

AN IMPLANTABLE TIME OF FLIGHT FLOW SENSOR

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ABSTRACT

A micro time of flight (TOF) electrochemical impedance (EI) flow sensor μ EIFS suitable for implantation and integration with a catheter was developed. The transducer utilizes two pairs of electrodes to monitor using EI measurement the passage of a gas bubble generated upstream. High precision measurement of bubble TOF (SD < 6% of mean) was achieved over the velocity range 0.83–83 μ m/s. The volumetric flow rate was inversely proportional (linearized, $r^2 = 0.99$) to time of flight. Biocompatible construction (only Parylene C and platinum), low power consumption, and low profile thin film format make the μ EIFS ideally suited for chronic *in vivo* monitoring with immediate application in tracking flow within hydrocephalus shunts.

INTRODUCTION

The commonly used thermal TOF flow sensor is limited by the dissipation of its heat tracer signal [1] which in turn reduces sensitivity, resolution, and flow measurement range. To realize high resolution *in vivo* TOF flow measurement, the tracer should accurately track flow with minimal degradation such as thermal dissipation or dissolution. Previously, dissolved oxygen was investigated as a flow tracer [2], but its low sensitivity limited resolution and restricted use to a small range of flow rates (0.83–12.45 μ m/s).

Here, electrolytically generated bubbles were selected as the tracer because they have been shown to remain in solution for sufficiently long durations of time (> 15 min) [3, 4] and are advantageous for measuring low flow rates with long time of flight. In addition, microbubble size can be measured in real time with high sensitivity (> 20 SNR) using an electrochemical impedance sensing technique [5]. Therefore, the μ EIFS employs electrolytically generated bubbles as tracers for the first time in TOF flow measurement.

DESIGN

The μ EIFS employs three pairs of electrodes positioned in parallel to the direction of fluid flow (fig 1). One pair of electrodes was designated for electrolytic bubble generation and the second and third pairs were used solely for measurement. This arrangement improves temporal resolution compared to having electrodes with shared EI sensing and electrolysis functions. The electrode arrangement is symmetric along the direction of flow and thus the sensing and electrolysis roles can be reassigned in the case of reverse or pulsating flow.

To perform a flow measurement, a bubble is first electrolytically generated with the upstream pair of electrodes (fig. 1a). At a sufficiently large size, the electrolysis current is terminated, the bubble detaches (fig. 1b), and the bubble is carried along with the flow through the sensing electrode pairs.

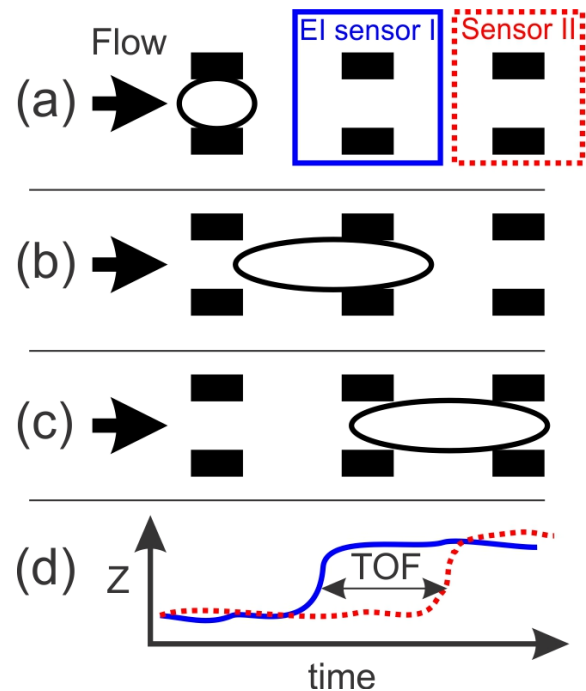


Figure 1: Schematic of sequence for time of flight (TOF) measurement. (a) Bubble is electrolytically generated at the leftmost electrode pair. (b) The electrochemical impedance magnitude increases as bubble passes through sensor I. (c) After bubble passes through sensor II, difference in time of electrochemical impedance rising edge is used to calculate TOF and flow rate. (d) Representative temporal EI response, illustrating the time of flight measurement.

Bubble sensing using electrochemical impedance methods has been studied and reported previously [3, 6, 7]. Briefly, a small AC signal is passed between two platinum electrodes residing within an electrolyte solution, and this system can be modeled with the Randles circuit in which the parallel combination of electrode charge transfer resistance and double layer capacitance is in series with the solution resistance R_s [8]. At a suitably high frequency, the measured impedance approximates the solution resistance R_s . As the bubble travels downstream, it disrupts the path of ionic current between each measurement electrode pair and this manifests as increased electrochemical impedance. The TOF measurement is observed as the difference in time between the increases of electrochemical impedance measured from the rising edge of the impedance signals.

Given the predefined flow channel and electrode geometry, flow velocity is derived from the difference in the time of the onset of measured impedance change at these two electrode pairs, which corresponds to the passage of the leading edge of the bubble and is expressed by the following formula:

$$\text{flow velocity} = \frac{d}{t_{TOF}} \quad (1)$$

where d is the distance between the electrochemical impedance sensors and t_{TOF} is the measured time of flight. Volumetric flow rate may then be determined given the cross sectional area of the flow channel. Two electrode spacing distances, 500 and 2500 μm , were fabricated to enable flow measurement in the range of 1-100 $\mu\text{m/s}$, which includes the clinically relevant flow velocities found in patients with hydrocephalus.

METHODS

Fabrication

The μEIFS consists of a Parylene-metal-Parylene sandwich created using standard Parylene microfabrication processes. To start, thin film platinum (200 nm thick, 20000 μm^2) electrodes were defined on a Parylene C (10 μm) coated silicon support wafer. An additional layer of Parylene (10 μm) was deposited for insulation, and the electrodes were subsequently exposed via oxygen plasma reactive ion etching (RIE) process. The die was etched out with a switched chemistry deep RIE [9] and then released in an acetone bath. A fabricated sensor is shown in fig. 2 along with other EI sensors under development. The generation and measurement electrodes are indicated.

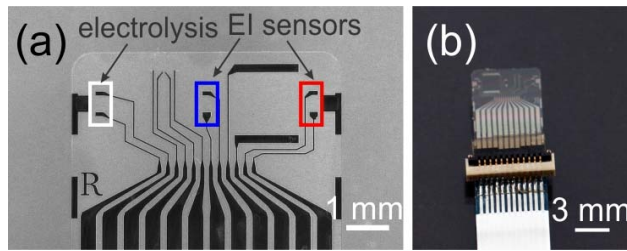


Figure 2: (a) Micrograph of sensor as fabricated and released from wafer and (b) attached to flat flexible cable for testing via zero insertion force connector. Additional electrodes on die were utilized for other electrochemical impedance measurements.

Experimental Setup

The μEIFS was designed for integration within the lumen of a commercially available luer lock connector (4 mm ID, fig. 3b). A thin slit was milled into the side of the connector, the sensor was inserted into the flow path through the slit, and subsequently the sensor cable-slit interface was sealed with biocompatible epoxy (EPO-TEK 353ND). This configuration was selected to allow subsequent testing of sensors with an extraventricular drain (EVD) used in acute clinical settings for managing elevated intracranial pressure and draining cerebrospinal fluid (CSF). For benchtop testing, the integrated sensor module was positioned such that the flow was parallel to ground level and was attached to a peristaltic pump (Watson-Marlow 400DM3) for flow calibration.

To mimic biological fluids, phosphate buffer solution (1X PBS) was used for sensor characterization. Electrochemical impedance spectroscopy yielded 10 kHz as the optimum frequency (minimum system phase) for EI

measurement (fig 4). Multiplexed EI measurement (1 Vp-p, < 1 nW) was conducted with a custom PCB attached to a precision LCR meter (Agilent E4980A). Data acquisition was carried out in a LabVIEW environment to realize high temporal resolution (50 ms sampling, limited by software) for TOF measurement.

Additional flow channel geometries and electrode arrangements were also tested (fig 3). The sensor was also directly inserted into a silicone catheter (1 mm ID) and clamped into a custom acrylic jig having a rectangular cross section channel (fig 3d). Spacing between EI sensing electrode pairs was assessed with two different electrode layouts (500 and 2500 μm separation).

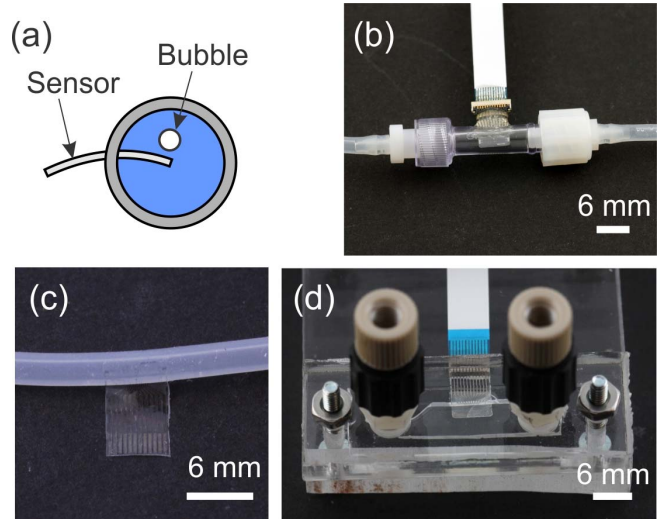


Figure 3: (a) Cross sectional view of sensor integrated into lumen of catheter, illustrating relative position of bubble within fluid. (b) Integration of sensor with luer lock interconnect. (c) Sensor directly inserted into silicone catheter. (d) Custom acrylic jig for flow calibration.

A bubble was electrolytically generated (50-70 μA , 30-45 s) within flowing PBS (10-1000 $\mu\text{L/min}$) at the upstream electrode pair and EI measurements were downstream at the two sensing electrode pairs. The TOF was calculated by noting the difference in time values when the measured impedance rose 10% above the baseline reading at each sensor.

RESULTS

High precision measurement of bubble TOF ($\text{SD} < 6\%$ of mean) was achieved with a flow velocity range of 8.3-830 $\times 10^{-7}$ m/s. Results were achieved using the luer lock integrated sensor module (additional testing underway). The volumetric flow rate was inversely proportional (linearized, $r^2 = 0.99$) with the bubble time of flight (fig. 7), confirming the relationship described in equation 1.

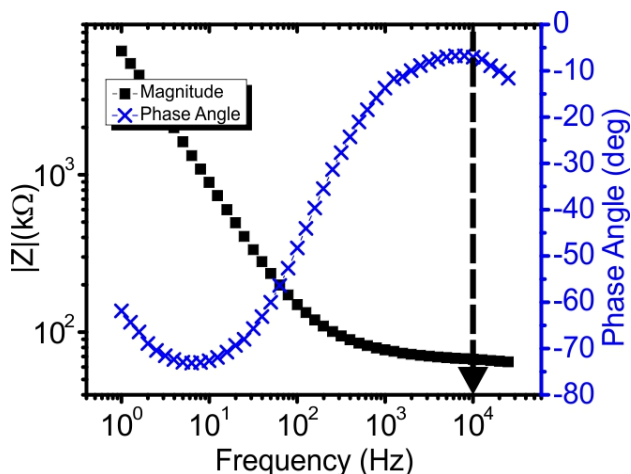


Figure 4: EI spectroscopy magnitude and phase plots of 1X PBS. To measure the solution resistance with minimum capacitive effects, measurement frequency was selected where phase is nearest 0 degrees.

Electrode spacing was selected to be 2500 μm because bubble TOF was indiscernible at most flow conditions (above 25 $\mu\text{m/s}$ flow velocity) with electrode spacing of 500 μm . This is largely attributed to the need to generate large bubbles relative to the diameter of the flow channel to encourage detachment from the hydrophobic Parylene surface. By further improving bubble generation via electrolysis, smaller bubbles may be used to thereby decrease the spacing requirement. With the 2500 μm spaced electrodes, flow measurements were taken at the rate of < 0.1 Hz (fig. 6).

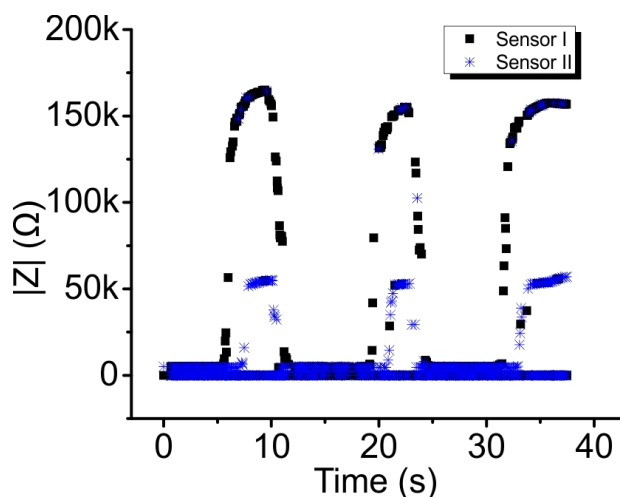


Figure 5: Impedance response of multiple bubbles passing through luer lock interconnect with flow sensor at 300 $\mu\text{L/min}$.

The discrepancy between the measured impedance of the two EI sensors (fig. 6) may be a result of process variation or variation in the position of the bubble from the first to the second electrode pair. An alternate electrode arrangement along the catheter walls is under development to reduce the position dependency of the bubble relative to the sensing electrodes.

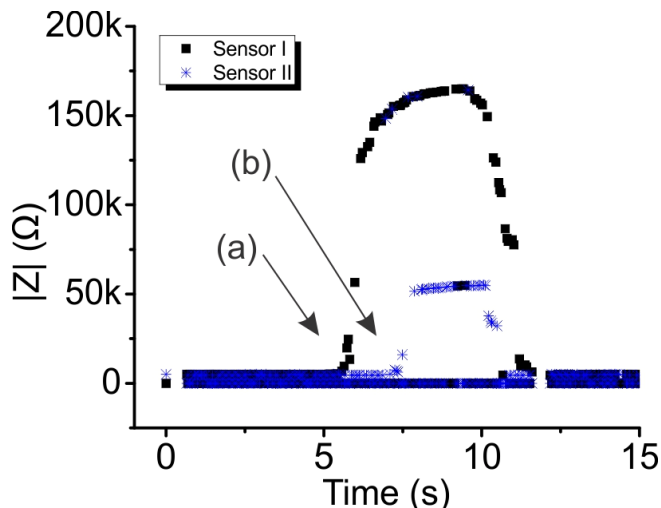


Figure 6: Passage of bubble is sensed as an increase in measured EI at sensor I (a), and eventually sensor II (b). Detection of bubble at each sensor initiates a rise in measured electrochemical impedance, and is used to derive time of flight.

Detachment from the Parylene surface of the μEIFS did not occur until the bubble was of a sufficiently large size. Smaller tracer bubbles require less power and time to create via electrolysis, and would be greatly beneficial to improving sensor performance. Modification of the surface chemistry [10] is a technique that has been explored and is currently under assessment. Variation of the electrode arrangement is also being considered to encourage detachment.

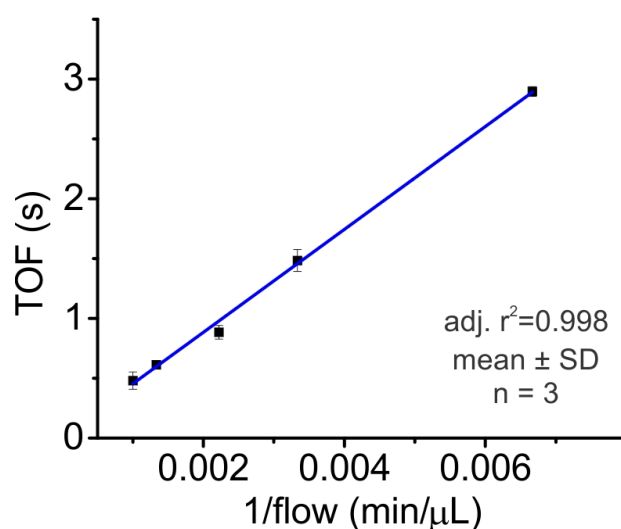


Figure 7: Relationship between flow rate and bubble time of flight is inversely proportional. Adjusted r^2 includes 10 $\mu\text{L/min}$ data (data not shown). Data taken from device integrated into 4 mm ID luer lock interconnect.

CONCLUSIONS

We have designed, fabricated, and tested a Parylene based liquid flow sensor utilizing an electrochemical impedance transduction technique. Microbubbles were employed as tracers to enable high dynamic range, high

sensitivity monitoring of flow. Additional sensor characterization is underway (varying electrolyte composition such as use of artificial and human CSF, sensor orientation and placement, electrode layout). Sensors will be attached to the external ventricular drain in clinical settings to achieve first-in-human demonstration.

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