ULTRASOUND-BASED TELEMETRY OF IMPLANTED MICROFLUIDICS FOR INTRACRANIAL PRESSURE SENSING

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ABSTRACT

Implantable wireless pressure sensors have been explored since the 1970s to measure intracranial pressure (ICP) for conditions like hydrocephalus, traumatic brain injuries, or brain tumors. However, existing ICP sensors suffer from stability issues due to their reliance on radiofrequency (RF) telemetry and thin membranes. This work introduces an innovative approach to monitor for elevated ICP, replacing RF telemetry with ultrasound telemetry for improved stability. Our sensor will be implanted into a burr hole in the skull and features a fluid-filled diaphragm connected to a microfluidic channel, which visualizes pressure changes as a series of bright "dots" in ultrasound images. Prototype testing demonstrates promising sensitivity and stability, suggesting a potential paradigm shift in physiological sensors, addressing previous limitations and paving the way for further research.

KEYWORDS

Pressure Sensor, Intracranial Pressure, Ultrasound Telemetry, Microfluidic, Physiological, Hydrocephalus, Shunt Failure

INTRODUCTION

Implantable wireless pressure sensors, explored since the 1970s [1], quantitatively measure intracranial pressure (ICP) and can guide treatment decisions for individuals with hydrocephalus, traumatic brain injuries, stroke, or brain tumors [2]. In total, these conditions accumulate >1.3 million new cases per year in the U.S. Unfortunately, the symptoms of increased intracranial pressure (ICP) are non-specific and difficult to diagnose. Symptoms may include headache, vomiting, nausea, blurred or double vision, problems with balance and coordination, personality or cognition changes including memory loss and ultimately death. Thus, there is a pressing need for a quantitative measurement of intracranial pressure, and many different approaches have been proposed over the decades, each suffering from significant drawbacks.

As many conditions are chronic and require frequent magnetic resonance (MR) imaging, there is a need for long-term, high-stability, accurate, MR-safe approach for quantitative measurements of intracranial pressure. Unfortunately, nearly all sensors rely on the same underlying technology that limits the stability: radiofrequency (RF) telemetry and a thin membrane that can deflect directly adjacent to a sealed air chamber or vacuum. Due to the size scales involved and the material constraints with traditional radio-frequency approaches, all these devices experience drift as air or water vapor diffuse across the thin membrane, induce stress in packaging materials [3], or from drift in the electronic components. Moreover, the electronics can also impose constraints on magnetic resonance imaging, a frequent need for neurological patients.

To address this barrier, we replace RF telemetry with an innovative ultrasound interrogation approach, in which ultrasound is used to image an implanted microsystems target that measures pressure. Ultrasound based telemetry enables reference air cavities to be buried deep within the device to increase their stability. Furthermore, ultrasound telemetry enables the use of inherently MRI-safe materials, as well as ceramics and metals which improve stability due to their low permeability to salt, air, and moisture.

SENSOR DESIGN AND FABRICATION

Design Premise and Overview

Our device was designed with the premise that using a radically different telemetry approach will remove the extra RF-imposed constraints that limit current sensor stability and performance and will enable new pressure sensor topologies. Our sensor will be implanted into a burr hole in the skull (Figure 1) and is comprised of a fluid-filled, pressure-sensitive diaphragm connected to an air-filled serpentine microfluidic channel. The diaphragm is thin and flexible. As pressure changes, the diaphragm will be distorted, and the fluid will be displaced into the microfluidic channel linearly with increasing pressure.

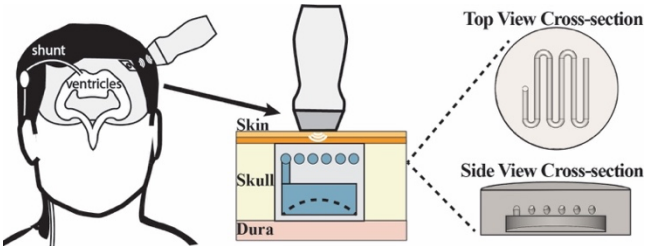

Figure 1: Overview of our pressure sensor. The device will be implanted in a burr hole in the skull. Additionally, the sensor is interrogated with ultrasound and provides real-time, quantitative measurements of ICP.

The foundation of our ultrasound-based telemetry approach leverages the acoustic impedance mismatch between the the air trapped in the microfluidic channel, the liquid displaced from the diaphragm, and the solid device "target" to create a visible reflection when using B-mode imaging. The trapped air and the solid device target have a large acoustic impedance mismatch. Hence, a gas filled channel within a solid structure produces a bright, visible signal on ultrasound. In contrast, the liquid and the solid device have a much smaller acoustic impedance mismatch between their interfaces. Therefore, when the serpentine channels become filled with water at higher pressures, there will be a much smaller reflection captured by ultrasound.

Thus, with this unique telemetry approach, the serpentine channel design also confers the unique ability to measure the sensor in a "digital" manner. By visualizing the cross section of the device, and with proper channel design, a series of bright "dots" (ON signal) will be present when the device is at a low pressure, since the channels will be filled with air. These dots disappear linearly with increasing pressure as the channels become filled with liquid (OFF signal). Hence, the pressure can be quickly determined by counting the number of dots.

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Empirically Optimized Features

Our design goal was to create a pressure sensor that can measure typical and elevated intracranial pressures (0 - 55 mm Hg), and accommodate large transient increases that occur naturally, such as from sneezing (~100 mm Hg). To ease translation, we designed the footprint of the device to fit within a burr hole cover. Based on these constraints, we were able to innovate a device that met all the required design criteria. This device specifically incorporates a fluid-filled reservoir below the ultrasound readout area that is next to a flexible membrane (Figure 1). Increased pressure deflects the membrane upwards and causes liquid to fill the serpentine channels. We then constructed an air "actuator" that could be attached to the bottom of this device and apply pressure (Figure 2). As expected, pressure increases caused the thin membrane to deflect upwards and forces fluid to flow into the ultrasound readout area.

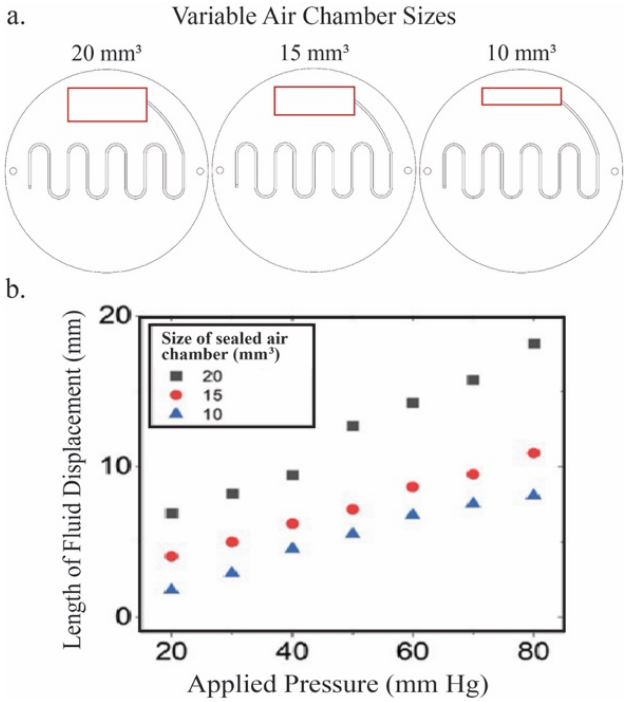

Figure 2: a) Fluid displacement in devices with air chambers of different volumes (outlined in red) was tested. b) Volume of fluid displaced with an air chamber volume of 15 mm³ (red circles) aligned well with the desired dimensions of our pressure sensor and thus this chamber volume was incorporated into the final design.

We tested the pressure sensitivity of our initial design using prototypes constructed from the three bonded layers of polydimethylsiloxane (PDMS). As PDMS is clear, we filled the diaphragm layer with water that was dyed red for visibility (Figure 2). Testing was performed by modulating the diaphragm pressure across physiologic values (0-55 mmHg) using an air-filled syringe pump with an inline pressure sensor. However, our initial designs did not have the sensitivity predicted by our analytical models of the deflecting diaphragm and associated volume/fluid change that would be coupled into the channels. The central challenge is that the air sealed in the channels acts as a cushion, effectively reducing the amount of fluid displacement. Our testing revealed that the sensitivity of the device could be increased by adding an air reservoir that allows for the air within the serpentine microfluidic channel to be compressed as fluid is displaced at higher pressures. Noting our aforementioned desired pressure sensitivity range and device footprint constraints, we added an air chamber connected to the fluidic channel to give trapped air a larger volume to compress into. We found that a chamber with a volume of 15 mm³ can fit on our device and responds linearly to our desired pressure range (Figure 2).

Additionally, by using rapid prototyping, we were able to optimize the dimensions of the microfluidic channels that are imaged with ultrasound. While the wavelength used for ultrasound imaging places theoretical constraints on the minimum channel size and spacing, predicting how this translates in less-than-optimal imaging environments remains difficult. We empirically tested many different serpentine channel dimensions and configurations to optimize the ultrasound readout. We found that a channel diameter of > 110 μm and a channel center-to-center spacing of 1 mm could be readily distinguished. We also found that the edges of the device create a very bright signal that can mask the signal generated by the channel. Thus, the channels must be a minimum of 1 mm away from a device edge. Notably, moving air filled channels away from the device edge for imaging also limits the diffusion of air across membranes, increasing stability.

Fabrication Process

While numerous materials are available for devices intended for implantation and medical use, we elected to make our devices from PDMS (Sylgard 184 Dow Inc.) as this material conferred several key advantages during our prototyping and development phases. Firstly, PDMS is quick and easy to work with and is one of the most common microsystems materials [4]. To produce PDMS, liquid precursors are mixed, bubbles are removed by placing the mixture into a vacuum, then the PDMS is poured into a mold and cured. The resulting solid can be easily removed from the mold it was casted in and has very high fidelity to the mold features. As such, another key advantage is that many exact copies of the original mold can be created.

Moreover, PDMS can be quickly assembled as layers of this material can be easily bonded together by treating with an oxygen plasma [4] and bringing them together. There are also silicone-based adhesives that work effectively for binding PDMS [4]. PDMS is also transparent, facilitating troubleshooting and performance testing for this device. By filling the devices with water containing food coloring, the movement of liquid in and out of the channels can be visually seen, and then tested with ultrasound, adding to the rigor of the experiments. The PDMS was also of an appropriate stiffness to enable our devices to have an appropriate mechanical sensitivity. Finally, PDMS is biocompatible and commonly used in medical implants. While other materials may be necessary for longer term stability studies and implantation, beginning with a biocompatible material can speed initial translational testing.

As reported by others, we used 3D printing to create molds in which PDMS could be poured, cured, and removed [4]. Like more commonly used soft lithograph, the molds enable high fidelity replicates to be created en masse for testing. However, soft lithography requires a significant infrastructure (cleanroom), operator training, and multiple specialized pieces of equipment. Typical timeframes for a mold range from one day to one week depending on the complexity. In contrast, 3D printed molds can be created in just a few hours including design time. Here, we created three molds, a transparent top to our device, a serpentine readout channel layer, and a diaphragm layer that moves in response to applied pressure.

Thus, we rapidly prototyped an epidural pressure sensor target by leveraging our experience with mechanical sensors [5], microfluidics [6], and rapid prototyping [7]. As mentioned, the

device was designed in layers (Figure 3), and molds were 3D printed using soft lithography molds created on a Boston Microfabrication MicroArch S120 (Figure 3) This system is unique in that it has 10 µm resolution and creates ready to cast molds, in contrast to other 3D printed molds that are used for soft lithography, which have issues with partial curing, leaching of material, or leaks after bonding. In our device, the smallest features, which are the channels that will be visualized by ultrasound, had a cross-section of 200 µm by 200 µm. Each layer is cast entirely in PDMS. After casting, the device layers can be quickly assembled with plasma bonding or microfluidic tape and filled with liquid (Figure 3).

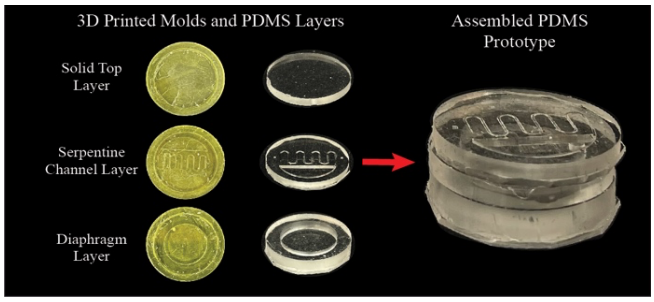

Figure 3: Our device consists of 3 PDMS layers that are cast in 3D printed molds. Molds are shown next to corresponding layers. Each layer is PDMS-bonded together and shown assembled on the right. The layers consist of a pressure-sensitive membrane and fluid-filled chamber (bottom), a serpentine micro-channel connected to an air chamber (middle), and a completely solid PDMS roof that seals the channels underneath (top).

The bottom-most layer of our device, the "diaphragm layer", consists of a hollow chamber that will be filled with liquid. This layer also contains a thin, flexible membrane that will deform under increased pressures. The middle layer, or "serpentine readout channel layer", consists of an air-filled serpentine microfluidic channel that will connect to the bottom-most diaphragm layer. The fluid from the diaphragm layer will be displaced into the serpentine channel at elevated pressures. Importantly, this layer contains the aforementioned 'air chamber' that creates a space for air to compress into as fluid is displaced into the serpentine channel. This layer also contains fiducial markers that assist with the alignment of the ultrasound transducer (Figure 3). The final layer is a simple, solid layer of PDMS that will be bonded on top of the serpentine channel. This layer serves as a seal to contain all the fluid in the device and also provides a thick enough interface for the ultrasound signal to be clear (Figure 3).

SENSOR CHARACTERIZATION

Pressure Sensitivity

We tested the pressure sensitivity of our design using prototypes constructed from the three bonded layers of PDMS. The pressure sensitivity of our device was verified visually and with ultrasound. As PDMS is clear, we filled the diaphragm layer with water that was dyed red for high visual contrast (Figure 4). Visual testing was performed by modulating the diaphragm pressure across physiologic values (0-55 mmHg) using an air-filled syringe pump with an inline pressure sensor. The diaphragm pressure was modulated repeatedly ten times to ensure consistency, and critical displacements were recorded on camera. The camera recordings were uploaded onto ImageJ and to calculate a precise approximation of fluid volume displaced across the range of physiological pressures. Our device shows a clear, linear relationship between fluid displacement and pressure (Figure 4). Slight variations can be attributed to fabrication methods which may have allowed for miniscule leaks of air from the device. However, this may be addressed with improved fabrication methods.

To test the ultrasound visualization and readout, the prototype was placed within a burr hole in a model human skull with tissue mimicking phantom covering the top and bottom of the device (to reflect in-vivo conditions). Fluid displacement through the serpentine channel was imaged using a programable ultrasound system (Vantage 256, Verasonics) equipped with a linear array probe (L11-5, ATL) at 5 MHz transmitting frequency (Figure 4). The diaphragm pressure was again modulated across physiological values (0-55 mmHg) using the same air-filled syringe pump setup (Figure 4). The diaphragm pressure was modulated repeatedly ten times to ensure consistency, and key B-mode images were recorded (Figure 4). The B-mode images showed clear ON/OFF signals that aligned with the visual pressure sensitivity measurements.

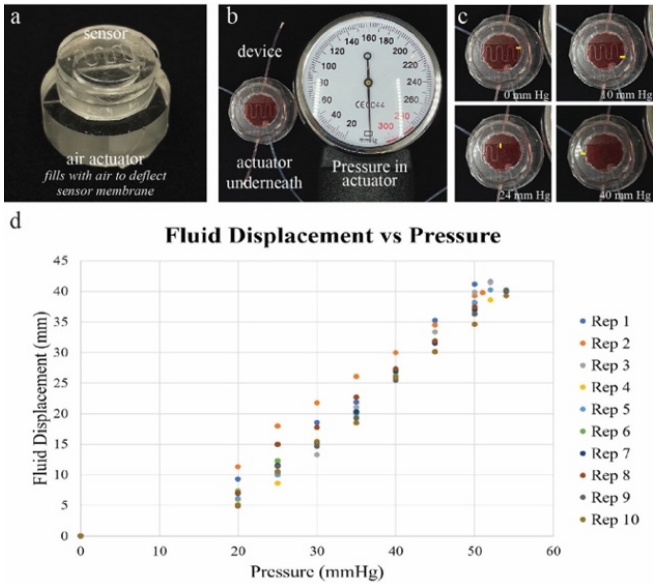

Figure 4: a and b) Pressure sensitivity setup with inline pressure sensor and pressure actuator. Device is filled with red-dyed water for visibility. c) Device close-ups at various pressures. Fluid level marked in yellow. d) Pressure sensitivity results. Fluid displacement has a linear relationship with pressure. Repetitions showed slight variation that may be attributed to drops of fluid being displaced into the air reservoir. Future iterations will have modified channels to avoid this issue.

Temperature Sensitivity

We tested the temperature sensitivity of the device by placing our sensor into an incubator and gradually changed the temperature from (22 ºC) to human fever temperature (39 ºC). Both the base level drift and the temperature on the integrated temperature sensor were recorded. We performed the testing in a static environment, and using this information, we can create a simple lookup table where the measured pressure can be "corrected" using measurements of the fluidic temperature sensor.

The sensitivity of our device changes at a consistent rate of 0.56 mm Hg/ºC (Figure 5). While this sensitivity is significant, we believe this change is again due to the microscopic gaps in the bonds between each of the device's layers which allow for gas to leak out of the sensor. This may be addressed with improved fabrication methods.

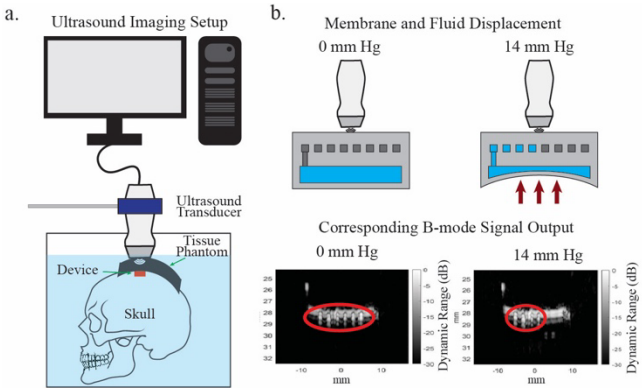

Figure 5: a) Ultrasound Imaging Setup. Sensor is placed into a burr hole in the skull and is covered with tissue-mimicking phantom. A programmable ultrasound system is used to acquire B-mode images of the device. b) Schematic and B-mode images of the device captured at 0 and 14 mmHg. The bright signals (ON) appear when the channel is initially filled with air and disappear (OFF) when filled with water.

Limitations

The current device has several limitations. 1) Using the current assembly approaches, the lifetimes of the devices are limited and degrade after several days due to spurious leaks and degassing of liquids. 2) The temperature sensitivity of the current device is significant (0.56 mm Hg/°C) and requires compensation 3) The current epidural topology does not provide accurate measurements of the mean intracranial pressure. While our primary goal is to create a device capable of intraventricular measurements, some utility has been proposed for epidural pressure sensing, specifically determining ICP waveform parameters such as pulse pressure amplitude and mean ICP wave amplitude [8].

CONCLUSION

Our premise is that using an ultrasound telemetry approach will remove the extra RF-imposed constraints that limit sensor stability and performance and enable new pressure sensor topologies. Our goal is to achieve the same outcomes in a much smaller package that is conducive to neurosurgical interventions.

Our data confirms that our device operates as expected, and thereby confirms the viability of our new approach. Our B-mode images show clear, bright signals through tissue-mimicking phantoms, supporting our device's ability to be imaged in-vivo. Additionally, our pressure to fluid displacement readings also support that our device produces consistent, repeatable readings. We were able to record the expected fluid displacement at critical physiological pressures. Future testing will include further lifetime testing of the device in in-vivo conditions. The experimental results show that intracranial pressure can be monitored continuously in-vitro and provide strong feasibility data for later in-vivo work. On a broader scale, these results support a new paradigm of sound-interrogated physiological sensors, which solve RF-based telemetry, radiation, and invasiveness issues of prior devices. The traditional challenge with RF-based devices is that increasing the stability and robustness of the device comes at the expense of sensitivity and reduces the ability of the device to transmit radiofrequency signals. Our novel approach solves these challenges by creating a topology that can be made thick enough to limit long-term diffusion in and out of the device for long-term stability, yet still be easily measured with standard tools available in the clinical setting.

This is because ultrasound-based telemetry is able to more effectively travel through layers of materials, which enables reference air cavities to be buried deep within the device. Furthermore, ultrasound telemetry also enables the use of MRI-safe metals or thick ceramics as a protective barrier, which is ideal due to their extremely low permeability to salt, air, and moisture, and creates a highly stable structure. To summarize, this device will exert a sustained, powerful influence on neurosurgical patients by: 1) providing long-term monitoring with an unambiguous pressure readout; 2) improving clinical practice by reducing misdiagnosis and mismanagement of patients with elevated ICP in cases where clinical personnel currently cannot determine the underlying cause of symptoms (~25% of cases [9, 10]); and 3) changing the post-surgical management of patients at risk for elevated ICP by enabling monitoring in the ICU and following discharge during normal activities.

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REFERENCES

[1] J. Hynecek, W. H. Ko, E. T. Yon, Miniature pressure transducer for medical use and assembly method, US Patent (1977). https://patentimages.storage.googleapis.com/42/e6/ea/193353b8374c85/US4023562.pdf.

[2] TBI Data (2023). https://www.cdc.gov/traumaticbraininjury/data/index.html.

[3] A. Kim, C. R. Powell, and B. Ziaie, "An Universal packaging technique for low-drift implantable pressure sensors", *Biomed. Microdevices*, vol. 18, no. 2, p. 32 (2016).

[4] A. Mata, A. J. Fleischman, and S. Roy, "Characterization of polydimethylsiloxane (PDMS) properties for biomedical micro/nanosystems", *Biomedical Microdevices*, *7*(4), 281–293 (2005).

[5] D. R. Myers, "Silicon carbide resonant tuning fork for microsensing applications in high-temperature and high G-shock environments", *J. Micro/Nanolithogr. MEMS MOEMS,* 8, 021116 (2009).

[6] D. R. Myers, Y. Sakurai, R. Tran, et al, "Endothelialized microfluidics for studying microvascular interactions in hematologic diseases". *J. Vis. Exp*., doi: 10.3791/3958 (2012).

[7] P. Delgado, O. Oshinowo, M. E. Fay, C. A. Luna, A. Dissanayaka, et al, "Universal pre-mixing dry-film stickers capable of retrofitting existing microfluidics", *Biomicrofluidics,* 17, 014104 (2023).

[8] P. K. Eide, "Comparison of simultaneous continuous intracranial pressure (ICP) signals from ICP sensors placed within the brain parenchyma and the epidural space", *Med. Eng. Phys*, 30, 34–40 (2008).

[9] J.C. Koerner, and D. I. Friedman, "Inpatient and emergency service utilization in patients with idiopathic intracranial hypertension", *J. Neuroophthalmol*, 34, 229–232 (2014).

[10] J. S. Jones, J. Nevai, M. P. Freeman, and D. E. McNinch, "Emergency department presentation of idiopathic intracranial hypertension", *Am. J. Emerg. Med*, 17, 517–521 (1999).

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