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Design, Fabrication, and Characterization of an Electrochemically-based Dose Tracking System for Closed-loop Drug Delivery*

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Abstract— **A real-time integrated electrochemically-based dose tracking system for closed-loop drug delivery is presented. Thin film Pt sensors were integrated in an electrolytic MEMS drug delivery pump to allow dose tracking via electrochemical impedance measurement. Measurement electrode placement and composition were investigated. A bolus resolution of 230 nL was demonstrated. The sensor was calibrated for use with water (low conductivity) and 1× PBS (high conductivity), the selected model aqueous drugs. The impedance response is dependent on delivered volume and not affected by actuation parameters. A graphical user interface was created for real-time impedance based dose tracking and leakage/blockage detection in the system. Drift in the impedance response of an idle system after perturbation (actuation) were investigated and mitigated through the use of Pt wire electrodes as opposed to thin film electrodes.**

I. INTRODUCTION

Drug delivery is essential in the treatment of chronic conditions that are projected to affect 50% of Americans by 2030 [1]. Most of these diseases have been shown to have a chronobiological pattern in their pathogenesis [2] and therefore can be more effectively treated with patient-tailored therapy regimens. Drug delivery devices that can deliver precise doses and include sensors that would enable the delivered dose to be tracked, confirmed, or modified would greatly increase treatment efficacy for these conditions [3].

Systems such as direct observation, microdialysis, and nuclear imaging have been utilized to track and confirm dosage. However, they are often limited in their resolution, accuracy, and/or detection limits, and cannot provide real-time feedback [4]. Efforts have been made to integrate traditional fluid monitoring techniques, such as flow sensor technologies within drug delivery devices [5], however, they often require complicated fabrication procedures and packaging challenges [4]. Impedance-based sensors, however, are attractive for this application due to their simplicity, sensitivity, and wide-compatibility.

Previous attempts in utilizing impedance based measurements for dose tracking in real-time in conjunction with active pumping were limited to rigid (silicon/Pyrex) structures intended for benchtop lab-on-a-chip systems and are unsuitable for implantation. Furthermore, the approach was limited to small drug delivery volumes (< 1.5 µL) and would not be appropriate for sustained drug delivery. The ability to accurately monitor and control delivered volume to within ±5 nL, however, was achieved [6].

We previously demonstrated impedance-based tracking and detection of physiologically-relevant drug volumes and on-the-fly flow rate variations using a pair of silver plated copper wires placed in the drug reservoir of a prototype MEMS drug infusion pump [4].

Here, we present the design, fabrication and characterization of a fully integrated electrochemically-based dose tracking system, capable of real-time tracking and confirmation of delivery, as well as detection of leaks and blockages in the pump system. It is important to note that although this dose tracking method was developed to accompany an electrochemically actuated infusion pump, the method can be easily integrated with other pumping formats.

II. DESIGN CONSIDERATIONS AND FABRICATION

The drug delivery pump operates based on electrolytic pneumatic actuation. A set of interdigitated platinum (Pt) electrodes electrolyze the water in the actuation chamber into hydrogen and oxygen. The resulting volume expansion is then harnessed to inflate the drug separating bellows which in turn displaces the fluid in the drug chamber and expels drug from the catheter to the delivery site [7].

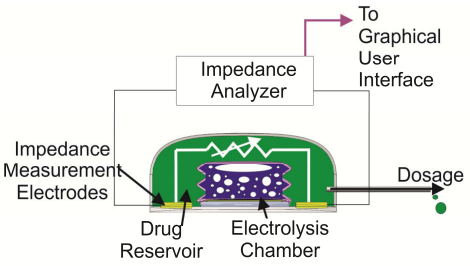

Figure 1: Cross-section illustration depicting proposed electrolysis-based pump system layout and impedance measurement concept.

Electrochemical dose tracking is achieved through measuring electrochemical impedance (EI) by applying a small sinusoidal excitation voltage across a different set of electrodes. When two electrodes are placed in an electrolytic fluid, the metal-electrolyte interface can be modeled by the simplified Randles circuit which consists of the solution (electrolyte) resistance in series with the parallel combination of the double layer capacitance and polarization resistance. At sufficiently high frequencies (1 kHz for water), the impedance response is dominated by the solution resistance, which in turn can be modeled as a simple variable resistance dependent on the cross sectional area of the fluid (Fig. 1). When the fluid is contained in a rigid chamber, this

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dependency can be used to correlate the measured impedance value with the volume of fluid remaining in the chamber.

EI measurements can be carried out under low power conditions (< 100 µW) and the magnitude of excitation voltage required is maintained in the "water window" (≤ 1 V_{pp}). Therefore all reactions are reversible and hydrolysis of water does not occur [8].

Interdigitated electrolysis pump electrodes (100 µm width/spacing) and thin film impedance measurement electrodes (3 mm × 2 mm) were fabricated on a soda lime substrate by liftoff (Ti/Pt 300 Å/2000 Å) and then potentiostatically cleaned at ±0.5 V in 1× phosphate buffered saline (PBS). 30 awg silver plated copper wires were affixed to the contact pads of both sets of electrodes using conductive epoxy to provide electrical connections. The electrolysis electrodes were coated with Nafion® to increase electrolysis efficiency [9]. Parylene bellows actuators were fabricated as detailed in [10], filled with DI water and attached to the electrolysis electrodes using marine epoxy. The drug reservoir parts were injection molded from poly propylene. A refill port was fashioned from polydimethylsiloxane (PDMS) in the reservoir cap. Parts were then assembled and joints reinforced with marine epoxy (Fig. 2).

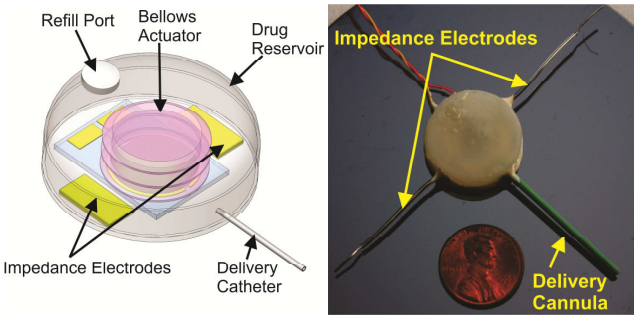

Figure 2: (a): Model of drug delivery pump system with integrated impedance electrodes for dose tracking, (b) photograph of integrated drug delivery pump system with impedance electrodes.

III. Experimental Methods

DI water and 1× PBS were used as aqueous drug analogs. The fluids were injected into the drug chamber through the PDMS refill port using a 30 gauge needle.

Electrolysis-based actuation was attained by applying a constant current value to electrolysis electrodes in the actuation chamber. A range of flow rates (0.33-141.9 µL/min) were achieved for 0.1-13mA applied current with <5% error [7]. The delivered volumes were monitored by either weighing the volume dispensed from catheter opening (for volumes > 15 µL) or by measuring the dispensed fluid's displacement in a 100 µL calibrated micropipette (for volumes < 15 µL).

Impedance measurements were acquired in real-time using a precision impedance analyzer connected to the thin film impedance electrodes and recorded via a LabVIEW interface. An alternating excitation voltage (1 V_{pp} and 1 kHz) was applied. At this voltage level, only completely reversible chemical processes took place at the electrodes and no chemical modification of the drug was observed.

IV. Results and Discussion

A. Electrode Placement Optimization

The drug delivery pump presented here is capable of delivering volumes from nLs to 100s of µLs. The complementary electrochemical dose tracking system should be able to accurately track these doses.

Bohm, et al. reported the placement of the impedance sensing electrodes within the electrolysis chamber on the same substrate as the electrolysis electrodes [6]. This electrochemical configuration is feasible for low delivery volumes of < 800 nL. However higher flow rates and delivery volumes require higher applied currents. Under this regime, the electrolysis electrodes act as a magnetic core in the magnetic field created by the EI electrodes. This field is quite small but becomes significant at high frequencies, i.e. the frequencies at which solution resistance becomes dominant and the measurements are made. The model circuit is therefore altered (Fig. 3) and the measurements are no longer reliable as they are not representative of solution resistance alone [11]. A series of two-electrode EI spectroscopies were obtained on thin film EI electrodes placed inside/outside the electrolysis chamber between 0.005-100 kHz while different current values were applied to the electrolysis electrodes (data not shown). The results confirmed that the EI electrodes should not be placed within the electrolysis chamber for high flow operation. Instead, EI electrodes should be placed externally with respect to the electrolysis cell enclosed by the bellows.

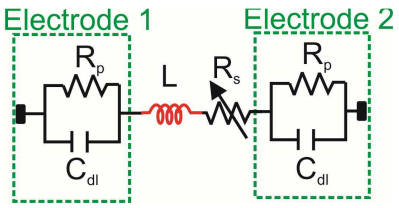

Figure 3: High frequency inductance observed when EI electrodes are placed inside the electrolysis chamber.

The electrodes placement with respect to the bellows actuator was also investigated. Electrodes were arranged opposite one another on either side of the bellows actuator or perpendicularly. Electrode separation from the bellows actuator was evaluated (3-5mm). The best resolution (230 nL bolus) was obtained for electrodes placed 3 mm from the bellows actuator and directly across from one another (data not shown).

B. Fluid-based Calibration

Two solutions, DI water and 1× PBS, were chosen as model drugs. Water has rather low conductivity (5.0×10^{-6} [S/m] at 25 ºC), where as 1× PBS is highly conductive (1.9×10^{-4} [S/m] at 25 ºC) by comparison. Each solution was loaded separately in the drug reservoir, and two-electrode EI spectroscopy was performed between 0.005 - 100× 10^3 Hz to determine the frequency range at which the solution resistance is dominant (Fig. 4). Based on these results, 1 kHz and 10 kHz were chosen for water and PBS, respectively. These values are sufficient to bypass the double layer electrode capacitance while avoiding parasitic effects encountered at higher frequencies.

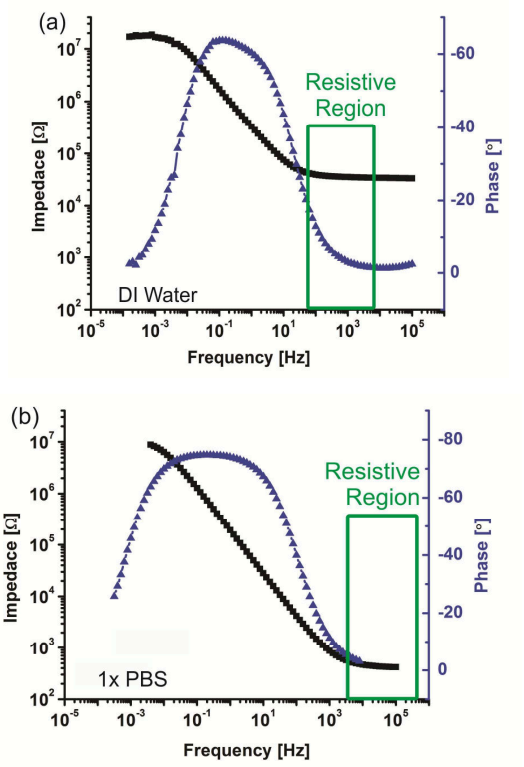

Figure 4: EI spectroscopy for (a) DI water, and (b) 1× PBS. The boxed region represents the frequency range at which the solution resistance is dominant.

1, 3, and 5 mA currents were applied to the electrolysis electrodes, for 2, 1, and 0.5 minutes, respectively. Each current value was applied 5 times. The volume dispensed from the pump, as well as the change in impedance was recorded for each run. The actuator was allowed to recombine between current applications. The results for each current value were used to obtain averaged trends. The impedance values were normalized to the baseline value for each measurement. The equation corresponding to the linear fit of the data was then used to calculate the calibration curve for each current.

The results showed that differing current values did not affect the calibration. Also once the appropriate frequency was chosen for the drug fluid, the calibration curve was no longer dependent on the fluid. This is attributed to the ability of the electrochemical pump to deliver fluid regardless of viscosity. Therefore the same calibration curve could be applied to other drug model solutions once the appropriate operating frequency for the impedance measurement is determined by EI spectroscopy.

Table 1: Calibration equations for DI water and 1x PBS.

DI Water	$delivered\ volume\ [\mu L] = \frac{normalized\ impedance}{1.44E^{-4}}$
1x PBS	$delivered\ volume\ [\mu L] = \frac{normalized\ impedance}{1.45E^{-4}}$

C. Real-time Leak/Blockage Detection

Based on the calibration results, a LabVIEW graphical user interface was created for real-time dose tracking. The controller takes as an input the fluid type (water/PBS), bolus volume of drug to be delivered, as well as the measurement frequency corresponding to the fluid to be pumped. The program would then use real-time measured impedance and the built-in calibration curves to supply power to the actuation pump and deliver the correct volume at the specified intervals. All data acquired by the LabVIEW interface was then saved for further analysis.

Furthermore, the program was also capable of detecting leaks and blockages in the system as they occurred. If there is a blockage in the catheter, fluid volume in the drug chamber does not change even though the actuator is actively pumping. In this situation, the slope of the impedance read-out would level off (Fig. 5a). In case of leakage across the bellows, the slope of the impedance read-out would become negative (Fig. 5b). The program would then notify the user that a blockage/leak has been detected and would automatically turn off the power supply to the actuation pump to protect the pump from any damage.

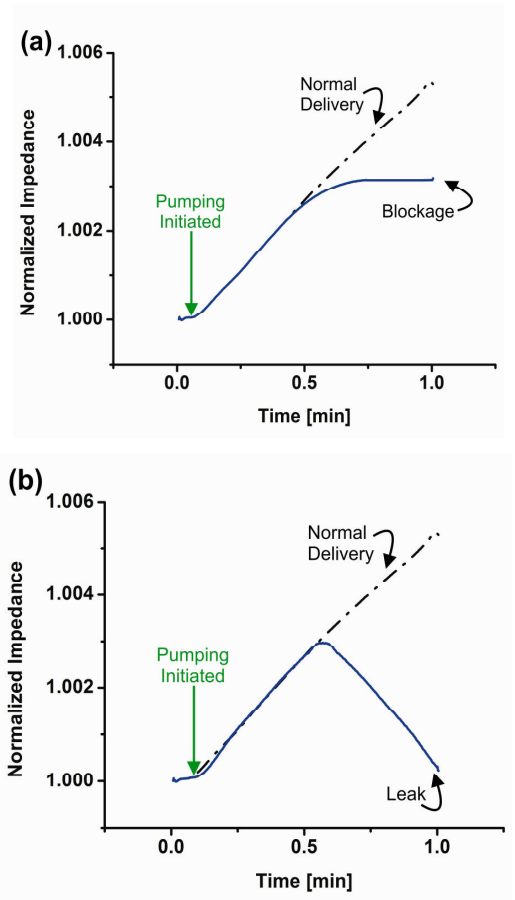

Figure 5: Examples of impedance response for (a) a blockage, and (b) a leakage across the bellows in the drug delivery system.

D. Addressing Drifts in Measurement

In EI measurements, typically an Ag/AgCl reference is preferred due to its high stability. However, Ag^{+} exerts toxic effects by interfering with transmembrane Ca^{++} flux. Therefore Pt, despite its inherent drift when used as a reference, has long been the preferred material *in vivo* [12]. These drifts need to be minimized to obtain accurate dose tracking in real-time, especially when actuation has ceased

and the volume in the drug reservoir remains constant. It has been documented that non-precious metals such as the silver plated copper wire as well as conductive epoxies can potentially introduce a considerable amount of noise and drift to the EI measurement system [13]. Increased electrode surface area and reduced excitation voltage magnitude have also been reported to reduce drift [13-14].

In order to minimize drift, 99.9% Pt wire (Ø 0.5 mm) was used as an alternative to the thin film impedance electrodes previously described. Heat shrink tubing was introduced as insulation. A 2 mm segment of the tip was exposed and then sanded to increase surface area. The electrodes were then electrochemically cleaned and packaged into the drug reservoir.

EI measurements (1 kHz, 1 V_{pp}) were carried out following delivery of DI water and compared to the previously mentioned electrodes to study the system in idle mode (Fig. 6).

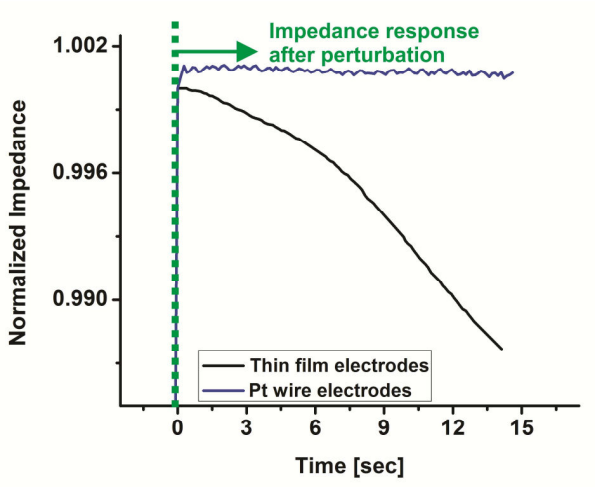

Figure 6: Normalized impedance response drift (1 V_{pp}, 1 kHz) after fluid delivery comparing thin film electrodes with epoxied wire and Pt wire electrodes.

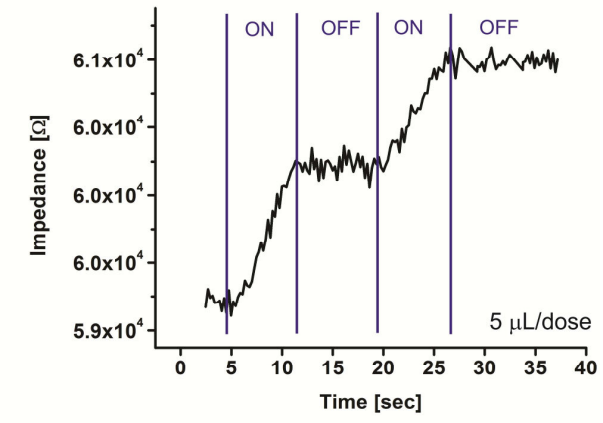

Figure 7: Bolus delivery (6/10 sec On/Off) impedance response (100 mV_{pp}, 1 kHz) . Two 5 µL boluses delivered with 5 mA applied current.

The Pt wire electrodes showed significantly less drift at 1 V_{pp} applied excitation voltage following a perturbation to the system (actuation). Also, while previously system noise rendered measurements at an excitation voltage below 1 V_{pp} ineffective (data not shown), with the Pt wire electrodes, accurate measurements could be made with 100 mV_{pp} excitation voltage. Reduced magnitude of the excitation voltage also leads to reduced power requirements for sensing. Fig. 7 shows On/Off bolus operation detection (100 mV_{pp}, 1 kHz). Two 5 µL boluses were delivered (5 mA current applied for 6 sec followed by 10 sec off). A corresponding increase of 2.5% was observed in the impedance magnitude over baseline.

V. Conclusion

A fully integrated dose tracking system capable of real-time delivery tracking and confirmation was presented. Electrochemical dose tracking is attractive for its simplicity, sensitivity, and wide-compatibility and can be easily adapted to other pumping methods. Pure Pt wire electrodes were shown to considerably reduce drift and voltage requirements which pave the way for long term use and wireless sensing, respectively.

Acknowledgment

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