A WIRELESS IMPLANTABLE DRUG INFUSION SYSTEM WITH INTEGRATED DOSING SENSORS

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ABSTRACT

A wireless electrolysis-based drug delivery system with integrated electrochemical dosing sensors suitable for management of chronic conditions is presented. Repeatable delivery performance for identical and variable bolus volumes and flow rates of phosphate buffer saline (PBS) was demonstrated. Successful delivery and sensing of 17.75 ± 0.48 µL boluses (1.78% of reservoir fill volume) of lidocaine was achieved.

KEYWORDS

Electrochemical sensors, drug delivery, electrolysis micropump.

INTRODUCTION

Patients suffering from chronic conditions often rely on external or implanted drug infusion pumps for therapeutic management. According to reports by the US Food and Drug Administration (FDA), of the 56,000 medical device reports relating to the use of infusion pumps in a five year period, approximately 65% were related to system malfunctions [1]. Current infusion pumps do not incorporate sensors to provide feedback on delivery parameters (e.g. dosed volume and rate), resulting in late diagnosis of malfunction until adverse physiological symptoms are reported by the patient. This could potentially lead to serious health complications, injury, or even death [2-5].

Sensors integrated into drug infusion pumps can track the drug administration and report on the state of the pump in real-time, allowing for active control of the delivery profile and, in addition, warning of pump malfunction. Such controlled drug administration may increase therapy efficacy up to 60% [6]. The improvement in dosing control can reduce the associated financial and human costs of pump malfunctions or dosing errors [7, 8]. While most commercially available implantable pumps operate in open loop and do not incorporate sensors, investigational implantable pumps, such as the Medallion (Medallion Therapeutics, Inc., Minneapolis-St. Paul, MN) [9], and research drug delivery devices, such as the intrathecal drug delivery system developed by [10], include integrated flow and pressure sensors to track delivery. Our approach uses a novel sensing method to track dosing and thereby provide information on potential pump malfunction.

Previously, the possibility of monitoring fluid delivery using changes in electrochemical impedance (EI) of a fluid container was demonstrated [11] followed by integration of these sensors with a wired, electrolysis-based micropump [12]. For implantable pumps, wireless power and data transmission eliminates transcutaneous wires and catheters thereby reducing surgical complexity, improving patient mobility, and allowing drug administration outside of clinical settings. Here, an advanced integrated system is presented that for the first time utilizes wireless powering and data telemetry to achieve a fully implantable electrolysis-based micropump with EI dosing sensors (Figure 1).

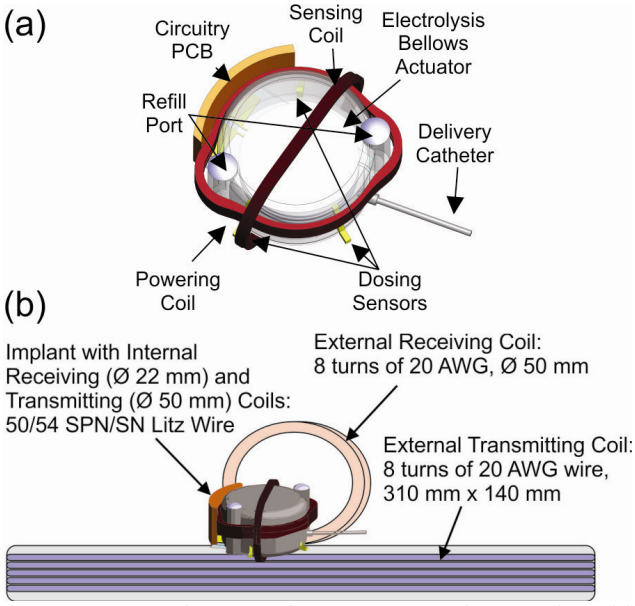

Figure 1: (a) Schematic diagram of wireless implantable drug delivery micropump with integrated dosing sensors, (b) system setup (not to scale): the micropump is placed on top of the external transmitting coil. The external coils are situated perpendicular to each other.

DESIGN

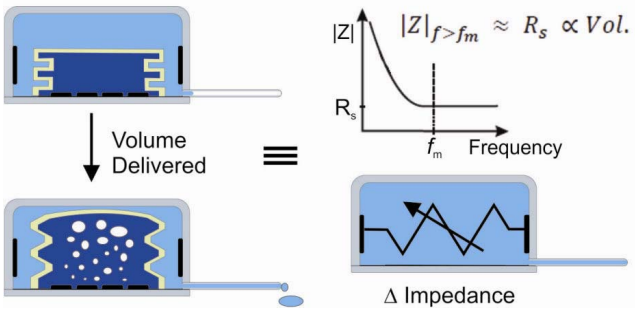

Figure 2: System operation concept.

The micropump is actuated by electrolysis. A pair of interdigitated platinum (Pt) microelectrodes fabricated on

borosilicate glass were used to electrolyze water. The gases generated increased pressure and inflated the reaction-encasing Parylene bellows, which in turn displaced the adjacent fluid in the drug reservoir through the delivery catheter. Two Pt sensing electrodes were placed in the fluid reservoir forming an electrochemical cell. By measuring electrochemical impedance at a sufficiently high frequency (>10 kHz), the solution resistance was isolated and any changes in the volumetric conduction path (e.g. decreased reservoir volume) registered as an increase in the measured impedance (Figure 2, Equation 1). The micropump was inductively powered using a class E system. In order to achieve bi-directional data telemetry between the dosing sensors and the external module, amplitude shift modulation (ASK) and frequency modulation data transfer were utilized. A fixed 500 kHz sensing signal was carried by the (2 MHZ) power signal transmitted over 2 cm to the remote implant. Once picked up by the internal receiving coil, the signal was fully rectified, fed through a current regulator, and applied to power the actuator. The received signal was also applied to the dosing sensors. The current through the sensors was held constant using a source-follower buffer. As such, changes in sensor impedance resulted in a change in voltage across an n-MOSFET (Equation 2), causing a change in its capacitance (Equation 3) and a corresponding shift in the resonance frequency of the implanted transmitted coil (Equation 4). This shift was reflected on the external receiving coil, measured externally, and correlated to changes in the reservoir fluid volume. To further improve the sampling speed and signal quality, the externally received signal was amplified and multiplied by the original transmitted signal (Figure 3).

$$\Delta Volume \propto \Delta R_{sensor} \quad (1)$$

$$\Delta R_{sensor} \propto \Delta V_{n-MOSFET} \quad (2)$$

$$\Delta V_{n-MOSFET} \propto e^{-\Delta C_{n-MOSFET}} \quad (3)$$

$$\Delta\left(\frac{1}{\sqrt{C_{n-MOSFET}}}\right) \propto \Delta f_{res} \propto \Delta sensor\ response \quad (4)$$

FABRICATION

Micropump with Integrated Sensors

Interdigitated Pt electrodes (100 µm wide elements separated by 100 µm gaps, 8 mm diameter footprint) were fabricated on a Borofloat® 33 glass wafers (University Wafer, Boston, MA) substrate by liftoff (Ti/Pt 300 Å/2000 Å) and coated with Nafion® (Dupont DE521 Solution, Ion Power, INC, New Castle, DE) by dip coating twice. Kynar™ silver plated copper wires (30 AWG, Jameco Electronics, Belmont, CA) were soldered to contact pads on the electrodes. The joint was strengthened and insulated with nonconductive marine epoxy (Loctite, Westlake, OH) [13]. Parylene bellows (2 convolutions; 10 mm outer diameter, 6 mm inner diameter) were fabricated as described in [14] using a two mold process by utilizing silicone rubber sheets (10:1 base-to-curing agent ratio Sylgard 184, Dow Corning, Midland, MI) and molten (~50°C) polyethylene glycol (PEG; 1,000 Mn, Sigma Aldrich, St. Louis, MO). A 13.5 µm layer of Parylene C (Specialty Coatings Systems, Indianapolis, IN) was deposited over the PEG mold, and PEG was dissolved by soaking in water at room temperature to complete the bellows. Electrolysis actuators were assembled by filling the bellows with double distilled (DD) water, and carefully combined with the Nafion®-coated interdigitated Pt electrodes using laser cut double-sided pressure sensitive adhesive film (3M™ Double Coated Tape 415, 3M, St. Paul, MN). The seal was reinforced with marine epoxy [15]. A circular reservoir (Ø 15 mm × 12 mm, 1 mL fill volume) was laser cut from optically clear Plexiglas® acrylic (McMaster-Carr, Santa Fe Springs, CA). Dosing sensors were fabricated from 99.9% Pt wire (Ø 0.5 mm) (California Fine Wire, Grover Beach, CA). A 2 mm segment of the tip was sanded (60 and 220 grit silicon carbide sandpaper) to increase surface area. The sensors were incorporated into the reservoir wall, bent through access ports and soldered to Kynar™ silver plated copper wires (30 AWG, Jameco Electronics, Belmont, CA) in order to make the connection with the wireless circuit. Once in place, marine epoxy was used to create a water-resistant seal. The actuator was then incorporated into the reservoir and sealed using marine epoxy.

Circuit Design and Layout

External Transmitter: A 2 MHz clock oscillator (ECS -2100, ECS international, Olathe, KS), along with a quad bilateral switch (CD4016BC, Fairchild Semiconductor, San Jose CA) controlled by a resistor-set oscillator (LTC 6906,

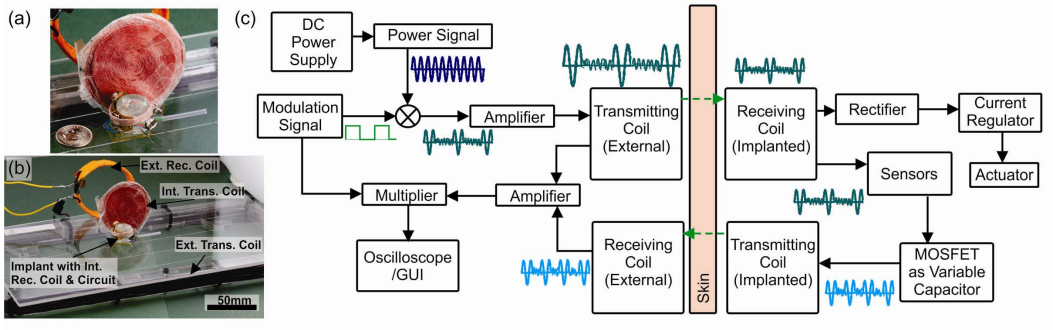

Figure 3: Photograph of (a) micropump with integrated dosing sensors, (b) system setup; (c) system architecture of wireless powering and communication circuit.

Linear Technologies, Milapitas, CA), were used to generate the power (2 MHz) and sensing signals (500 kHz), respectively. The generated signal was then amplified in two stages before being applied to a tuned transmitting coil (8 turns of 20 AWG single strand wire, size: 310 mm x 140 mm).

Internal Transmitter & Receiver: Litz wire (6 turns, 50/54 SPN/SN Litz Wire, Wiretron, Volcano, CA) was used for the receiving coil (Ø 22 mm). The flat internal transmitting coil (L = 110 µH at 500 kHz. Ø 50 mm) was also fabricated using Litz wire (50/54 SPN/SN Litz Wire, Wiretron, Volcano, CA). The circuit components and the electrolysis micropump require a direct current (DC) power signal. Therefore, the received alternating signal was fully rectified using two Schottky diodes (BAT54A and BAT54C, Fairchild Semiconductor, San Jose, CA). The modulation signal was separated by half-wave rectification (BAT54A) and applied to the sensors. An n-MOSFET (Si8424CDB, Vishay Siliconix, Singapore) was used as a voltage controlled variable capacitor and placed in parallel with the sensors. A p- MOSFET (Si8429DB, Vishay Siliconix, Singapore) and a BJT (2N4401, Fairchild Semiconductor, San Jose, CA) were used in a source-follower buffer configuration to maintain constant current through the sensors (~ 100 µA).

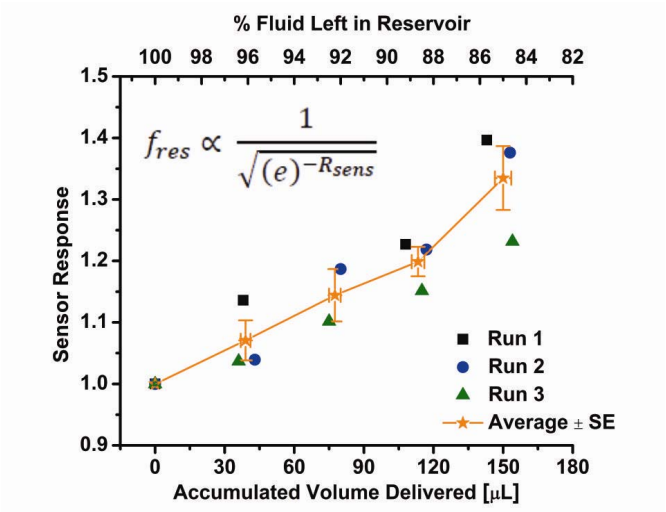

Figure 4: Wireless sensing with the infusion pump: each 37.5 ± 0.75 µL bolus (3.75 % of reservoir fill volume) led to a non-linear shift in the resonance frequency of the internal transmitting coil, inset shows relationship between frequency shift and sensor resistance.

EXPERIMENTS AND RESULTS

A range of voltages (V_{DS} = 0 - 2 V) were applied across the n-MOSFET serving as the variable capacitor in order to confirm the linear response range provided by the manufacturer's data sheet. Capacitance varied linearly with applied voltage (2.5 – 1 nF for V_{DS} = 0 – 2 V respectively, data not shown). The constant current value applied across the sensors should be chosen such that the voltage across the sensors (and the n-MOSFET) varies between 0 – 2 V for the expected sensor resistance range for the reservoir's deliverable volume. The resistance range is dependent on the ionic conductivity of the drug fluid and the size of the reservoir. Based on these values, a constant current of 100 µA was applied to the sensors.

The micropump with integrated sensors was connected to the internal circuit. The reservoir was filled with 1× PBS as a model drug. System performance was evaluated during the delivery of identical and differing bolus volumes of PBS. The final multiplied signal was recorded prior to and after bolus delivery. For each run, four boluses were delivered (3 mA current applied to the actuator for 90 seconds) totaling 150 ± 3.5 µL (~83% of the actuator deliverable volume). As expected, a repeatable non-linear response was observed between the volume remaining in the reservoir and the recorded multiplication results (Figure 4).

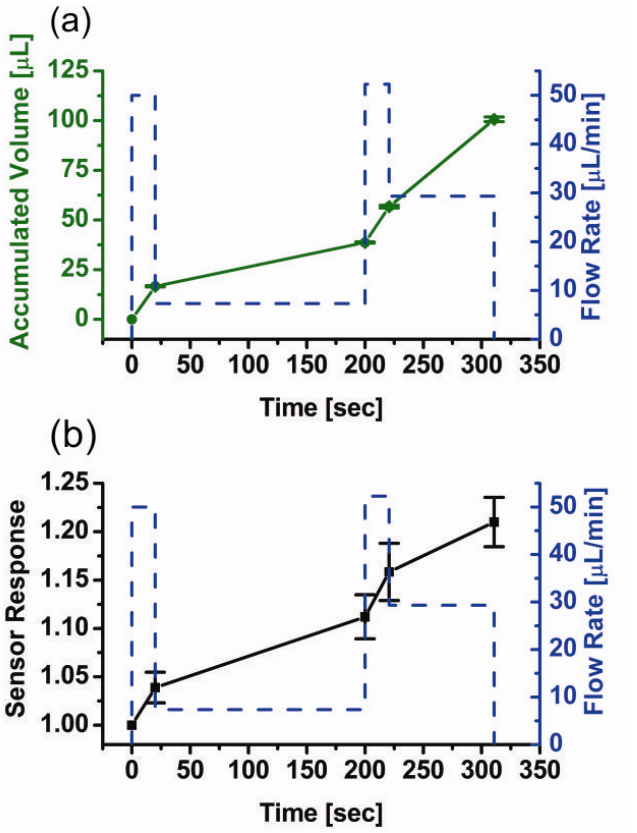

Figure 5: (a) Pump performance and (b) sensor response to changes in applied current to the microactuator leading to a change in the delivery flow rate (n=3, mean ± SE).

Different bolus volumes were delivered by changing the current applied to the pump actuator (5, 1, 5, and 3 mA successively for 20, 180, 20, and 90 seconds, respectively; Figure 5). The slope of the accumulated volume over time correlated to changes in the output flow rate; this, in turn, was reflected in the sensor response.

Lastly, four 17.75 ± 0.48 µL boluses of lidocaine HCl (20 mg/mL in saline), a common local anesthetic and

antiarrhythmic drug, were delivered using the micropump (20 sec on, 1 min off; Figure 6). A slight drift in measured impedance leads to a dip in the sensor response during the off periods. The drift amount is not constant and does not follow a predetermined trend [16].

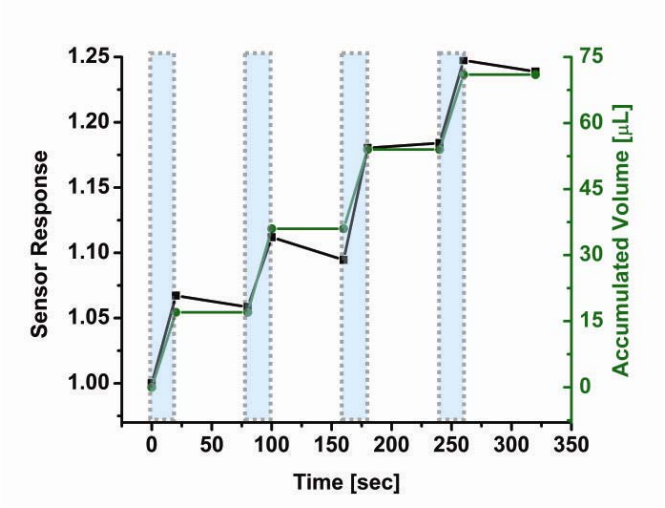

Figure 6: Delivery of 17.75 ± 0.48 µL boluses (1.78% of reservoir fill volume) of lidocaine HCl dissolved in saline (20mg/mL). Shaded areas indicate 20 seconds on, followed by 1 minute off.

CONCLUSION

Inductive powering and bidirectional data telemetry were used to achieve wireless operation of an implantable drug delivery system with integrated dosing sensors. Successful and repeatable delivery and sensing for identical and variable bolus volumes and flow rates of PBS and lidocaine was demonstrated.

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