

Biology, Medical Devices, and Systems

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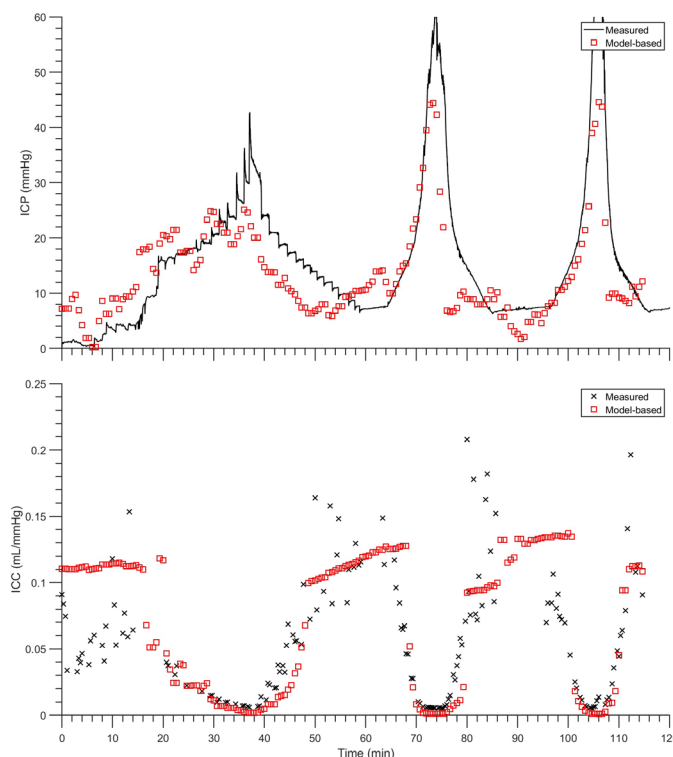
Model-based Noninvasive Intracranial Compliance and Vascular Resistance Estimation

S. M. Imaduddin, C. G. Sodini, T. Heldt

Sponsorship: Analog Devices, Inc. via MIT Medical Electronic Device Realization Center

Existing neuromonitoring methods used for patients with severe head injury tend to be highly invasive and carry a risk of tissue damage and infection. In particular, fluid infusion/withdrawal studies via indwelling catheters are needed to determine intracranial compliance (ICC)—an index of the propensity of rise in intracranial pressure (ICP) in response to changes in cranio-spinal volume. Despite their potential to serve as early indicators of intracranial hypertension, ICC measurements are rarely performed owing to time-consuming, invasive measurement protocols. In addition, measurements of cerebrovascular resistance (CVR) to blood flow are useful in assessing cerebral autoregulation and tracking pathological vascular narrowing such as in moyamoya disease. Like ICC, however, CVR is not regularly obtained at the bedside as the requisite measurements—arterial blood pressure (ABP), cerebral arterial blood flow (CBF), and ICP—are rarely monitored simultaneously.

We have developed a noninvasive, model-based approach for ICP, ICC, and CVR estimation that is driven by subjects' ABP and CBF measurements. Our system was initially validated qualitatively in healthy adult volunteers undergoing head-up tilts. We are now in the process of quantitatively validating our approach in an animal model. ICP is raised experimentally and measurements of the ABP, CBF, ICP, ICC, and CVR are acquired. Model-based estimates of the ICP, ICC, and CVR are then compared to invasive reference measurements. Initial results suggest that our model-based estimates are close to the reference measurements; further validation is now underway. Simultaneously, we have deployed our data collection approach at Boston Children's Hospital to evaluate the system's efficacy in pediatric patient cohorts. If proven successful, our approach can pave the way towards convenient and safe neuromonitoring across a wide spectrum of pathologies, patient age, and disease severity.



▲ Figure 1: Illustration of invasive measurements and model-based estimates of ICP and ICC, respectively, for one subject in the rabbit model.

CNT-coated Paper Electrospray Sources for Mass Spectrometry

A. Kachkine, L. F. Velásquez-García
Sponsorship: Empiriko Corporation

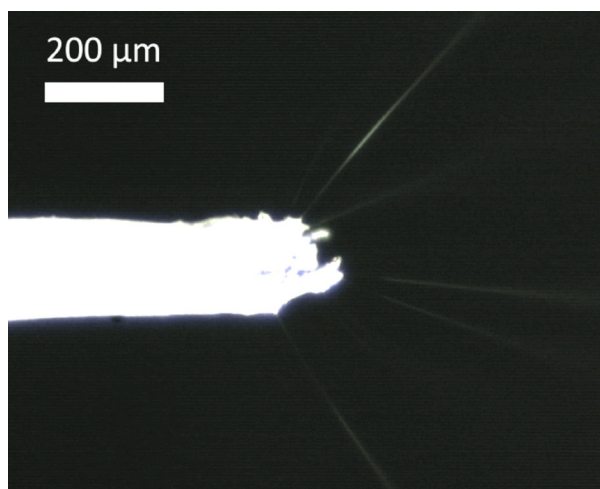
Clinical mass spectrometry (MS) requires high-performance and low-cost ion sources. Classical electrospray, based on jetting of ions from an electrically stressed liquid, can be accomplished with carbon nanotube (CNT)-coated paper as a substrate. In this study we investigated the properties of such emitters, finding unambiguous classical behavior in opposition to reported low-voltage activation of some CNT paper sources in the literature. We suspect that nebulization or other statistical ion formation phenomena, but not electrospray, underly their behavior.

CNT-coated paper sources are made by dip-coating grade 5 chromatography paper triangles in a 0.04 wt% dispersion of CNTs in N-N dimethylformamide. Emitters were positioned 1 mm away from a cylindrical capillary inlet of a portable MS instrument (Bayspec Continuity). Five- μL droplets of 95% methanol and 5% water spiked with 10 pharmaceutically relevant compounds at 1 $\mu\text{g}/\text{ml}$ were deposited on the emitters

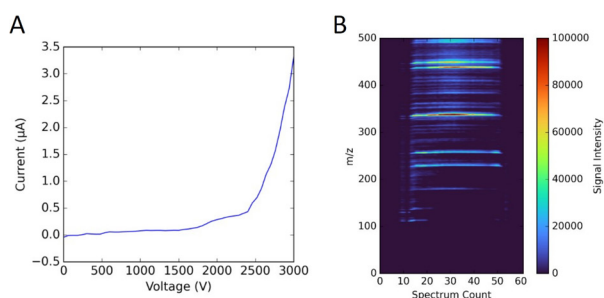
prior to voltage application.

Optical characterization (Figure 1) shows the formation of many jets at the protrusions of individual paper fibers, with solvent reaching them via the surface porosity introduced by the CNTs. Electrical and MS characterization (Figure 2) shows a startup voltage of about 1.5 kV and sufficient signal intensity for compound identification. No ionization is observed at low voltages.

The oft-repeated hypothesis that electric fields at CNT tips drive ambient ionization is incommensurate with fluid physics and optical results here; solvents fully wet forests of nanoscale features. We suspect that low-voltage ionization mechanics underly results reported in the literature, with potential relevance of vibrating edge nebulizers and the specific targets being analyzed. Further characterization, especially optical, is needed of low-voltage CNT paper sources to corroborate any conclusions on ionization mechanics.



▲ Figure 1: Optical image showing steady state electrospray at 2.5 kV, with several jets emerging from paper follicles.



▲ Figure 2: A) I-V plot of 5 replicates showing electrospray formation beginning at 1.5 kV. B) MS transient spectrum showing clear peaks of targets during steady state operation at 3.0 kV. We record no ionization at voltages <1 kV.

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Heart Rate Varies with Mental Workload and Performance in Virtual Reality Flight Tasks

J. Koerner, H. M. Rao, K. McAlpin, G. Ciccarelli, T. Heldt

Sponsorship: MIT Presidential Fellowship, NSERC Doctoral Scholarship (Application ID PGSD3-547366-2020), U.S. Air Force Research Laboratory and U.S. Air Force Artificial Intelligence Accelerator (Cooperative Agreement No. FA8750-19-2-1000)

Heart rate (HR) has been shown to correlate with cognitive metrics, particularly mental workload, in a variety of settings. In real aviation settings, there is broad consensus that HR is positively correlated with mental workload which makes HR an ideal signal to track as a potential surrogate for mental workload. With the growing use of virtual reality (VR) in different areas of training and education, including pilot training, the question arises if the same relationship between HR and mental workload holds in VR-simulated environments. To this end, this work investigates HR responses derived from electrocardiogram (ECG) recordings in 20 subjects performing flight maneuvers in a VR setting and explores the relationship between HR, mental workload, and flight performance. We find that mean HR increases by 2% ($p < 0.05$) across difficulty levels of the virtual flight scenario, decreases by 5% ($p < 0.01$)

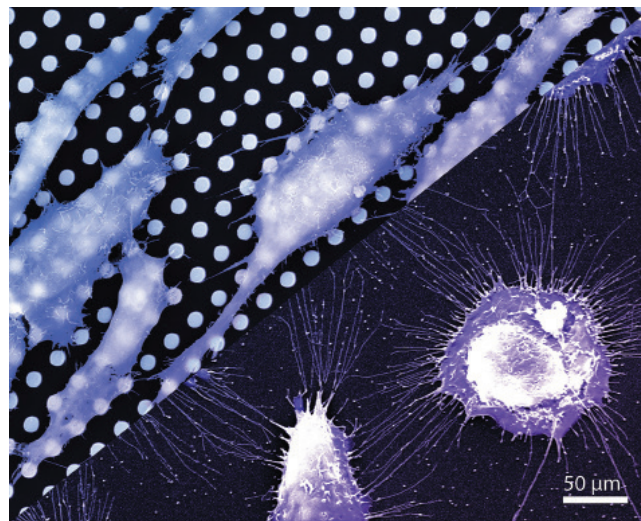
across repeated runs of the same difficulty level, and increases by 3% ($p < 0.01$) during the final landing period (with respect to the beginning of the flight). We observe HR to mirror the trend in mental workload and find a statistically significant correlation between HR and flight performance across different flight phases. Although the effect size observed is moderate, the findings are statistically significant and consistent across participants' experience levels. Our findings lend credence to the use of VR simulators for training purposes, and to the idea of titrating training difficulty based on real-time physiological responses in VR-simulated environments. Finally, we show that the ECG-derived HR trends can similarly be derived from photoplethysmography (PPG) signals. Given the existence of PPG sensors approved for cockpit use in real aircraft, our findings have significance beyond the VR setting.

Mediating Cell Adhesion Using Microtextured Polystyrene Surfaces

C. McCue, A. Atari, S. Parks, M. Tseng, K. K. Varanasi
Sponsorship: Broad SPARC Grant, MIT-Takeda Fellowship

Enzymatic cell detachment strategies for cell culture are popular, but are labor-intensive, can potentially lead to accumulation of genetic mutations, and produce large quantities of waste. Thus, there is a need for surfaces that lower cell adhesion strength while maintaining cell growth to enable enzyme-free cell culture. In this study, we investigated the use of microtexture alone to control cell adhesion. We developed a fast, simple, and inexpensive process for creating microtextured polystyrene surfaces. This fabrication method can transform any design produced with traditional lithography into a PDMS stamp with which we can mold polystyrene, and can be easily scaled for high throughput cell culture as well as create high aspect ratio mi-

cron-sized features with high precision and reproducibility. These cell culture surfaces enable decreased cell adhesion strength while maintaining high cell viability and proliferation through a simple reduction in the cell-surface contact area. Using image analysis to quantify cell morphology, we found that surface textures decreased cell area by half and led to much more elongated cell shape compared to flat surfaces. We designed a microfluidic shear force measurement platform to quantify the removal of cells from these surfaces, and showed that significantly more cells were removed from the microtextured surfaces than the flat surfaces, demonstrating that our surfaces lead to decreased cell adhesion.



▲ Figure 1: SEM image of MG63 cancer cells grown on microtextured polystyrene (left), compared with cells grown on flat polystyrene (right), showing how surface texture alone can significantly change cell morphology.

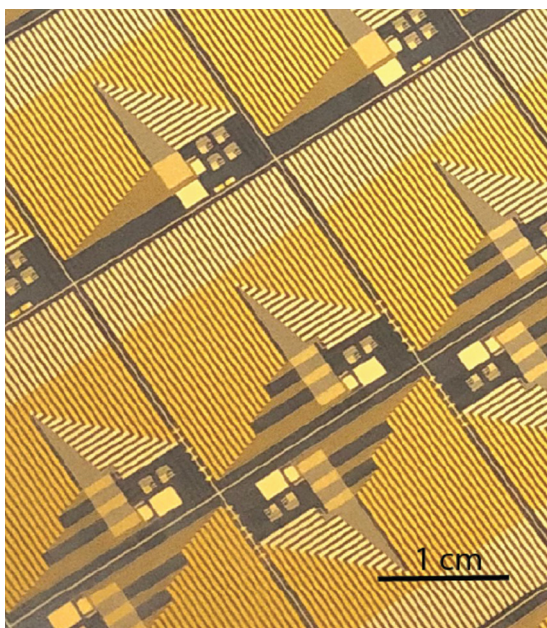
Chamber Design of a Portable Breathalyzer for Disease Diagnosis

D. Morales, M. Xue, T. Palacios

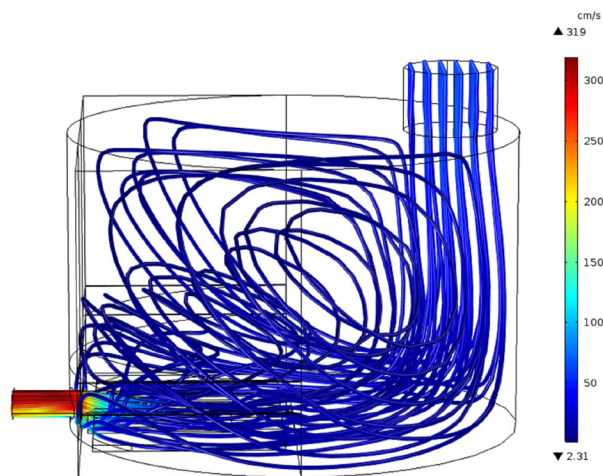
Sponsorship: NSF Center for Integrated Quantum Materials

Our group has built a graphene-based sensor array that can accurately measure the concentration and type of different chemicals of interest. In this project, we have developed a chamber design that allows using this sensor as a portable breathalyzer for non-invasive, cheap, and fast diagnosis of diseases. Although significant research has been made in this field over the years, none has focused on the optimal chamber design of these devices, which has to optimize contact between sensors and air samples and address issues such as moisture, air velocity control, recirculation, and turbulence. Our work studies the airflow properties in different cylindrical chamber models and, with the help of fluid mechanics simulations and experiments with the analysis sensors, attempts to create a reusable in situ breathalyzer design. These results will help develop devices for use in clinical trials; in the future, the devices may be used to diagnose diabetes, Parkinson's Disease, and other conditions.

The current device consists of two chambers that are separate but connected by a piece that acts as the roof of the bottom chamber and the base of the top chamber. The measuring sensor is placed on this piece. The top chamber is designed to house a heater that can enhance the sensor's performance and accelerate drying when necessary. It also contains a humidity sensor, which is crucial for correctly interpreting the results obtained. The bottom chamber contains three stacked printed circuit boards that are screwed to the middle piece. The cables for all the components of the top chamber pass through this piece and are connected to the boards. The device is completely wireless and has a Bluetooth antenna, which allows it to send data to a mobile app that is connected to a database which is used for storing, visualizing, and analyzing the data.



▲ Figure 1: Microscope image of the graphene-based sensor array fabricated on a 4-inch wafer.



▲ Figure 2: Upper chamber fluid mechanics simulations.

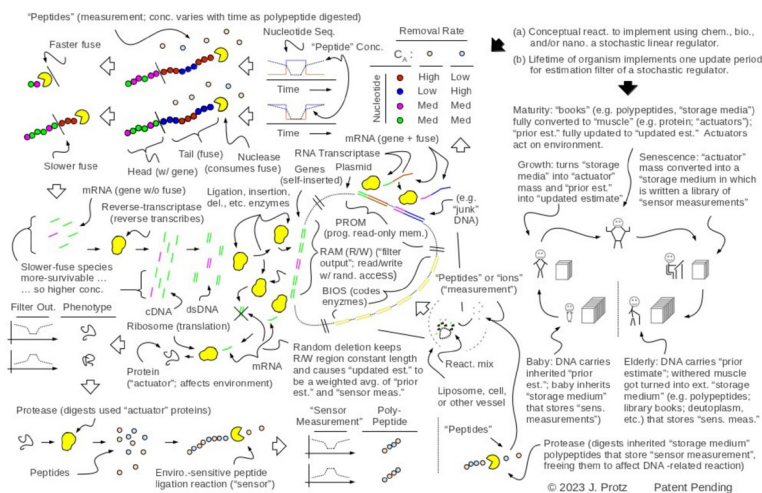
Feedback Regulator and Estimation Filter Implementable Using Bio/Nano Chemistry and Useful for “Intelligent Design”

J. Protz

Sponsorship: Protz Lab Group and the former BioMolecular Nanodevices, LLC

Information storage in polymers has been a focus of the performer for two decades and has recently become of greater interest at MIT. The present effort explores chemical and biological implementation of a stochastic linear regulator. It builds on a conceptual reaction mixture considered by the performer two years ago. First, “PROM”-type “junk DNA” in a plasmid transcribes into mRNA strands that are attacked by exonucleases coded for in a basic input/output system region of the plasmid; the activity of the nucleases depends jointly on the species of nucleotide being removed and on peptides pulled from polypeptides present alongside the plasmid. This activity causes the mix of surviving mRNA to depend on the polypeptide composition. The surviving mRNA reverse-transcribes into DNA that overwrites partly a random-access memory region of coding DNA in the plasmid, evolving it from a “prior estimate” of the environmental state to an “updated estimate” of it. This DNA expresses phenotypically as “actuator” proteins that are

assembled by ribosomes from the free peptides and that “actuate” the surrounding environment. Separately, a “sensor” reaction uses proteases and environmentally-sensitive peptide ligation reactions to recycle used “actuator” proteins back into free peptides that are then assembled into the aforementioned “sensor measurement”-storing polypeptides. One period of this cycle represents one update interval for an estimation filter. Implemented in a cell or organism, with the “sensor measurement”-storing polypeptides doubling as, e.g., a spindle apparatus or yolk, the lifetime of one cell or organism could constitute one update cycle of a stochastic regulator implemented by way of a cell line, organism family line, or society. Progress on this effort may allow the engineering of cell lines that evolve themselves and their environment deterministically according to “intelligent design” and also explain the existence of aging, death, reproduction, and variable life expectancy.



▲ Figure 1: (a) Schematic illustration of a conceptual reaction that implements a feedback regulator and estimation filter; (b) when implemented in a multi-generation cell line, one generation's lifetime implements one update period of a stochastic regulator useful in “intelligent design.”

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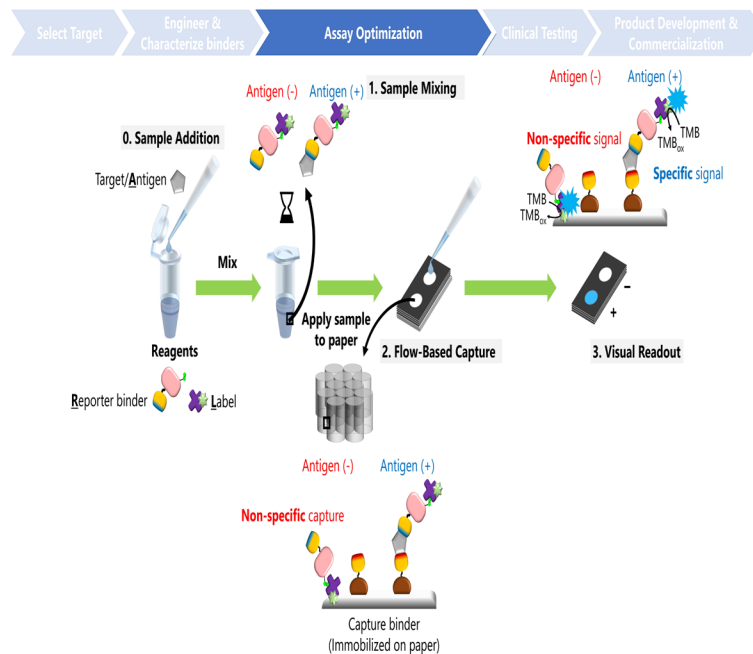
Accelerating the Optimization of Vertical Flow Assay Performance Guided by a Rational Systematic Model-based Approach

D. M. Y. Tay, S. Kim, Y. Hao, E. H. Yee, H. Jia, J. Voldman, H. D. Sikes

Sponsorship: HKUST-MIT Research Alliance Consortium, Singapore's National Research Foundation, MIT Summer Research Program (MSRP)

Rapid diagnostic tests (RDTs) have shown to be instrumental in healthcare and disease control. However, the laborious and empirical, yet necessary, development and optimization process for the attainment of clinically relevant sensitivity remains inefficient. While various studies have sought to model paper-based RDTs, they do not encompass all possible operation regimes. It is also unclear how the model predictions may be utilized for optimizing assay performance. Here, we propose a streamlined and simplified model-based framework for the acceleration of assay optimization, which relies on minimal experimental data. These models are

based on physically rational formulations accounting for relevant physical phenomena such as mixing and diffusion. We show that our models can recapitulate experimental data and estimate of several pertinent assay performance metrics such as limit-of-detection, sensitivity, signal-to-noise ratio and difference. We believe that our proposed workflow would be a valuable addition to the toolset of any assay developer, regardless of the amount of resources they have in their arsenal, and aid assay optimization at any stage in their assay development process.



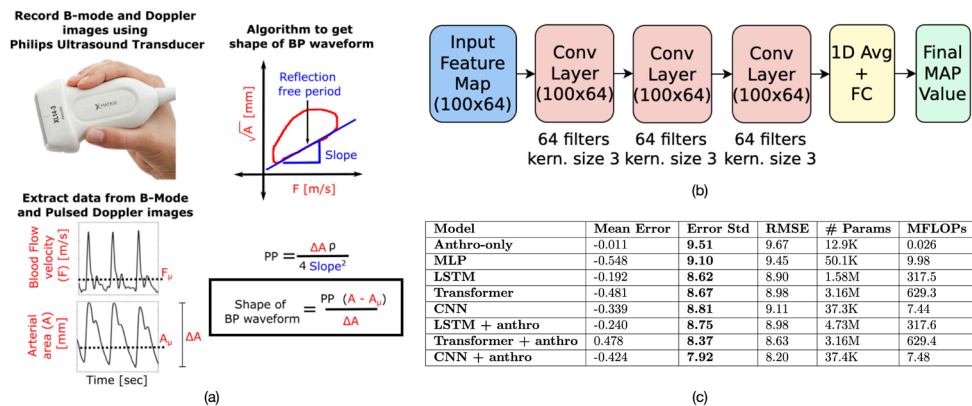
▲ Figure 1: Schematic of proposed assay optimization workflow

Cyb Machine Learning for Arterial Blood Pressure Prediction

H. Wang*, J. Zheng*, A. Chandrasekhar, J. Seo, A. Aguirre, S. Han, C. G. Sodini, H.-S. Lee
Sponsorship: MIT J-Clinic, Philips, Analog Devices, MIT-IBM Watson AI Lab, NSF CAREER Award

High blood pressure is a major risk factor for cardiovascular disease. As such, accurate blood pressure (BP) measurement is critical. Clinicians measure BP with an invasive arterial catheter or via a non-invasive arm or finger cuff. However, an arterial catheter can be painful for the patient and not ideal outside an intensive care unit (ICU). Cuff-based devices are non-invasive, but they cannot provide continuous measurement, and they measure from peripheral blood vessels whose BP waveforms differ significantly from those closer to the heart. Hence, there is an urgent need to develop a measurement protocol for converting easily measured non-invasive data into accurate BP values. In this work, we propose a non-invasive approach to predict BP from arterial area and blood flow velocity signals measured from a Philips ultrasound transducer (XL-143) on large arteries close to heart. We developed the protocol and collected data from 72 subjects. The shape of BP (relative BP) can be theoretically calculated from these

waveforms, but there is no established theory to obtain absolute BP values. Therefore, we further employ data-driven machine learning models to predict the mean arterial blood pressure (MAP), from which the absolute BP can be deduced. We propose several different machine learning algorithms to optimize the prediction accuracy. We find that long short-term memory (LSTM), transformer, and one-dimensional convolutional neural network (1D-CNN) algorithms using the BP shape and blood flow velocity waveforms as inputs can achieve 8.6, 8.7, and 8.8-mm Hg average standard deviation of the prediction error, respectively, without anthropometric data (age, sex, heart rate, height, weight). Furthermore, the 1D-CNN model can achieve 7.9-mm Hg when anthropometric data are added as inputs, improving upon an anthropometric-only model of 9.5-mm Hg. This machine-learning algorithm can be a software modality that converts ultrasound data to MAP values to help physicians make clinical decisions.



▲ Figure 1: (a) The whole pipeline of using machine learning-based algorithms to get BP waveforms from ultrasound data (b) CNN model architecture (c) Performance summary.

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Progress and Challenges with Implantable Microphones for Cochlear Implants

E. F. Wawrzynek, J. Z. Zhang, A. Yeiser, C. I. McHugh, L. Graf, M. E. Ravicz, E. S. Olson, I. Kymissis, H. H. Nakajima, J. H. Lang
Sponsorship: National Institute on Deafness and Other Communication Disorders/NIH R01DC016874, NSF Graduate Research Fellowship Program Grant No. 1745302, the Edwin S. Webster Graduate Fellowship

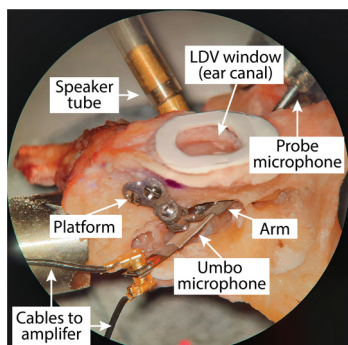
We have developed two microphone designs for a fully implantable cochlear implant. The Umbo Microphone (UM) (Figure 1) senses the motion of the umbo, while the Cochlear Microphone (CM) detects sound via intracochlear pressure. Implantable microphones utilize the natural filtering of the ear and enable the use of hearing assistive devices in all environments.

The transduction mechanism of our implantable microphones is based on the piezoelectric properties of polyvinylidene fluoride (PVDF), a common plastic that can be manufactured as a film. PVDF is biocompatible and used in medical devices. The UM is two layers of PVDF separated by a backing and detects sound signals via bending. This output is the amplified difference between the two signals from the PVDF layers, thus providing good common mode rejection. The signal-to-noise characteristics of the cantilever microphone are comparable to those of hearing aid external microphones (Figure 2-3). The CM works through deformation of the PVDF material due to fluid pressure in the scala tympani. A strip of

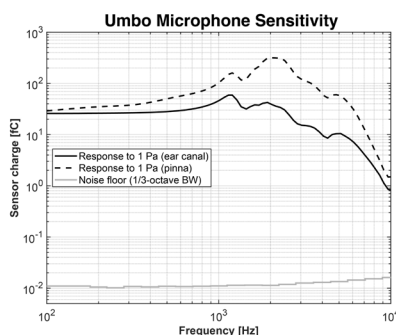
PVDF is inserted into the scala tympani alongside an electrode array. This design is attractive because it can be directly integrated with cochlear implant electrode arrays.

Our recent research focuses on making our current UM biocompatible without sacrificing performance. We have replaced the aluminum conductive layers of our earlier prototype with biocompatible titanium. Furthermore, we have developed a titanium mounting structure that holds the microphone against the umbo and can be implanted during tympanotomy surgery. For the CM, we have investigated novel designs that use different geometry and piezoelectric material to improve sensitivity. We are developing designs that can be integrated with existing electrode arrays of cochlear implants.

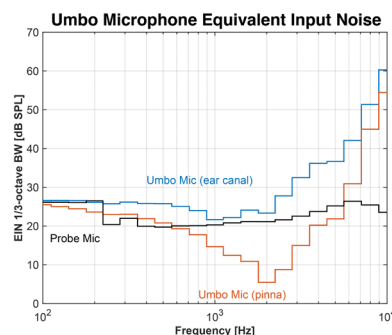
By focusing on material choice, integration, and structural methods for implanting our sensors, we are taking important steps towards an implantable microphone for fully implantable assistive hearing devices.



▲ Figure 1: Experimental setup for testing UM in human cadaver. Custom “mounting structure” holds UM inside middle ear cavity. Tip of UM contacts umbo and sound pressure is introduced at eardrum. Commercial probe microphone measures sound pressure for referential data.



▲ Figure 2: Sensitivity of UM in human cadavers. Charge output is referenced to 1 Pa sound pressure and shows that UM has relatively flat frequency response up to 1 kHz. Dotted line simulates pressure gain provided by external ear structure. Commercial probe microphone measures sound pressure for referential data.



▲ Figure 3: Equivalent Input Noise (EIN) of UM compared to EIN of commercial Knowles microphone. Orange line simulates pressure gain provided by external ear structure. Including pressure gain, EIN of our UM is comparable to that of commercial probe microphone.

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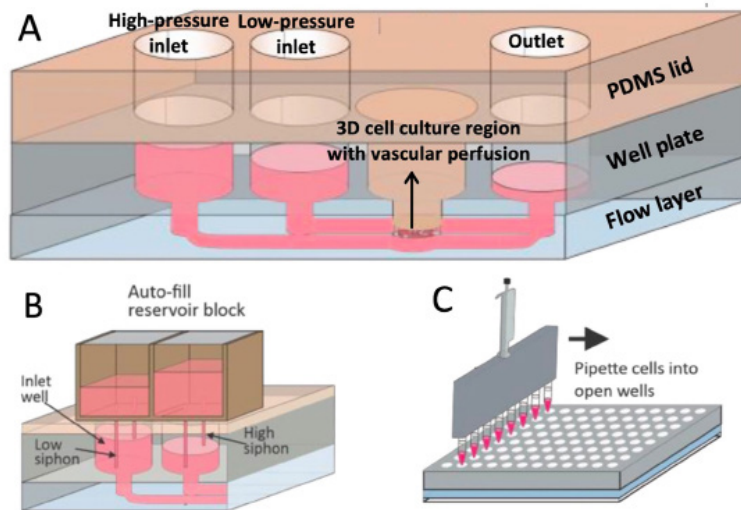
A High-throughput Open-well Microfluidic Organ-on-chip System for Blood-brain Barrier

F. Xue, U. Lee, W. Liao, J. Voldman
Sponsorship: NIH

Blood-brain barrier (BBB) on-chip constructed by microfluidic technology has assisted researchers in understanding BBB physiology and developing therapies for neurological diseases. However, the existing systems typically account for the biological relevance of BBBs at the expense of robustness, throughput, or ease of operation.

In this work, a BBB on-chip is developed incorporating all four factors above. The system aims to maintain biological sophistication by modeling the

architecture of in-vivo BBB and enabling vascular perfusion. The open-well design eliminates bubble-prone tubing operations and improves robustness, and coupling with a standard 96-well plate enables high-throughput operation. A siphon-based design maintains fluid levels at the inlets to ensure gravity-driven flow at a constant perfusion rate. The system can be used to investigate BBB functioning robustly and productively, enabling faster development of therapies for neurological diseases such as Alzheimer's.



▲ Figure 1: Open-Well Microfluidic Organ-on-Chip System. A) Perfusion culture region. B) Siphon-based autofill reservoir maintains a constant fluid level at the inlets. C) Open-well design allow easy access to fluid and culture region.