Wireless Sensor-Integrated Platform for Localized Dissolved Oxygen Sensing in Bioreactors

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***Abstract*— This work presents a miniaturized electrochemical sensor-integrated bioprocess monitoring pod (bPod) that wirelessly monitors local dissolved oxygen (DO) saturation within bioreactors in real-time. The system comprises a compact printed circuit board (PCB) that integrates a potentiostat analog-front-end (AFE) and a Bluetooth Low Energy (BLE) microcontroller with an electrochemical DO sensor. *In situ* detection of DO within the bioreactor is enabled via a 3-D printed ABS-M30i shell, representing a robust and biocompatible packaging solution for prolonged monitoring. The platform is evaluated in a bench-scale bioreactor filled with aqueous media, and data is extracted wirelessly via a custom-developed application. A linear response corresponding to DO saturation levels was achieved using chronoamperometry (CA), exhibiting a dynamic voltage range between 1.3 V (−4.9 μA) and 0.87 V (−11.1 μA), corresponding to 0% and 100% DO saturation respectively, with a sensitivity of 6.3 mV/DO%. This work highlights a unique sensor assembly and packaging approach to overcome challenges for localized bioprocess monitoring platforms in bioreactors. [2020-0149]**

***Index Terms*— Dissolved oxygen, bioreactor, bluetooth low energy, electrochemical sensor, wireless electronics.**

I. Introduction

PROCESS parameter (i.e. DO and pH) inhomogeneities in large-scale bioreactors are known to be a significant source of product non-uniformity in biopharmaceuticals and can potentially lead to low production yield with non-uniform products that have differing efficacy based on their structure [1], [2]. Industry and academic researchers alike have focused on limiting sources of heterogeneity for the production and scale-up of monoclonal antibodies (mAbs), the dominant biotherapeutic on the market [3], [4]. However, existing commercial monitoring technologies, such as inline instrumental probes, generate a single-point measurement taken as the averaged value for an entire cell reactor [5], which is unable to capture the distribution of process parameters within a bioreactor. Emerging technologies that permeate the bioreactor flows and continuously record spatial variation in key parameters would help improve bioreactor design and enable the real-time adjustment of process conditions necessary to achieve a more uniform product [6].

Wireless *in situ* devices are a promising technology for locally interacting with solutions/feedstocks in the bioreactor environment. Similar platforms have been developed for monitoring pH and flow characteristics within photo- and single-use bioreactors respectively [7]–[9]. However, among these, no microsystems have been developed that wirelessly monitor DO using free-floating sensors. DO plays a critical role in cell proliferation in batch cultures and various bioreactor systems by maintaining a homogeneous oxygen distribution to ensure proper oxygen uptake in cells that is essential for successful operation [10]. We previously designed and demonstrated a larger proof-of-concept bPod [11], highlighting the potential utility of wireless DO sensing in a bioreactor. However, to enable integration of the bPod into a realistic bioreactor environment, the system requires (1) an overall form factor below 25 mm diameter (bioreactor process piping diameter) [12] and (2) a more rapid and reliable electrochemical response to dynamically changing DO saturation relative to the measurement location.

In this work, we have significantly advanced the PCB-electronics design, DO sensor, and packaging to achieve the overall system miniaturization desired for use in realistic bioreactor environments. The bPod uses custom microfabricated electrochemical sensors and off-the-shelf components to realize a reliable wireless platform for autonomous amperometric measurement of DO using chronoamperometry (CA). Furthermore, a mechanically robust and biocompatible 3-D printed shell made from ABS-M30i was utilized to avoid device failure and ensure leak-proof operation. The current mesoscale system is 24 mm in diameter and was deployed in a 10-L bench-top bioreactor for evaluation of DO percent (DO%) saturation. Overall, this work progresses the current

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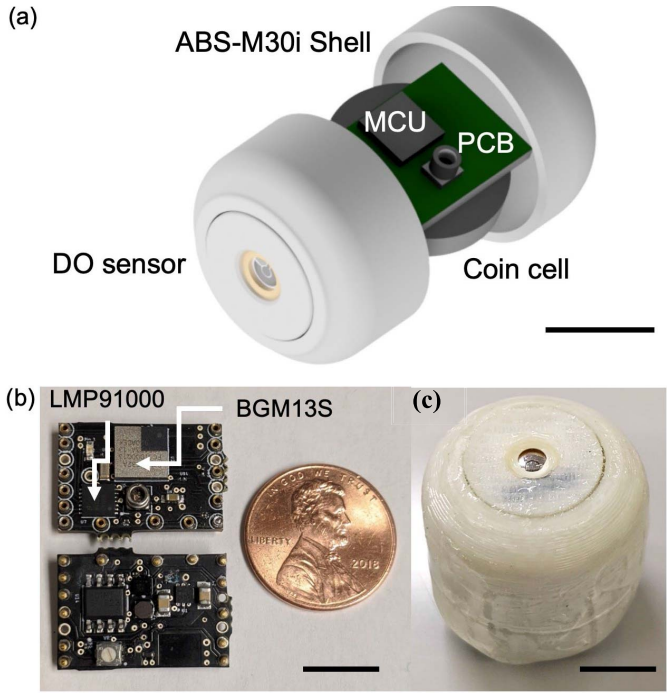

Fig. 1. Overview of bPod design: (a) Exploded schematic view of the sensor-integrated platform housed in a 3-D printed biocompatible ABS-M30i shell, (b) optical images of the PCB equipped with an AFE (LMP91000) and BLE MCU (BGM13S), and (c) the packaged bPod used for testing in the bioreactor (scale bars: 10 mm).

state-of-the-art of wireless *in situ* modules designed to improve precision of localized online bioreactor monitoring for biomanufacturing applications.

II. Materials and Methods

A. Design of Sensor Integrated Platform

Fig. 1a shows the bPod, comprising a PCB module, microfabricated Clark-type DO sensor, and 3-D printed ABS-M30i shell. The PCB layout was designed using EAGLE (Autodesk, San Rafael, CA) to create two separate electronics boards: a circular 13 mm Sensor-PCB with a 9 mm x 9 mm open-air quad flat no-lead (QFN) package (Quikpak, Escondido, CA) to interface with the DO sensor and a MCU-PCB, containing the analog-front-end (AFE) circuit and Bluetooth Low Energy (BLE) microcontroller (MCU).

Specifically, the MCU-PCB incorporates three main off-the-shelf components: (1) an AFE potentiostat IC, LMP91000 (Texas Instruments, Dallas, TX) to maintain the excitation voltage across the working and reference electrodes, as well as to amplify and convert the sensor current into a readable voltage, (2) a BLE programmable MCU, BGM13S (Silicon Labs, Austin, TX) with an integrated 2.45 GHz transceiver antenna (0 to +18 dBm) for wireless communication, and (3) a CR2032 coin cell battery, 20 mm diameter, (Energizer. St. Louis, MO) with an accompanying 3.3 V voltage regulator, TPS61291 (Texas Instruments, Dallas, TX) to power the electronics. The PCB's were commercially fabricated on a double-sided, 4-layer FR-4 ceramic substrate (Sunstone Circuits, Mulino, OR), including the soldering of surface mount IC components onto the PCB (Screaming Circuits, Canby, OR). The MCU-PCB (W: 18 mm and L: 23 mm), as shown in Fig. 1b, was designed to reduce the scale of the previously developed proof-of-concept prototype from 60 mm to 25 mm in diameter. The MCU was designed to minimize power consumption of the bPod by toggling between two energy modes: low-power mode (2.5 μA), when idle, and active mode (10 mA spikes), when transmitting data. The CR2032 coin cell battery (energy capacity of 225 mAh) was chosen, considering a measurement interval of 3-5 minutes and measurement duration of 15 s, to allow a worst case expected battery lifetime of 18.8 days.

In order to minimize the possible cytotoxic effects of the shell material on the cell culture within the reactor, a biocompatible thermoplastic, ABS-M30i (Stratasys, Rehovot, Israel), was chosen. The ABS-M30i filament possessed a high impact resistance, which improved the mechanical robustness of the bPod under severe sparging conditions and was compatible with standard sterilization techniques, such as gamma radiation and ethylene oxide (EtO). The bPod package, fabricated using a fused deposition modeling (FDM) 3-D printer, Fortus 250mc (Stratasys, Rehovot, Israel), was designed in 3 separate parts: (1) a circular top (15 mm diameter) with a 6 mm opening to expose the DO sensor while creating a leak-proof seal about the Sensor-PCB and (2) a 24 mm diameter shell (thickness 1.4 mm) split into two halves to encapsulate the electronics. Fig. 1c shows the fully assembled bPod platform containing both PCBs, the coin cell battery, and DO sensor prior to deployment in the bioreactor.

B. Fabrication and Assembly of Dissolved Oxygen Sensor

The DO sensor, comprising a three electrode-system depicted in Fig. 2a, is fabricated using a two-step liftoff process on a Pyrex wafer with Ti/Pt (20 nm/200 nm) as both the working (WE, 1 mm diameter) and counter (CE) electrodes and Ag (300 nm) for the reference (RE) electrode (treated with 0.1M KCl in DI water for Ag/AgCl reference). To complete the Clark-type electrode system, a gas permeable fluorinated ethylene propylene (FEP) membrane (Strathkelvin, Dublin, Ireland) is fixed above the DO sensor (with tape at a 360μm thickness), encapsulating 10 μL of 0.1 M KCl.

The assembly process for the sensor reservoir and biocompatible packaging is depicted in Fig. 2b. In summary, the sensor wafer was first diced (7.4 mm x 7.6 mm) for placement within the open-air QFN package (Fig. 2b (i)). Sensor contact pads for the CE, WE, and RE pins of the sensor were aligned to minimize the distance of the electrical connections with the designed Sensor-PCB. Next, two layers of type-470 (3M, St. Paul, MN) tape were aligned with the sensor contacts and cut to form a 5 mm circular well using a biopsy punch. The first tape layer was adhered directly to the glass substrate centered around the concentric sensor to form the electrolyte reservoir. The type-470 tape is both moisture and chemically resistant, as well as capable of forming a watertight interface between the Pyrex surface (Fig. 2b (ii)). Using a third tape layer (4 mm opening), a small circular FEP membrane (6 mm diameter) was brought into contact with the KCl droplet and carefully sealed by applying pressure between

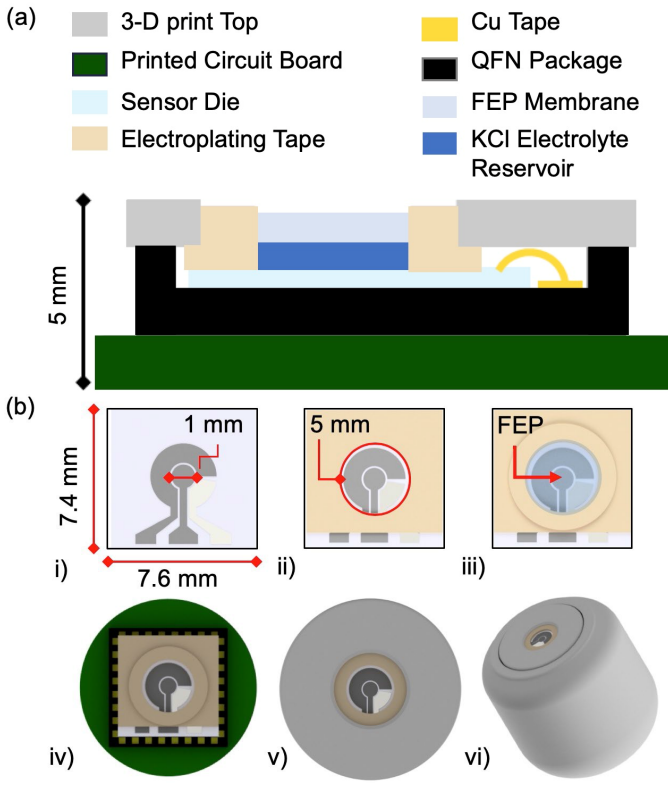

Fig. 2. Cross section of (a) assembled DO sensor and Sensor-PCB. (b) Step-by-step assembly process: the DO sensor wafer is first diced (i), then a KCl reservoir is formed with tape (thickness: 360 μm) (ii) and an FEP membrane is attached (iii). The die is adhered to the Sensor-PCB with double-sided tape (iv), covered by a 3-D printed top (v), and positioned into the ABS-M30i shell with the MCU-PCB and coin cell battery (vi).

the second and third tape layers until no bubbles were trapped in the reservoir (Fig. 2b (iii)). The opening and membrane diameters were shown to minimize leaking in and out of the sensor reservoir, as well as to maximize the available sensor surface area exposed to the media.

The sensor die is then attached using double-sided tape to the QFN package, which is soldered to the Sensor-PCB, (Fig. 2b (iv)). The electrical connections between the sensor contact pads and the bond pads were created using strips of conductive copper tape. Alternatively, the copper tape can be replaced with wire bonds (Au) to the internal QFN package pads for quicker assembly. A separate ABS-M30i 3-D printed top (15 mm diameter) was then placed over the sensor die and circular Sensor-PCB, protecting the sensor contacts during handling and allowing facile packaging of the sensor with the remaining MCU-PCB electronics (Fig. 2b (v)). The 3-D printed top was fixed to the Sensor-PCB with a friction fit (tolerance of 0.3 mm) and sealed to be watertight, with a small layer of epoxy placed around the FEP membrane over the sensor. Connections between the Sensor-PCB, MCU-PCB, and the coin cell battery were made using 36-gauge wires and then subsequently positioned internally within the ABS-M30i shell. One half of the shell has a 16 mm diameter opening to align with the capped Sensor-PCB. All interfaces between the 3-D printed components were then sealed with epoxy (Fig. 2b (vi)).

This packaging method was designed to isolate the sensor contacts from the liquid environment as well as allow for replacement of the DO sensor during the evaluation of the platform. Further miniaturization of the electronics assembly is possible by subdividing the IC components onto additional PCBs and arranging them with the Sensor-PCB and MCU-PCB into a stacked configuration [13]. However, this scaling is limited by the required energy capacity of the battery and necessary shell thickness to bolster the impact resistance of the packaging.

C. Beaker-Level Electrochemical Characterization

For the characterization of the DO sensor prior to integration with the portable electronics, beaker-level testing utilized cyclic voltammetry (CV), performed by a bench-top potentiostat (VSP-300, BioLogic, Seyssinet-Pariset, France), to determine an excitation bias voltage and evaluate the dynamic current range of the fabricated DO sensor. The electrochemical analysis was conducted in DI water at room temperature for nitrogen-saturated (0% DO saturation) and air-saturated (ambient) settings. The nitrogen- and air-saturated conditions were created by flowing pure N_2 from a gas cylinder (AirGas, Radnor Township, PA) and compressed air into the solution for 5 minutes, respectively. CV was performed at each condition by a linear voltage sweep from 0.0 to -0.4 V (vs Ag/AgCl) at a scan rate of 20 mV/s.

D. Bench-Top Electrochemical Characterization

For evaluation of the assembled system components, the bPod was deployed in a 10-L glass bioreactor controlled by the BioFlo 310 fermenter (Eppendorf, Hamburg, Germany). In order to generate a specific DO-saturation state, two separate gas lines of O_2 and N_2 pressure regulated at 34.5 kPa (5 psi), were inserted into the BioFlo 310 fermenter and combined using a built-in flow controller. Gas mixtures of O_2 and N_2 were released through a single gas inlet connected to the 10-L vessel using polyethylene tubing. Gases were bubbled into the solution at a constant volumetric flow rate (2.0 SLPM) and stirred with a single Rushton turbine impeller spinning at 100 RPM. The DO% was varied by adjusting the duty cycle, or percent ratio, of O_2 and N_2 (O_2:N_2) passed to the bioreactor vessel via a control interface. Four configurations of 0% (0:100), 25% (25:7), 50% (50:50), and 100% (100:0) saturation were measured after 3 minutes of sparging and compared to a reference commercial polarographic DO probe (Mettler Toledo, Columbus, OH).

III. Results and Discussion

A. Electrochemical Characterization of Do Sensor

Fig. 3 shows the cyclic voltammogram (CV) of the DO sensor, separate from the bPod, in both ambient air and N_2-saturated solutions. CV peaks of DO were observed for cathodic currents in the potential range between 0 V and -0.4 V. While sweeping the excitation voltage, an increasingly negative current response was observed as a result of the reduction reaction with DO until, starting at -0.25 V

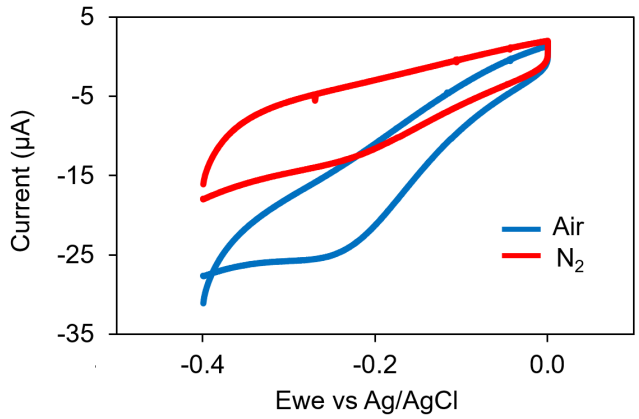

Fig. 3. Characterization of the Pt DO sensor: cyclic voltammogram of the sensor in 0.1M KCl solution at air-saturated (blue) and N_2-saturated (red) states. Voltage sweep from 0 V to −0.4 V (vs. Ag/AgCl at scan rate of 20 mV/s) with a BioLogic VSP-300 potentiostat.

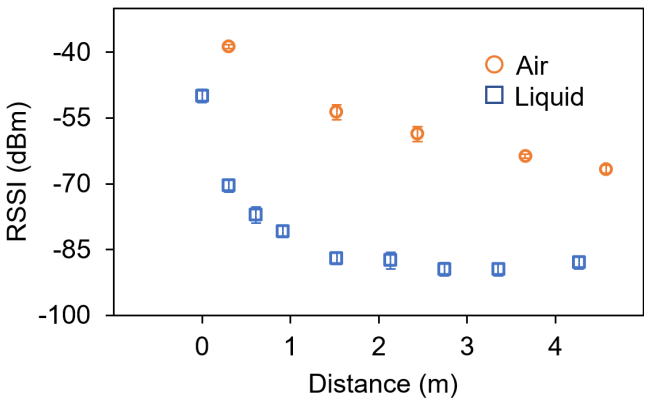

Fig. 4. Characterization of wireless communication: Wireless signal transmission is compared between the phone and bPod in air (orange) and submerged in the 10-L bioreactor filled with DI water (blue) (N = 6). The relative signal strength (RSSI) showed sustained communication until 4.3 m. Measurement error: 1.14 dBm.

(vs. Ag/AgCl), diffusion-limited behavior (plateaued current response) occurred. Excitation voltages that placed the sensor response within the diffusion-limited region were ideal as they represent a linear relation between the changing DO% saturation of the solution (−0.25 to −0.39 V). The range of the peak current response was observed between −28 μA (100% DO state) and −15 μA (0% DO state). Though the raw current values measured with the bench-top potentiostat do not directly translate to the readout of the MCU-PCB because of differences during signal amplification, we were able to clearly distinguish an expected deviation between two unique DO% saturation states with the sensor and provide an acceptable current range to tune the AFE potentiostat IC.

As a result, the AFE was optimized to excite the sensor at a −0.25 V (vs. Ag/AgCl) potential bias with an expected absolute current range of −1 to −30 μA, which was accomplished by adjusting the gain of the transimpedance amplifier (TIA) for the LMP91000 (feedback resistance, R_{TIA}, was set to 70 kΩ). Additionally, since the MCU-PCB was powered using a single-sided supply of 3.3 V, the output voltage was offset by 1.65 V, creating a virtual ground. This enabled the bPod to both excite the Pt WE with a 'negative' bias voltage (between 0 to 1.65 V) and record the negative output currents expected from the electrochemical DO reaction.

B. Bluetooth Low Energy Wireless Communication

In order to determine the efficacy of data acquisition using Bluetooth in an aqueous environment, the relative received signal strength (RSSI), or relative power level of the signal, between the bPod platform and phone was recorded. Fig. 4 compares the RSSI of the bPod submerged in a 10-L bioreactor filled with DI water to the signal measured through air. The phone was held by the observer at the same height as the bPod, and the separation distance was increased at 0.3 or 0.6 m (1 or 2 ft) intervals until connection failure. Measurements were recorded unobstructed in both scenarios, and line-of-sight (LOS) between the phone and bPod were maintained throughout.

In the bioreactor, reliable data transmission was maintained up to 4.3 m, with a max RSSI of −90 dBm before disconnecting from the bPod (antenna sensitivity is −92 dBm). An average of 6 values were recorded at each location with the RSSI, decreasing exponentially from an average baseline (25 mm separation) of −50 dBm in DI water and −39 dBm in air.

It is expected that over a cell culture growth period in a bioreactor, the RSSI will be greatly influenced by the mixing conditions and increasing biomass, ultimately resulting in a depreciated signal and a diminished transmission distance. The authors recognize that further characterization of the wireless signal propagation is necessary to ensure a robust Bluetooth link in the bioreactor environment under non-ideal conditions. However, the current capabilities of the bPod were demonstrated to be suitable for most glass and plastic walled vessels with stainless steel large-scale bioreactor vessels as an exception.

C. Calibration of the bPod in a Bench-Scale Bioreactor

Prior to generating the calibration curve for the bPod, a two-point calibration was recorded at gas flow ratios of 0:100 (nitrogen-saturated) and 100:0 (oxygen-saturated) to determine the expected DO concentration that could be achieved by the BioFlo 310 fermenter. Fig. 5a compares the averaged chronoamperometric (CA) measurements performed by the bPod with an excitation voltage of −0.25 V (vs. Ag/AgCl) for 15 s (at 10Hz sampling frequency). Measurements were recorded with the bPod at each saturation state every 3 minutes, corresponding to a new DO% saturation confirmed by the polarographic DO reference probe, then wirelessly transmitted to the phone application. The current response, i_b, of the sensor was expressed as a positive readout voltage, V_{Out}, calculated as shown in (1), where R_{TIA} is the feedback resistance of the TIA and V_{Bias} is the offset voltage (1.65 V) of the measurement. Increasingly negative currents correspond to values closer to 0 V and are dependent on the previously set current bounds. A voltage range between 1.3 V, V_0, (−4.9 μA) and 0.87 V, V_{100}, (−11.1 μA) was observed

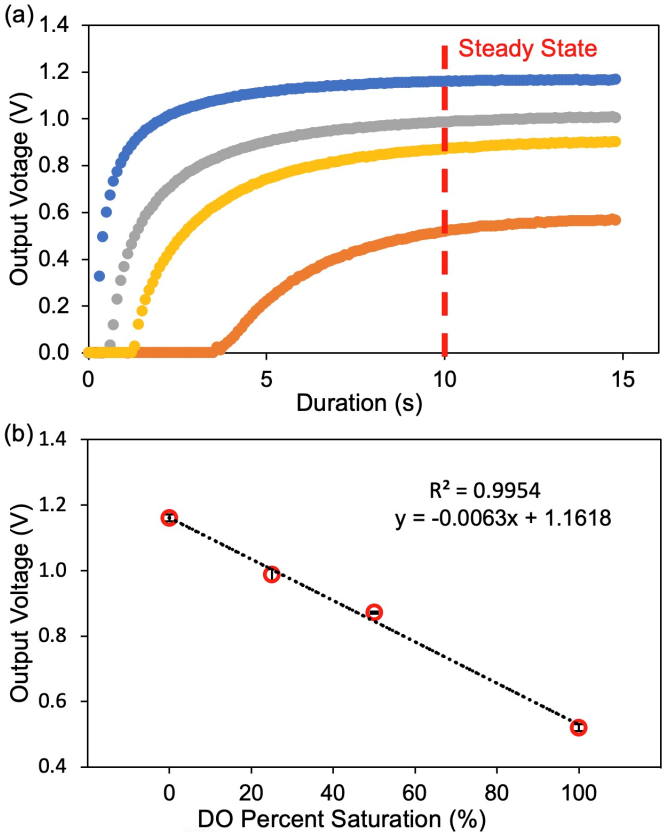

Fig. 5. Electrochemical characterization of the submerged bPod: (a) chronoamperogram of the averaged output voltage recorded by the bPod in DI water, with 3-minute intervals between saturation states (sample rate = 100 ms, N = 3). The O_2:N_2 gas ratio was adjusted for four DO saturation states 0% (0:100, blue), 25% (25:75, grey), 50% (50:50, yellow), and 100% (100:0, orange). Measurement error was negligible at ±20 mV. (b) A calibration curve was generated for steady state (10 s) and displayed a linear response (correlation coefficient R^2 = 0.9954) and sensitivity of 6.3 mV/DO%. Measurement error: ±10 mV.

in Fig. 5a and assigned to be the 0% and 100% DO saturation points, respectively. The DO% was calculated, using (2), for each sparging condition.

$$V_{Out} = i_b \cdot R_{TIA} + V_{Bias} \tag{1}$$

$$DO\% = \frac{V_0 - V_{Out}}{V_0 - V_{100}} \times 100 \tag{2}$$

A delay in the output voltage was observed as O_2 in the solution was increased (4 s delay at 100% DO saturation). This discrepancy is reflective of the −30 μA current bound previously set for the AFE and can be easily removed by decreasing the signal gain, at the cost of signal resolution at steady state. A steady state response was observed after 10 s at each investigated DO% state with excellent repeatability. These results indicate reliable and rapid response of the miniaturized bPod to a dynamically changing DO% saturation within the bioreactor.

The resulting calibration plot, shown in Fig. 5b, was found by correlating DO% saturation to the output voltage acquired after 10 s (steady state), displaying a linear response (correlation coefficient R^2 = 0.9954) with a sensitivity of 6.3 mV/DO% and limit-of-detection of 5.53% DO saturation. To achieve localized DO monitoring capabilities under stirred flow conditions, the steady state sensor response of the bPod would need to occur much faster than 10 s. Further experimentation is required to establish an optimal steady state point, balancing accuracy of the measured DO concentration with minimal sensor response time. One approach using the bPod would be to adjust the sensor gain and align the chronoamperograms across the expected DO concentration range of a specific bioreactor process, then record the steady state point at earlier times or compare the slope of each of the impulse responses. While most cell culture bioreactors utilize a combination of pure N_2, pure O_2, and air (22% O_2) to obtain a desired DO% for each bioreactor, the demonstrated calibration capabilities and excellent sensitivity of the bPod provide a significant advantage for monitoring a wide range of DO concentrations.

IV. Conclusion

In this work, a miniaturized sensor integrated platform was demonstrated for the wireless in situ evaluation of bioreactor DO saturation. Combining a Pt Clark-type DO sensor with PCB electronics into a biocompatible ABS-M30i package has allowed direct implementation into the bioreactor environment, leveraging improved sensor reliability and an almost 14-fold reduction in form factor compared to our previously reported work. Noted improvements from previous system designs include a larger battery capacity and a greatly stabilized sensor response that was produced with minimal error during several hours of sensor and bPod characterization.

Various limitations were noted during the characterization of the bPod in the 10-L bioreactor. The operational lifetime of the bPod was found to be most limited by the packaging robustness. The bPod mass was adjusted so that the sensor would remain fully submerged, and a floating condition was maintained, minimizing collisions with the bioreactor impeller blades. This bottleneck can be resolved by adjusting the shell thickness and geometry to further improve impact resistance without compromising biocompatibility or increasing the bPod's overall form factor. Ideally, power consumption would be further optimized to allow for use of smaller batteries. Furthermore, all experiments were conducted in DI water for 2 hours to clearly assess the device performance. In this simulated environment, the sensors and electronics were found to be readily reusable with no significant degradation in performance observed, while the protective 3-D printed ABS-M30i shell was seldom replaced. Also, no device failures were encountered during testing. However, concerns of path loss of the wireless signal due to cell growth, long-term energy consumption, sensor lifetime, and interference with sensor stability from bubbles or degradation of the FEP membrane are remaining challenges that need to be overcome.

Future work will aim to modify the platform with additional electrochemical sensor types (e.g. temperature, pH, and pressure sensors), assess the long-term robustness and biocompatibility of the sensor and packaging in a cell media (up to ∼2 weeks), modify the assembly process to allow for sterilization of the bPod unit, as well as connect several

devices using a sensor network communication protocol to more reliably assess distributed culture parameters within the bioreactor. Overall, this platform demonstrates improved sensor reliability and a significantly smaller form factor for implementation in bioreactors to promote large-scale production of more homogenous bioreactor products.

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Dr. Ghodssi is a fellow of AVS and ASME. He is an Associate Editor of *Biomedical Microdevices* (BMMD) and served as an Associate Editor of *Journal of Microelectromechanical Systems* (JMEMS) for twelve years from 2008 to 2020.