INGESTIBLE BIOIMPEDANCE SENSING DEVICE FOR LOCALIZED FEEDBACK-DRIVEN DRUG DELIVERY

Mateo W. Lim[1], Brian M. Holt[1], Joshua A. Levy[1], Justin M. Stine[1], Luke A. Beardslee[1], and Reza Ghodssi[1]*
[1]University of Maryland, College Park, MD, USA

ABSTRACT

This work demonstrates the first example of a bioimpedance sensing ingestible device capable of feedback-driven, localized microneedle drug delivery into gastrointestinal (GI) tissue. The system integrates a thin-film, tetrapolar bioimpedance sensor with a potentiostat circuit and Bluetooth-enabled microcontroller (MCU) to trigger delivery of drug-loaded microneedles using a cantilever actuator. The sensor-driven trigger mechanism utilizes a dynamic bioimpedance threshold value, programmed via mobile phone, to initiate thermomechanical release of the drug cantilever. This behavior was validated using ex vivo small intestinal porcine tissue samples of varied conductivity, resulting in impedance-dependent delivery in ~1.59 seconds. This technology provides a foundation for rapid, localized treatment of GI disease facilitating minimally invasive oral treatment with minimal side effects.

KEYWORDS

Bioimpedance, Drug Delivery, Closed-Loop, Ingestible Device

INTRODUCTION

The GI tract is implicated in many autoimmune, systemic, and GI-specific disorders. Localized drug delivery within the GI tract can increase drug efficacy and reduce side effects attributed with drug absorption in non-afflicted tissue regions. However, achieving localized drug delivery mandates rapid sensing tools for identification of afflicted sites combined with on-command actuation technologies. Ingestible capsules are a viable vehicle for controlled therapeutics with higher patient compliance than injection. Endoscopic capsules, like the PillCam, are already employed to aid in diagnosis of GI conditions; however, due to power and sizing constraints, few ingestible devices combining sensing and drug delivery have been implemented, and none utilize wireless monitoring and autonomous operation [1].

Ingestible sensors, such as imaging, bioimpedance, and pH, have been employed to assess the state of intestinal tissue at specific locations. Additionally, ingestible actuators including [2-3] have been developed to deliver drugs on command. Our group has previously developed ingestible devices capable of impedance sensing and drug delivery, respectively, but combined operation has yet to be achieved [3-4]. This is a multifaceted challenge attributed to (1) a lack of suitable low-power sensing modalities that measure local tissue properties, (2) limited space and power for integration of each module and (3) safety and reliability issues during transit.

In this work, we demonstrate the first example of localized drug delivery using bioimpedance sensing as a triggering mechanism. In the context of inflammatory bowel disease, for example, failure of intestinal ion transport channels manifests, reducing epithelial tissue impedance. This capsule utilizes a tetrapolar bioimpedance sensor driven by an analog front-end (AFE) on rigid-flex PCB, a 3D-printed capsule shell, and a cantilever actuator deployed through thermomechanical actuation. This implementation is the first example of closed-loop actuation from ingestible devices and a major step toward autonomous localized treatment of lesions in the GI tract.

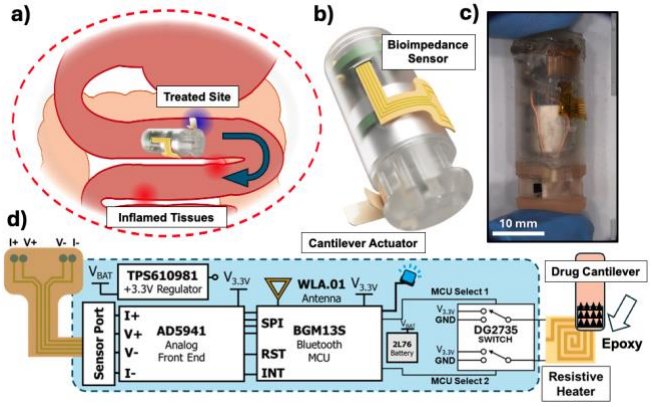

Figure 1: (a) Principle of bioimpedance detection and closed-loop drug delivery, (b) rendering of the ingestible capsule with sensing and actuation functionalities, (c) image of the capsule, (d) electronics schematic highlighting the AFE, MCU, bioimpedance sensor, and heating element.

MATERIALS AND METHODS

The bioimpedance-drug delivery capsule is comprised of: (1) a bioimpedance sensing module and (2) a thermomechanical release actuator module interfaced using capsule electronics described in [4]. Both flexible sensors are fabricated with a Au lift-off process on Kapton® Polyimide described in [5]. The bioimpedance sensor utilizes a tetrapolar configuration along with a PEDOT:PSS surface treatment to mitigate contact resistance and interfacial impedances. The resistive heater geometry and resistance (70 Ω) was optimized to efficiently dissipate heat into a low-melt ethylene vinyl acetate (EVA) to facilitate cantilever release. Cantilevers are laser cut from 254 µm thick polyether ether ketone (PEEK) sheets and topped with a drug-loaded microneedle array to deliver into intestinal tissue as previously presented in [3].

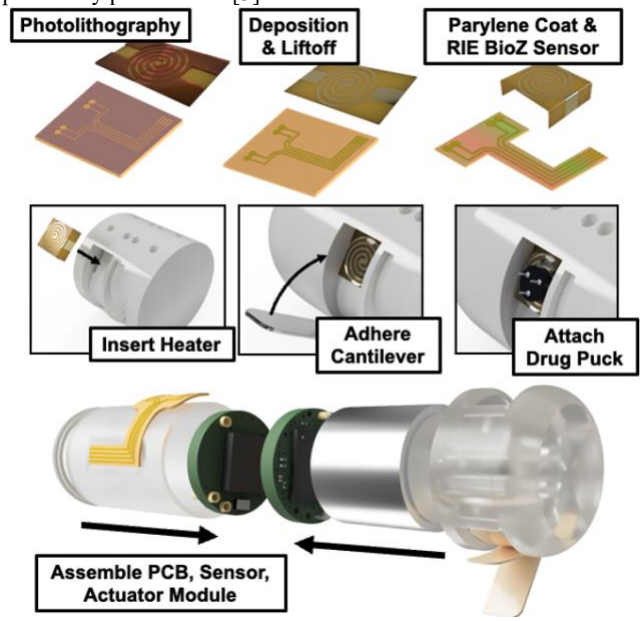

Figure 2: Component fabrication and device assembly process.

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The device can support two drug-loaded cantilever actuators. One is located proximal to the impedance sensor and another on the reverse side. A DG2735 analog switch interfaces with two MCU select ports to apply 3.3 V regulator output across each heater. The capsule shell is fabricated using a Phrozen Sonic Mini 8K vat photo-polymerization (VPP) 3D printer with FormLabs Surgical Guide V2 Resin. The heater is electrically connected to PCBs using silver conductive epoxy and 28 AWG insulated wires. Bioimpedance sensors are connected using a flat-flex connector port. The capsule is assembled using a biocompatible urethane adhesive.

RESULTS AND DISCUSSION

Remote Deployment of the Cantilever Actuator

The capsule is capable of remotely triggering the deployment of the cantilever using a Bluetooth-enabled device, such as a mobile phone. Following device assembly, repeated release of the cantilever was performed using the programmed capsule and EFR Connect (Silicon Labs) app to characterize the response time (N=4), resulting in an average deployment time of 1.59±0.48 s (*Fig. 3*), suitable for immediate delivery into afflicted tissue.

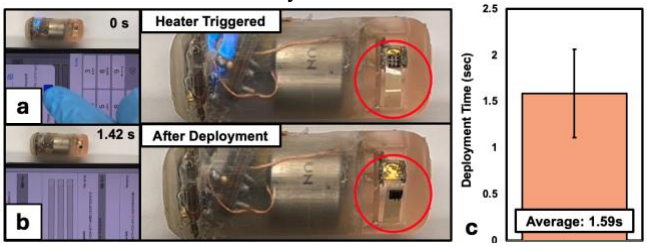

Figure 3: Deployment of the cantilever using a mobile app. (a) Before the cantilever is deployed (t=0 s), (b) after the cantilever deploys (t=1.42 s), (c) actuator response time between mobile activation and successful deployment (N=4).

Bioimpedance Sensing on Ex Vivo Intestinal Tissue

A tissue model was devised consisting of porcine small intestine samples untreated (N.T.) and soaked in dyed phosphate-buffered saline (PBS) for validating the wireless bioimpedance readout. A motor-driven linear actuator translates the capsule device across the tissue model at a constant rate (*Fig. 4a*). Low variation in bioimpedance magnitude is observed across PBS-treated tissue compared to N.T. tissue. Therefore, a drug delivery activation threshold was set at 1500Ω for wireless deployment (*Fig. 4b-c*). The threshold value is adjustable based on target tissue type or state.

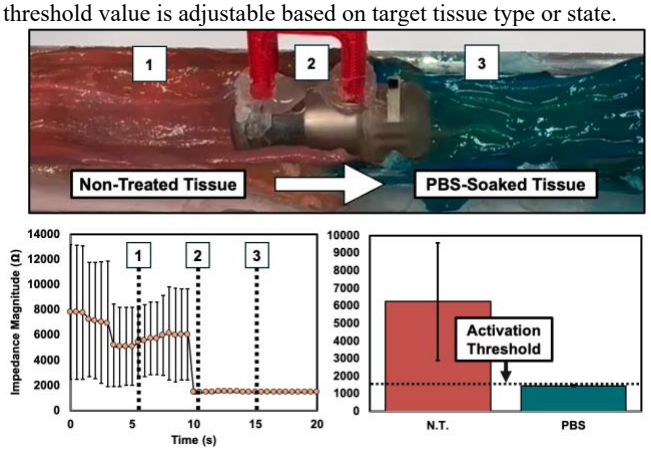

Figure 4: (a) Translation of device across tissue model, (b) wireless bioimpedance magnitude measurement, (c) average impedance values obtained on non-treated and PBS-soaked tissues (N=3).

Closed-Loop Sensing and Delivery

To demonstrate closed-loop drug delivery, the Bluetooth-enabled microcontroller is programmed to apply a high voltage across the resistive heater in response to an acute impedance magnitude drop below the bioimpedance threshold value. Based on the previous tissue characterization, the threshold was wirelessly programmed to be 1500 Ω and the drug-loaded actuator is re-assembled to the capsule device on the reverse side. Translation across the tissue model confirms deployment of the drug delivery actuator in response to bioimpedance sensor contact with PBS-soaked tissue (*Fig. 5*). This experiment simulates activation of the device in response to relative changes in tissue impedance. Following delivery, the cantilever actuator separates from the device and passes naturally.

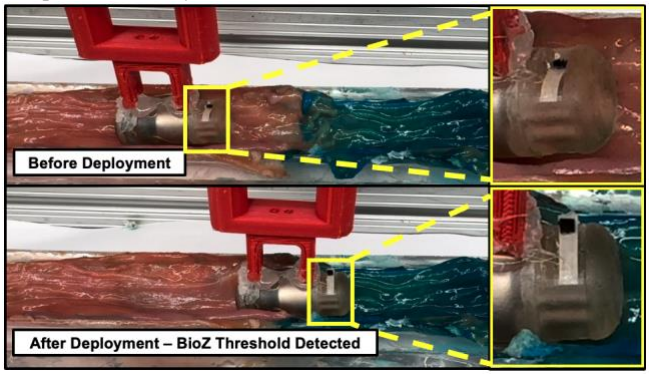

Figure 5: Bioimpedance-triggered activation of cantilever actuator before deployment (top) and after deployment (bottom). Actuator is located on reverse side for demonstration purposes.

CONCLUSION

We demonstrate the first example of bioimpedance-triggered actuation for localized drug delivery in the GI tract. The developed device can wirelessly report bioimpedance changes in intestinal tissue ex vivo and rapidly deploy the cantilever in response to these changes in tissue state. The device developed here is a major milestone toward autonomous ingestible device operation, demonstrating the viability of closed-loop control of sensors and actuators. The systems integration approach in this work utilizes capabilities of novel MEMS sensor and actuator technologies with electronics to significantly improve treatment for patients by enabling localized monitoring and drug delivery for improved disease diagnostics and treatment with reduced side effects.

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CONTACT

*R. Ghodssi, tel: +1-301-405-8158; ghodssi@umd.edu