A CALORIMETRIC FLOW SENSOR FOR ULTRA-LOW FLOW APPLICATIONS USING ELECTROCHEMICAL IMPEDANCE

Alex Baldwin, Trevor Hudson, and Ellis Meng

University of Southern California, USA

ABSTRACT

We present a calorimetric flow sensor which utilizes electrochemical impedance (EI) measurement to sense flow-mediated heat transfer. Sensors were fabricated from thin-film platinum and Parylene C, rendering them biocompatible, flexible, and corrosion-resistant. A novel sensing method based on asymmetric impedance dips during heater pulsing allowed flow measurement at ultra-low flow velocities (less than 200 µm/s), and simultaneous EI measurement from multiple electrode pairs using a custom multiplexer setup enabled highly sensitive, bidirectional flow transduction. Sensors tested in phosphate-buffered saline achieved a 2σ resolution of 19.1 µm/s, which represents a greater than 4x improvement over previously reported EI-based sensors. The sensor's biocompatible and flexible construction is ideal for microfluidics, lab-on-chip, and *in vivo* applications.

INTRODUCTION

Measuring flow rate or flow velocity is vital for numerous applications ranging from microfluidics and medical devices to industrial manufacturing and HVAC systems. Accurate measurement of ultra-low flow rates is especially important for medical applications, as drug infusion rates are often on the order of microliters to nanoliters per minute and microfluidic diagnostic devices must operate with nanoliter precision. Due to the small diameters of microfluidic channels, typical flow velocities for microfluidic devices can range from 10 to 100 µm/s.

Flow sensing can be accomplished via mechanical or electromechanical devices, but by far the most common type of flow sensors are thermal flow sensors [1], which measure changes in heat transfer due to flow. Thermal flow sensors can be placed into three broad categories: thermal anemometers, which use a single heater and measure the rate of flow-mediated cooling; time-of-flight sensors, which generate a heat pulse and track its peak via one or more downstream temperature-sensitive elements; and calorimetric sensors, which use the difference in temperature upstream and downstream of a central heater to transduce flow. Thermal flow sensors have seen commercial success for gas flow sensing, but commercial sensors employ high overheat temperatures and semiconductor materials which corrode in aqueous environments [2], preventing widespread use for *in vivo* or fluidic applications.

Many solutions have been proposed in literature for flow sensing in fluidic, aqueous environments. Flow sensors which do not corrode in aqueous solutions can be constructed out of thin-film metal on biocompatible polymer substrates [3, 4], but the low temperature sensitivity of thin-film metals (~0.1%/°C) necessitates a high overheat temperature that precludes *in vivo* use.

Alternately, flow sensors which utilize the electrochemical impedance between electrodes directly exposed to an aqueous solution have been explored. An impedance-based "anemometer" has been reported which measures ionic pathway changes between electrodes perpendicular to flow [5], and time of flight flow sensors have been developed which transduce flow rate by tracking dissolved oxygen produced by an electrochemical cell [6] or by tracking a microbubble generated via electrolysis [7]. However, these methods are not able to measure the ultra-low flow rates required for many medical applications.

Recently, we developed a flow sensor which combines thermal and impedimetric methods [8, 9]. The solution resistance of aqueous solutions is highly sensitive to temperature changes, with a temperature coefficient of around -2%/°C [10, 11]; this resistance can be accurately measured via the high-frequency electrochemical impedance between two electrodes. Our previous work transduced flow by measuring the time of flight of a heat pulse using a pair of impedance electrodes, and we achieved a resolution of 86.6 µm/s with only a 1°C overheat temperature [8].

Here, we extended our work on impedimetric flow sensors to the development of a calorimetric flow sensor for ultra-low flow velocities based on electrochemical impedance measurement (Figure 1). Heat is delivered by a central heater in pulses, both to save power [12] and to eliminate the effects of impedance drift which occurs in a two-electrode system. The difference in the impedance dip upstream and downstream of the heater during pulsing is used to transduce flow rate. This sensor achieved a resolution of 19.1 µm/s and flexible, biocompatible construction out of platinum and Parylene C enables simple integration into medical devices or microfluidics.

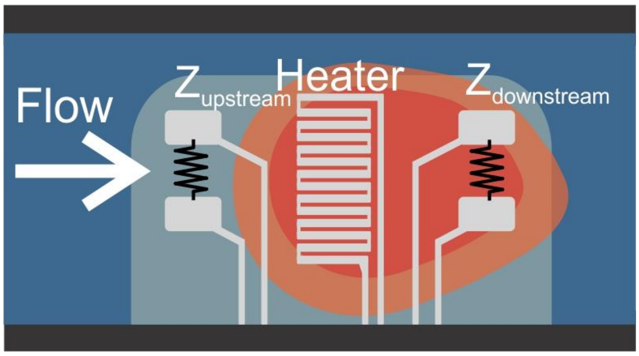

Figure 1. When heated, the temperature upstream and downstream of the heater changes at different rates due to the heat transfer asymmetry induced by flow. This difference in temperature can be transduced by measuring the electrochemical impedance upstream ($Z_{upstream}$) and downstream ($Z_{downstream}$) of the heater using pairs of exposed electrodes. At sufficiently high measurement

frequency, the impedance is approximated by the solution resistance, illustrated as resistors.

METHODS

Sensor Design

Our flow sensor consists of a central heater and two pairs of exposed impedance-measurement electrodes constructed out of thin-film platinum on a Parylene C substrate (Figure 2). The heater is constructed of 25 µm wide traces and has a nominal resistance of around 600 Ω. Electrodes are placed perpendicular to the direction of flow with a separation distance of 500 µm, and are positioned 1 mm upstream and downstream of the heater. Each electrode has an exposed area of 150 x 200 µm^2.

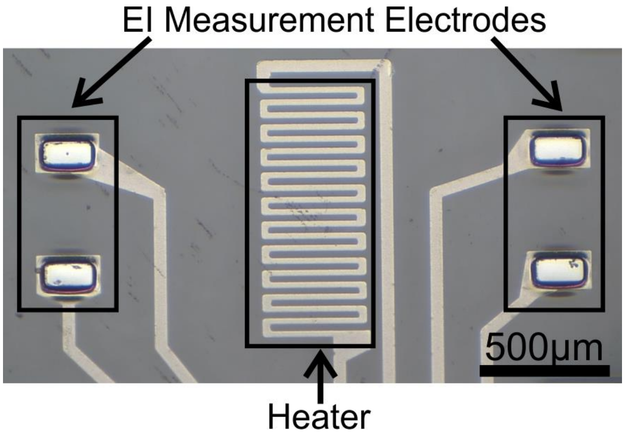

Figure 2. Image of microfabricated flow sensor, which consists of a platinum resistive heater and two pairs of impedance-sensing electrodes on a Parylene C substrate.

Fabrication

Sensor fabrication followed from previously reported micromachining processes on Parylene C [13]. First, 15 µm of Parylene C was chemical vapor deposited on a silicon carrier wafer. 2000 Å of platinum was then sputter-deposited and patterned via liftoff in hot acetone using AZ5214 image reversal photoresist. A second 15 µm Parylene C layer was deposited for insulation, and electrodes and contact pads were exposed via reactive ion etching in oxygen plasma, with AZ4620 photoresist used as an etch mask. Finally, devices were released from their carrier wafer by gently peeling while immersed in deionized water. To achieve electrical contact, a PEEK backing was applied to device contact pads and devices were inserted into a zero insertion force connector connected to a flat flexible cable (FFC) [14].

Testing Methods

For flow testing, sensors were packaged in luer lock modules (ID 3.25 mm), which enabled simple integration into testing equipment and into catheter systems currently used in the hospital. Flow sensors were centered inside the luer lock module and sealed with EpoTek 353NDT biocompatible epoxy. A custom multiplexer board was constructed which allowed simultaneous measurement of impedance magnitude and phase from electrodes upstream and downstream of the heater at a rate >5 Hz each. The multiplexer board consisted of four ADG1206 multiplexer ICs on a custom printed circuit board and could be controlled via LabVIEW. Impedance was measured at 100 kHz and 0.1 V_{PP} using an Agilent 4980A precision LCR meter, the resistive heater was activated using 3.3 V square pulses from a Keithley SourceMeter, and flow was delivered via syringe pump (Figure 3). Phosphate-buffered saline (PBS), a common analog for physiological fluids which is isotonic with cerebrospinal fluid, was chosen for benchtop testing.

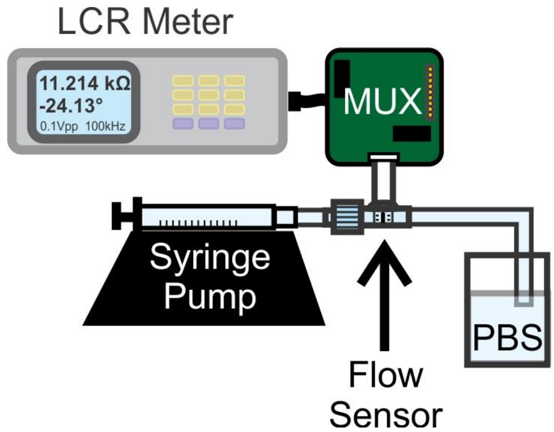

Figure 3. A custom multiplexer (MUX) setup was designed to simultaneously measure impedance from two electrode pairs with a sampling rate >5 Hz each. Phosphate-buffered saline (PBS) was flowed using a syringe pump, electrode impedance at 100 kHz was measured with an LCR meter, and a Keithley SourceMeter delivered 3.3 V to the heater.

To transduce flow rate, the impedance magnitude across each pair of flow electrodes was measured before and during heater activation. Impedance values were normalized as a percent change from the baseline impedance just before heater activation, and the impedance dip, defined as the percent difference between the baseline impedance and the impedance at the end of the heat pulse, was used to transduce flow rate (Figure 4).

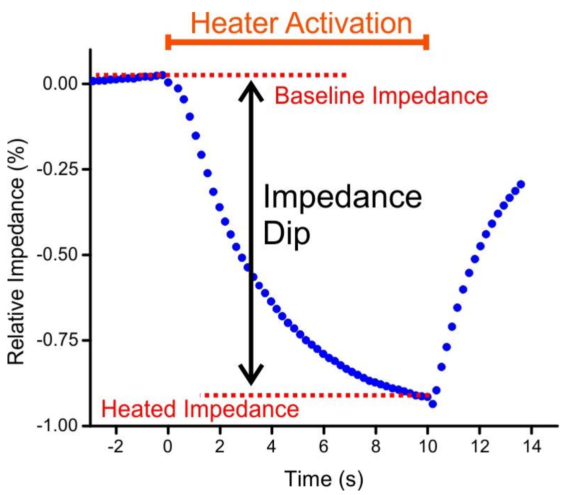

Figure 4. To measure flow rate, the impedance across an electrode pair is measured in response to an applied heat pulse. The impedance dip, defined as the percent change in impedance at the end of heater activation, is used to transduce flow velocity.

EXPERIMENTAL RESULTS

To determine the ideal heat pulse width for flow transduction, the impedance dip of a single downstream electrode pair was measured at flow rates between 0 and 200 µm/s during 1, 5, 10, and 20 second heat pulses (Figure 5). The sensitivity of impedance dip to flow velocity increased with pulse width up to 10 seconds, but no significant difference in sensitivity was observed between 10 and 20 second pulses, so 10 second pulses were used for all subsequent tests.

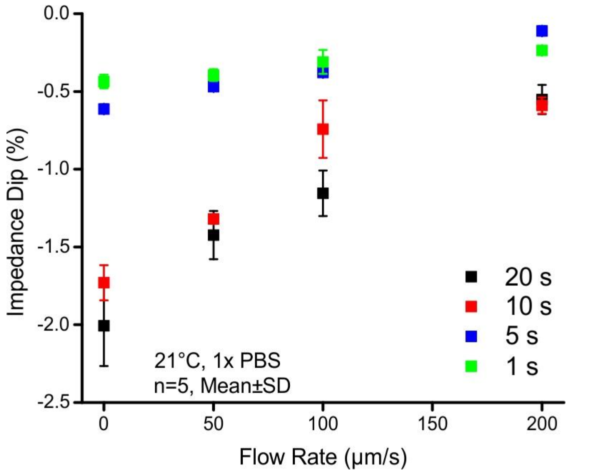

Figure 5. Data from a single pair of electrodes downstream of the heater revealed that sensitivity increased with heat pulse length up to 10 s, but there was no significant improvement between 10 and 20 s.

Tests using the custom multiplexer showed that accurate impedance measurements could be achieved from upstream and downstream electrodes simultaneously at a rate >5 Hz for each electrode pair; differences in heat transfer due to flow were clearly visible as differences in the impedance dip between the upstream and downstream electrodes (Figure 6). Sensors were tested under flow velocities between ±400 µm/s, revealing that as flow velocity was increased, the magnitude of the impedance dip increased for downstream electrodes and decreased for upstream electrodes, as would be expected (Figure 7).

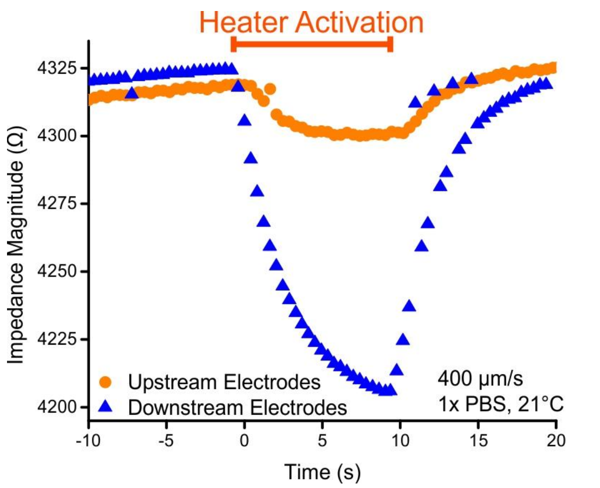

Figure 6. Using a custom multiplexer setup, both upstream and downstream electrode response to heat was simultaneously measured. Heat was asymmetrically distributed upstream and downstream of the heater as a function of flow velocity.

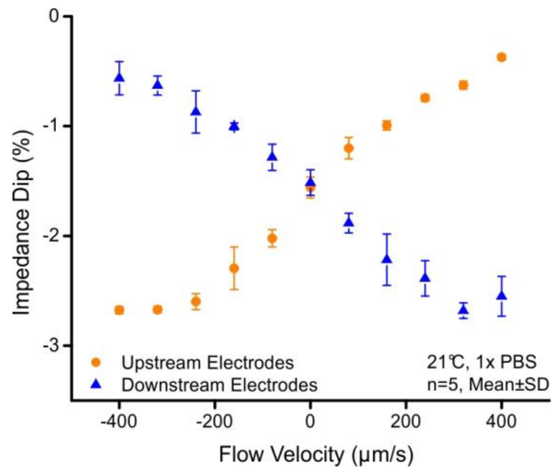

Figure 7. Both upstream and downstream electrodes can be used to simultaneously measure flow rate. Using multiple, independent flow measurements increased accuracy and added redundancy. These are important for chronic in vivo applications in which electrodes may experience biofouling or degradation.

The difference in impedance dip between upstream and downstream electrodes was used to transduce flow velocity. Figure 8 shows the relationship between the impedance dip difference (upstream dip minus downstream dip) and the flow velocity. The profile is symmetric around 0 µm/s flow velocity and has a sigmoidal shape. Between ±200 µm/s, the response is linear with a sensitivity of 0.035%/µm/s and a 2σ resolution of 19.1 µm/s.

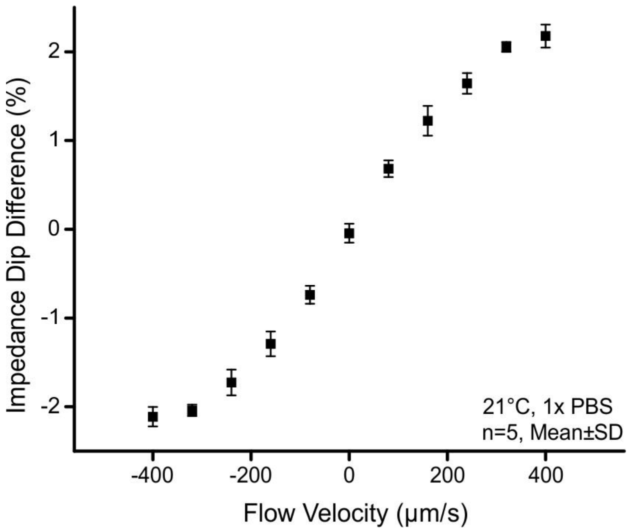

Figure 8. The difference between upstream and downstream impedance dip response allows highly sensitive flow measurement, with a 2σ resolution of 19.1 µm/s for ultra-low flow velocities (-200 to 200 µm/s).

DISCUSSION

Our sensor was able to transduce ultra-low flow rates with high precision by leveraging high-frequency electrochemical impedance to measure temperature differences upstream and downstream of a microfabricated heater. While only a single electrode pair is necessary for flow measurement, simultaneous impedance measurement from two electrode pairs significantly improved measurement resolution. Using our custom multiplexer, a 2σ measurement resolution of 19.1 μm/s was achieved, which is significantly higher than any other reported impedance-based flow sensor and a 4x improvement over our previous work (Table 1).

Table 1. This work compared with other EI flow sensors reported in literature [5-8]. Our sensor exhibits a 4x higher resolution at ultra-low flow velocities.

Paper	**Sensing Method**	**Resolution (μm/s)**	**Range (μm/s)**
Wu 2001	ToF, dissolved O_2 tracer	-	16-250
Ayliffe 2003	Ionic pathway changes	$2x10^4$	$0\text{-}4.6x10^5$
Yu 2015	ToF, microbubble tracer	896	0-2780
Baldwin 2016	ToF, thermal tracer	86.6	±800
This Work	**Calorimetric**	**19.1**	**±200**

Simultaneous measurement from multiple electrode pairs may improve sensor robustness against biofouling, drift, or degradation which are concerns for chronic *in vivo* implementation. Compared to other reported flow sensors, our measurement range is limited (±200 μm/s), but both the measurement range and sensor resolution could be further improved through the addition of more electrode pairs at varying distances upstream and downstream from the heater. The sensor's flexible, biocompatible construction is ideal for integration into lab-on-a-chip or benchtop microfluidic devices, and its low overheat temperature make it attractive for use as a chronically implantable medical device.

Future work will involve the development of sensors with additional electrode pairs for extending measurement range and improving accuracy, investigating sensor operation in various physiological and non-physiological fluids, miniaturizing the custom multiplexer and designing packaging and electronics to enable simple integration with existing medical hardware, and optimizing the sensor for chronic use in implantable medical devices such as hydrocephalus shunts.

ACKNOWLEDGEMENTS

We would like to thank Dr. Henri Etame and Derek Hu for their help with device characterization and testing, Dr. Donghai Zhu for cleanroom and fabrication assistance, and all the members of the Biomedical Microsystems Lab for their help and support. This work was funded in part by the NSF under award number EFRI-1332394 and by the Alfred E. Mann Institute Fellowship (AB).

REFERENCES

[1] J. T. W. Kuo, L. Yu, and E. Meng, "Micromachined Thermal Flow Sensors—A Review," *Micromachines,* vol. 3, pp. 550-573, 2012.

[2] A. Vanhoestenberghe and N. Donaldson, "Corrosion of silicon integrated circuits and lifetime predictions in implantable electronic devices," *Journal of Neural Engineering,* vol. 10, p. 031002, 2013.

[3] E. Meng, P.-Y. Li, and Y.-C. Tai, "A biocompatible Parylene thermal flow sensing array," *Sensors and Actuators A: Physical,* vol. 144, pp. 18-28, 5/28/ 2008.

[4] S. Shibata, Y. Niimi, and M. Shikida, "Flexible thermal MEMS flow sensor based on Cu on polyimide substrate," in *IEEE SENSORS 2014 Proceedings*, 2014, pp. 424-427.

[5] H. E. Ayliffe and R. Rabbitt, "An electric impedance based microelectromechanical system flow sensor for ionic solutions," *Meas Sci Technol,* vol. 14, pp. 1321-1327, Aug 2003.

[6] J. Wu and W. Sansen, "Electrochemical time of flight flow sensor," *Sensors and Actuators A*, pp. 68-74, 18 October 2001 2001.

[7] L. Yu, B. J. Kim, and E. Meng, "An implantable time of flight flow sensor," in *2015 28th IEEE International Conference on Micro Electro Mechanical Systems (MEMS)*, 2015, pp. 620-623.

[8] A. Baldwin, L. Yu, and E. Meng, "An Electrochemical Impedance-Based Thermal Flow Sensor for Physiological Fluids," *Journal of Microelectromechanical Systems,* vol. 25, pp. 1015-1024, 2016.

[9] A. Baldwin, L. Yu, and E. Meng, "An electrochemical-based thermal flow sensor," in *Micro Electro Mechanical Systems (MEMS), 2016 IEEE 29th International Conference on*, 2016, pp. 341-344.

[10] S. B. Baumann, D. R. Wozny, S. K. Kelly, and F. M. Meno, "The Electrical Conductivity of Human Cerebrospinal Fluid at Body Temperature," *IEEE Transactions on Biomedical Engineering,* vol. 44, 1997.

[11] R. A. Robinson and R. H. Stokes, *Electrolyte solutions*: Courier Corporation, 2002.

[12] N. Hartgenbusch, M. Borysov, R. Jedermann, and W. Lang, "Reduction of power consumption and expansion of the measurement range by pulsed excitation of thermal flow sensors," *Sensors and Actuators A: Physical,* vol. 265, pp. 313-320, 2017.

[13] B. J. Kim and E. Meng, "Micromachining of Parylene C for bioMEMS," *Polymers for Advanced Technologies,* 2015.

[14] C. A. Gutierrez, C. Lee, B. Kim, and E. Meng, "Epoxy-less packaging methods for electrical contact to parylene-based flat flexible cables," in *2011 16th International Solid-State Sensors, Actuators and Microsystems Conference*, 2011, pp. 2299-2302.

CONTACT

*E. Meng, tel: +1-213-7406952; ellis.meng@usc.edu