, 2.5, and 5 wt.% TiO_2 loaded hydrogel:
  - Swelling rate: 0.84, 0.81, 0.76 mm/pH
  - Max. swelling ratio: 2.33, 2.07, and 1.74 mm/mm
- Maximum swelling ratio was impeded by 11.39% for 2.5 wt.% and by 26% for 5 wt.% TiO_2 loaded hydrogel.

II. Ultrasonic Test Results

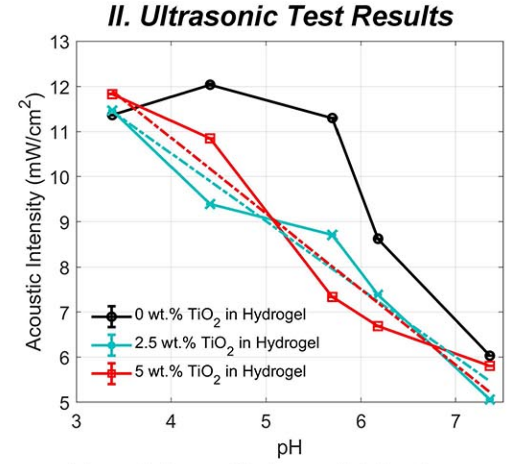

Figure 6. Transmitted acoustic intensity vs. pH of the medium

- Improved linearity in pH sensing (R^2 = 0.72 for 0 wt.% and R^2 = 0.95 for both 2.5, 5 wt.% TiO_2 loaded hydrogel.
- Rate of change in acoustic intensities were 1.50 mW/cm²/pH for 2.5 wt.%, and 1.68 mW/cm²/pH for 5 wt.% TiO_2 loaded hydrogel.

VII. Conclusion

- A new wireless chemical sensing scheme is reported using smart hydrogel material.
- The sensor is non-consumable and does not require recalibration due to the reversible swelling behavior of hydrogel and the use of ultrasonic waves.
- Preliminary dataset was obtained for future machine learning enabled sensing for more accurate and robust pH monitoring

VIII. Acknowledgements

This research is supported by the startup fund (A.K.) provided by the College of Engineering at Temple University.