Wound management involves repeated clinical trips and procedures of lab tests over days. To eliminate this time lag and provide real-time monitoring of a wound’s progress, we have designed an enzymatic biosensor for determining uric acid (UA) in wound fluid. Uric Acid is a biomarker, having an established correlation with wounds and their healing. This electrochemical biosensor comprises enzyme urate oxidase (uratec, UOX) entrapped in a polyvinyl alcohol based cationic polymer for enhanced stability. Results show that the use of a redox electron shuttle, ferrocene carboxylic acid (FCA), enabled electron transfer between the enzyme and the transducer. The immobilized uricase in the polymer matrix provided stable continuous measurements at body temperature for a week with minimal deviation. Detection of uric acid in wound fluid has been determined from volumes as low as 0.5–50µL. Studies from different wound samples have shown an average recovery of 107%. The sensor has been interfaced with LMP91000 potentiostat and controlled by CC2650 microcontroller on a Kapton tape-based miniaturized flexible platform.

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Materials.—UOx lyophilized powder containing 15–30 U mg\(^{-1}\) was purchased from Sigma Aldrich, for UA oxidation. The electron transfer mediator FCA was purchased from Chem-Impex International, Inc. Poly (vinyl alcohol) N-methyl-4(4’-formylstyril)-pyridinium-metho-sulfate-acetal (PV A-SbQ) purchased from Polysciences, Inc., was used to entrap UOx on screen-printed carbon electrodes (SPCE) purchased from CH Instruments, Inc., United States and the wound dressing. The flexible electrodes on the wound dressing were screen printed using a 305-mesh screen with conductive graphite and Ag/AgCl pastes (Gwent Group, UK) on adhesive vinyl (Silhouette America, USA). UA, sodium hydroxide, hydrogen peroxide, sodium phosphate monobasic (NaH\(_2\)PO\(_4\)), sodium phosphate dibasic (Na\(_2\)HPO\(_4\)) and boric acid were of analytical grade. All aqueous solutions were prepared using deionized DI water. Phosphate buffer (20 mM) and boric acid (20 mM) were prepared for pH 8 to pH 10 solutions. UA assay kit was purchased from ThermoFisher Sc. to analyze clinical samples. The sensor was interfaced with LMP91000 miniaturized potentiostat having an analog front end (AFE), an ultra-low-power microcontroller (CC2650) integrated with a bluetooth module and LP2591 power management system from Texas Instruments(TI). A MCP72831 charge controller, 12-bit digital-to-analog converter (DAC) with integrated electrically erasable programmable read-only memory (EEPROM) and a I2C compatible serial interface from Microchip were used for building the electronic circuit.

Apparatus and methods.—Cyclic voltammetry (CV) and differential pulse voltammetry (DPV) were performed using the analytical system model CHI-230B potentiostat from CH Instruments, Inc. The standard electrochemical method was carried out in a classical three-electrode system consisting of SPCE, external Ag/AgCl as reference electrode and Pt counter electrode. The testing of three-electrode system was carried out in an electrochemical cell setup with 3ml electrolyte solution for both classical and flexible electrodes. The CVs were measured in the potential window of −0.2 to 0.7 V at the scan rate of 0.02 V s\(^{-1}\). The DPVs were measured in the same potential window with the amplitude of 0.05 V. The electrodes tested were (i) PVA-SbQ (polymer), (ii) UOx (physisorbed), and (iii) UOx in PVA-SbQ (entrapped). UOx was immobilized on the working electrode through entrapment in cationic polymer, PVA-SbQ. PVA-SbQ solution was prepared with DI water in a ratio of 2.5:0.5 [V/V], while 0.5 U cm\(^{-2}\) UOx was prepared in 0.02 M PBS solution (pH 7.8). The physisorbed and polymer functionalized electrodes were prepared by drop-casting 0.25 U cm\(^{-2}\) UOx and 0.0532 mg cm\(^{-2}\) PVA-SbQ on the electrodes respectively. To prepare the entrapped enzymatic electrode, 0.25 U cm\(^{-2}\) UOx was injected in 0.0532 mg cm\(^{-2}\) PVA-SbQ matrix and dried for 10 min in N\(_2\) flow on the electrode surface. Drying in nitrogen enabled removal of excess water from the electrode surface, forming a gel like structure. These immobilization steps were carried out in an ice box to prevent enzyme denaturation. These modified electrodes were then washed in 0.02 M PBS (pH 7.8) to remove un-entrapped enzymes. The effect of pH on the enzyme activity was performed in Evolution 201 UV-Visible Spectrophotometer, ThermoFisher Sc. Enzyme electrode characterizations were carried out using Raman spectroscopy with a 514.5 nm Ar laser. The ThermoFisher Sc. microplate absorbance reader was used to conduct assay experiments.

Uric acid extraction from wound dressing.—Four discarded wound dressing samples from de-identified patients at the wound clinic in the University of Miami were collected for UA extraction. Each dressing, about 10 cm × 10 cm, were carefully cut to the areas as shown in Fig. 2 to extract most part of the fluid that diffused through the dressing. Each of these samples was immersed in NaOH solution prepared in DI water (pH 12) and incubated at 37°C for 45 mins. They were then ultra-sonicated in a homogenizer for 60 s at 20 Hz to extract the samples from the dressings. The extracted wound solutions were tested on the UOx enzymatic flexible electrodes. Assays for correlating concentrations of UA in different wound samples were conducted using standard colorimetric assay protocol at 570 nm.

Electrode fabrication on IoT platform.—Fabrication of electrodes on wound dressing was achieved through screen printing using conductive graphite paste on adhesive vinyl sheet with a 9 × 14 mesh screen. This graphite coated adhesive substrate was dried in nitrogen for 4 hours. Electrode design was created on Silhouette Studio for precise cutting of the electrodes. This was then transferred onto flexible wound dressing. Conductive Ag/AgCl paste was coated to create the reference electrode. This flexible fabricated electrode system on the

Figure 1. Schematic representing the convergence of smart wound care management and IOT.
wound dressing comprised of carbon working and counter electrodes and a Ag/AgCl reference electrode. On the working electrode, the enzyme was entrapped using PVA-SbQ as mentioned previously in classical SPCE. These fabrication steps are schematically represented in Fig. 3.

Results and Discussion

Uricase for uric acid detection.—UOx is an enzyme that belongs to the catabolism of the purine degradation pathway. It plays an integral role in the enzymatic conversion of UA (C₅H₄N₄O₃) to 5-hydroxyisourate (C₅H₄N₄O₄) through oxidation (Eq. 1). The formed 5-hydroxyisourate reacts with water to produce carbon dioxide and allantoin (C₄H₆N₄O₃) which is the soluble form of urate (Eq. 2). In the reaction as shown by Mahler et al., the oxidation of urate to racemic allantoin occurs through the formation of unstable intermediates. In this reaction, C-5 of urate is converted to C-4 of allantoin, while C-2 of urate was recovered as C-2 of allantoin. In widely used oxidase enzymes, FCA receives electrons from the enzyme’s co-factor leading to MET. Glucose oxidase with flavin adenine dinucleotide (FAD) is one such example, where FCA act as an electron shuttle between FAD and the electrode. However, UOx has no prosthetic group or cofactor involved in the substrate oxidation, therefore the possibility of electron transfer from the active site of UOx to FCA is lower. Also, the $E^0$ of UA (0.59 V) being higher than FCA, it is highly unlikely that the electron transfers between the UA reaction in the active site and FCA. Instead, the electron transfer is more favorable to the native two electron O₂ reduction reaction forming H₂O₂. It is also evident from literature and the results, there is a shift in potential and $I_p$ of H₂O₂ in presence of FCA compared to its absence. This shows plausible electron transfer between the by-product H₂O₂ ($E^0 = -0.68$ V) and FCA.

Characterization of entrapped enzyme.—The enzyme entrapment mechanism involves electrostatic interaction between the cationic amide group of the styrylpyridinium side chains in the PVA backbone and the negatively charged UOx, holding the UOx

\[
\text{UA} + \text{O}_2 + \text{H}_2\text{O} \rightarrow 5\text{-hydroxyisourate} + \text{H}_2\text{O}_2 \quad [1]
\]

\[
5\text{-hydroxyisourate} + \text{H}_2\text{O} \rightarrow \text{allantoin} + \text{CO}_2 \quad [2]
\]
within the polymer chains. The net charge of UOx is negative in pH 7.8, due to its pKa value (4.64) and isoelectric point (7.5).34 PV A-SbQ with the entrapped enzyme physically adsorbs onto the electrode surface due to adhesion and Van-der-Waal’s interactions. Raman spectroscopy was used to characterize both the entrapped as well as physisorbed UOx. To understand structure-functional relationships of UOx with PVA-SbQ, the presence of functional groups on the polymer-UOx substrate has been assessed using Raman spectroscopy with 514 nm laser excitation. The spectrum exhibited in Fig. 4 depicts two main zones at intermediate (1,100–1,400 cm\(^{-1}\)) and high (1,500–1,700 cm\(^{-1}\)) frequencies, representing dominant PVA-SbQ peaks. The entrapped enzyme provided peaks for amide III band of UOx and phenylalanine at 1324 cm\(^{-1}\) and 1116.99 cm\(^{-1}\), respectively. Peaks for other amino acid residues like arginine also provided lower intensity as seen from Fig. 4, due to stretching and vibrations of the carboxyl and amino groups on the polymer-enzyme modified surface. As compared to physisorbed, there appears to be a slight shift of the amide band from 1578.78 cm\(^{-1}\). This shift can be attributed to C-C and -C-O-C interactions and a change in the \(\alpha\)-helical structure and \(\beta\)-sheets of the enzyme due to the electrostatic interactions between the \(\delta^-\) of the amino acid chains and positive charge of pyridine in PVA-SbQ. These results comply with those previously investigated for these functional groups.36,37 Copper, being embedded within the amino acid chains, displayed a relatively small peak with a shift around 985.7 cm\(^{-1}\).

Effect of wound environment on UOx.—Wound healing is characterized by the successful completion of distinct overlapping phases. A key factor that influences the process is the pH of the area surrounding the wound. Chronic non-healing wounds are known to have an elevated alkaline pH (7.15 to 8.9). As healing progresses, the pH becomes more acidic, approaching that of normal skin (4–6) (Fig. 5 inset).21,39 The pH of a wound can directly impact many factors, including oxygen release, angiogenesis, protease activity, and bacterial toxicity.39 As enzymes can only function in specific pH environment; it is necessary to evaluate the activity of UOx in various pH environments. Doing so, provides an understanding of how the wound’s severity and environment affect the biosensor. The effect of pH on UOx was studied from pH 5 to 10 using absorption spectroscopy. Specific activity of UOx was calculated from the absorption values and plotted in Fig. 5. Results show that the highest activity (9.3 U mg\(^{-1}\)) of UOx is in the pH region of 7 to 9. Based on these results, pH 7.8 was chosen for the electrochemical experiments.

Sensing performance of the uric acid biosensor.—Electrochemical response of entrapped enzyme.—Determination of UA was performed through the monitoring of FCA redox reaction on the enzymatic electrode. The plausible electron transfer mechanism involves \(\text{H}_2\text{O}_2\) acting as a reducing agent, reducing FCA. The reduced \(\text{Fe}^{2+}\) (metal ion in FCA) undergoes a facile one-electron oxidation on the electrode to the ferricinium state (Fig. 6a).40 Ferrocene, through reversible oxidation, generates ferrocinium ions (\(\text{Fe}^{3+}\)) under low potentials facilitating the monitoring of enzyme activity on the electrode surface. The signal of the oxidized \(\text{H}_2\text{O}_2\) in the presence of FCA can be seen in Fig. 6b. For FCA at a pH of 7.8, a bare electrode has an \(E_{\text{pA}}\) of 0.4 V and an \(I_{\text{pA}}\) of 2.6 μA. On the same electrode, the peak separation, \(\Delta E\) (30 mV) and peak currents (\(I_{p}\)) of the anode and cathode show that FCA undergoes a reversible redox reaction.

The formal potential (\(E^{\text{m}}\)) of all three electrodes (bare, enzyme entrapped and physisorbed) for FCA is 0.385 V, while \(E_{\text{pA}}\) and \(\Delta E\) remain the same for all three. In presence of UA, there was an 800 nA
increase in $I_{pa}$ on the bare electrode. With the addition of polymer on the electrode, however, $I_{pa}$ decreased by 350 nA. The working area of the electrode was blocked, thus preventing sufficient diffusion of the analyte to its working area. In comparison, a UOx physisorbed electrode provided better response to H$_2$O$_2$ with a 400 nA increase in $I_{pa}$ compared to the bare electrode due to the hydrophilic nature of the enzyme. Additionally, the UOx entrapped electrode showed a superior response with an 800 nA increase in $I_{pa}$ compared to the bare electrode. This increase can be attributed to an improved diffusion of the analyte to the electrode’s working area through the polymer-enzyme hybrid matrix. Compared to the other two electrodes, the enzyme entrapped electrode has a characteristic steady state response in the scan beyond 0.4 V.

The biosensor was evaluated by testing it with consecutive UA concentrations (0, 12~300 μM). The results show a linear increase in $I_{pa}$ with respect to UA concentration (Fig. 6b inset). These studies were repeated using the DPV technique as well (Fig. 6c). In DPV studies, a UOx entrapped electrode provided increased current compared to a UOx physisorbed electrode. The linear calibration (Fig. 6c inset) also shows that the UOx physisorbed electrode cannot be used for UA detection due to its ultra-low sensitivity value (0.001 μA μM$^{-1}$ cm$^{-2}$). The sensitivity of the entrapped electrode was 0.155 μA μM$^{-1}$ cm$^{-2}$. The UOx entrapped electrode showed superior response, with enzyme activity retained through irreversible immobilization of the enzyme in its working area. It can be inferred from our studies that, enhanced response of the UOx electrode can be attributed to the presence of FCA, which facilitates electron transfer between the enzyme and the electrode surface. With the entrapment technique also providing improved mechanical stability and minimized leaching within its microenvironment, all analyses were performed with enzyme functionalized electrodes, entrapped in a polymeric matrix.

Repeatability, stability and continuous monitoring.—Denaturation of proteins occurs at elevated temperatures and enzymatic electrodes can hence be unstable in nature, being sensitive to temperature and pH. Studies to determine the stability of the sensor was performed over a week in the buffer solution containing UA (48 μM). Results show the entrapped sensor provides improved stability over multiple days with repeated use (Fig. 7a). The physisorbed electrode, however, showed reduced performance by ~60% after day 1 on comparison as seen. The biosensor was tested under physiological temperatures to analyze its performance and feasibility on a transdermal wearable platform. Measurements conducted at body temperature provided stable performance over a week (Fig. 7b) in the buffer solution with UA. Studies to determine stability during continuous monitoring of UA were performed over 30 min maintaining the same concentration of UA (48 μM) (Fig. 7c). Results show that there is a gradual reduction in response after 12 min. After ~20 min., the prepared biosensor still maintains 80% of the signal. With each continuous measurement up to 12 min, this biosensor can provide stable response within ~10% variation over 3 days (Fig. 7b). This shows the entrapped UOx biosensor provides stable measurements of UA in physiologically relevant conditions.
Effect of sample volume on sensing performance.—A low sample production rate creates insufficient liquid channels between the electrodes in the three-electrode system. Sufficient volume is necessary to facilitate charge and ion transport. The effects of different sample volumes (0.5 to 50 μL) were tested using polydimethylsiloxane (PDMS) as a biocompatible substrate for holding small volumes. (inset: Fig. 8b). To enable uniform distribution of the sample on the electrode assembly, a sandwich setup was used. The setup includes a layer of PDMS containing the desired volume of the sample, and a wound dressing and then the transducer. For small volume measures, even across the surface of the working electrode; these volumes are just enough to allow conduction of ions between the electrodes and to amplify signal effectively.

Clinical sample analyses.—As discussed in previous sections, healing progress can be monitored from correlations of UA concentrations in wound fluid. The extracted wound fluids from the four different samples (experimental section) were analyzed using standard UA assay protocols to determine UA concentrations in wound fluid samples. The concentration values of the samples are given in Table I, in the added column. To evaluate the UOx biosensor, electrochemical studies were performed to correlate the results with those obtained from the assay. Different wound fluid samples were tested against a linear calibration curve obtained from the standard assay concentrations. As given in Table I, four de-identified patients were selected for this study, with wounds of varying severity. These studies provided us varying recovery of 85%–150% with an RSD of about 5% as shown in Table I. At any given time, debridement oozing through dressings in multiple patients may have varying levels of components (electrolytes, lactate, glucose, and proteins). Some deviation in response can thus be accredited to differences in wound fluid composition from the patients. Such interferent measurements which may tend to occlude the sensor and limit its sensing performance will be explored in future studies.

IoT platform integrated potentiostat.—The enzymatic sensor was interfaced with an analog front end (AFE), LMP91000 on a flexible platform. The customized printed circuit board (PCB) was manufactured on flexible Kapton tape with a two-layer board ~ 800 microns thick (Fig. 9a). It was designed to accommodate the low-cost potentiostat (LMP91000) with a low power data processing microcontroller, CC2650 integrated with a Bluetooth module for wireless data transmission. A schematic of the potentiostat is given in Fig. 9b. The arrangement of the circuit is that of a non-inverting operational amplifier. The voltage supplied by the source was closely followed by the voltage between the reference and working electrodes. All three electrodes on the dressing were connected to corresponding pins of the AFE, linked to the microcontroller, CC2650 as shown in Fig. 9c. Electronic components including the microcontroller, AFE, power management systems with BLE Antenna, I/O device chip, MPU, memory chip and associated circuitry were mounted on the top layer as shown in Fig. 9c.

Operation of potentiostat and micro-controller.—LMP91000 was configured via the microcontroller, CC2650 to perform three electrode amperometry according to the schematic in Fig. 9b. As depicted, amplifier A1 is the control amplifier that implements the potentiostat circuit. The variable bias block provides a constant potential across the working electrode to a proportional voltage, connected to Vref. This converts the current flowing between the counter and working electrodes to a proportional voltage, connected to Voc.

Microcontroller, CC2650 is used as an integrated wireless microcontroller with bluetooth low energy (BLE) capabilities to provide

| Sample | Added (μM) | Found (μM) | Recovery (%) | RSD |
|--------|------------|------------|--------------|-----|
| S1     | 76.64      | 65.21      | 85.09        | 4.64|
| S2     | 96.40      | 85.12      | 88.29        | 0.46|
| S3     | 106.40     | 115.83     | 108.86       | 3.91|
| S4     | 34.02      | 50.61      | 148.75       | 30.37|

S1, S2, S3 and S4 represent the wound fluid samples from de-identified patients.

Figure 8. Effect of low sample volume on (a) Ep vs. Ag/AgCl and (b) Ip vs. Ag/AgCl of the biosensor, where 48μM uric acid was measured. The dotted lines in both graphs represent the upper and lower limits. The plots in the (a) and (b) insets are normal distribution curves representing potential and current, respectively. The inset schematic in (b) is the experimental setup.
wireless communication and peripheral controls remotely at ultra-low-power cost-effectively with its 2.4 GHz transceiver. It was connected to the LMP via the I2C interface, as in Fig. 9c. $V_{\text{ref}}$ from the LMP91000 was routed to the microcontroller general purpose input/output, where it was conditioned by an internal analog-to-digital converter for interpretation. The internal feedback resistor was optimized for optimal amplifier gain through $R_{\text{fb}}$ interpretation. The reference voltage ($V_{\text{ref}}$) to the AFE sensing device was externally provided by the digital to analog converter. The developed wearable platform operated on a 3.7 VDC lithium-ion (Li-ion) battery capable of providing up to 350 mAh. The Li-ion battery used can be recharged on the wearable platform through a micro-USB device connected directly onto a charging circuit allowing simultaneous system operation and charging. Battery voltage was regulated to provide a constant 0.3 VDC source to the system in through a battery voltage range of 3 VDC ≤ $V_{\text{DC}}$ ≤ 3.7 VDC. When Bluetooth capabilities were enabled by the user, the current consumption of the system increased $^{45}$ from 2 to $\sim$ 40 mA. This current generated by the potentiostat from a standard deviation of 0.6 μA was observed as depicted in Fig. 9d. A slight shift in potential was also noticed with a standard deviation of 0.01 V as seen in Fig. 9e. This information was then sent wirelessly via Bluetooth to the receiver which possesses abilities to send the data to the cloud. Information processed and sent from the Bluetooth module to the receiving device was encrypted to avoid data compromise and enable secure transmission.$^{46}$

Conclusions

An enzymatic potentiometric biosensor has been developed for non-invasive real-time monitoring of UA from wounds. Electrochemical analyses with different immobilization techniques investigated have shown entrapped enzyme in a cationic polymer (PVA-SbQ) matrix provides enhanced response as compared to physisorbed. The use of FCA as a redox electron shuttle provided enhanced electron transfer between the enzyme and the transducer over a broad physiological

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Figure 9. (a) Flexible electronics; (b) Schematic of the potentiostat and connections; (c) Circuit design of components embedded on the PCB interfaced with the flexible wound sensor; Bland-Altman plots representing variation in (d) current and (e) potential from studies using classical setup and IoT platform in presence of 100 μM UA, measured at 20 mV s$^{-1}$. E1 and E2 represent the classical SPCE and biosensor on fabric respectively.
range. With stable response over multiple days at body temperature, this biosensor shows the potential of continuous monitoring. Detection of UA from wound fluid provides a pathway for developing a dressing-embedded biosensor system in wound care on a non-invasive, wearable platform.

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