Biological, Medical Devices, and Systems

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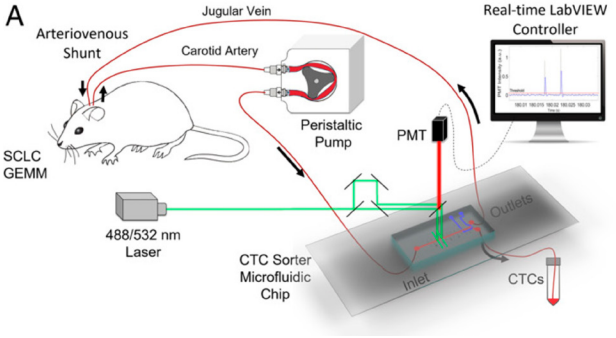
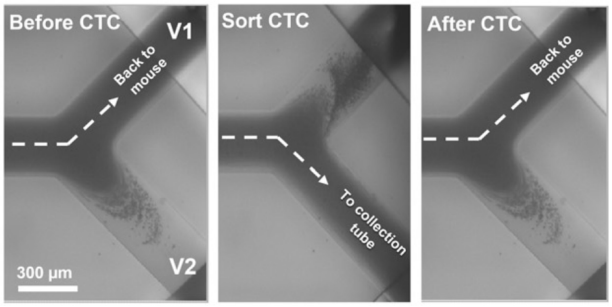
Optofluidic Real-time Cell Sorter for Longitudinal CTC Studies in Mouse Models of Cancer

B. Hamza, S. R. Ng, S. M. Prakadan, F. F. Delgado, C. R. Chin, E. M. King, L. F. Yang, S. M. Davidson, K. L. DeGouveiab, N. Cermak, A. W. Naviab, P. S. Winter, R. S. Drake, J. S. Bagnall, S. M. Knudsen, M. G. Vander Heiden, S. C. Wasserman, T. Jacks, A. K. Shalek, S. R. Manalis
Sponsorship: NIH, Ludwig

Circulating tumor cells (CTCs) play a fundamental role in cancer progression. However, in mice, limited blood volume and the rarity of CTCs in the bloodstream preclude longitudinal, in-depth studies of these cells using existing liquid biopsy techniques. We developed an optofluidic system (Figures 1, 2) that continuously collects fluorescently labeled CTCs from a genetically engineered mouse model (GEMM) for several hours per day over multiple days or weeks. The system is based on a microfluidic cell-sorting chip connected serially to an unanesthetized mouse via an implanted arteriovenous shunt. Pneumatically controlled microfluidic valves capture CTCs as they flow through the device, and CTC-depleted blood is returned back to the mouse via the shunt. To demonstrate the utility of our system, we profile CTCs isolated longitudinally from animals over four days of treatment with the BET inhibitor JQ1 using single-cell RNA sequencing (scRNA-Seq) and show that our approach eliminates potential biases driven by inter-mouse heterogeneity that can occur when CTCs are collected across different mice. The CTC isolation and sorting technology presented here provides a research tool to help reveal details of how CTCs evolve over time, allowing studies to credential changes in CTCs as biomarkers of drug response and facilitating future studies to understand the role of CTCs in metastasis.



▲Figure 1: Peristaltic pump withdraws blood from a surgically implanted cannula in the carotid artery of a mouse. The blood is directed into the main flow channel of the CTC sorter chip. For tdTomato-positive cells, a green (532-nm) laser illuminates two points along the main flow channel of the CTC chip separated by a known distance. Thus, fluorescent CTCs emit two red-shifted pulses of light, which are detected by a photomultiplier tube. Based on the timing of the pulses, a LabVIEW program computes the velocity of the cells and operates computer-controlled pneumatic valves to redirect fluorescent CTCs toward a collection tube. After exiting the chip, CTC-depleted blood returns to the jugular vein of the mouse via a second surgically implanted cannula.



▲Figure 2: Outlet by which blood is returned to the mouse is briefly sealed while the opposite outlet is opened to allow for CTC isolation in real time. After collection, CTCs are further enriched by a secondary CTC sorting chip designed with a parallel channel to flush CTCs into wells containing cell lysis buffer for downstream scRNA-Seq.

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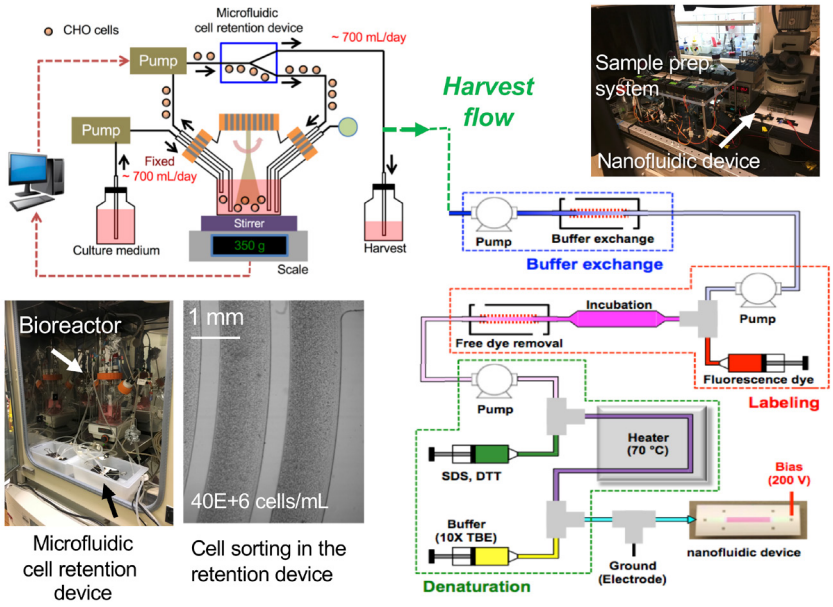
Continuous Online Monitoring of Biologics Quality during Continuous Biomanufacturing using Micro/Nanofluidic System

T. Kwon, S. H. Ko, J.-F. P. Hamel, J. Han
Sponsorship: Singapore-MIT Alliance for Research and Technology (SMART) Centre BioSyM IRG, DARPA, Samsung Scholarship

The growing trend in the biopharmaceutical industry is to adopt continuous biomanufacturing to reduce manufacturing cost and improve product quality. However, several challenges must be solved. First, a reliable and efficient cell retention device is required. Currently, using a hollow fiber membrane is a widely adopted cell retention method in industry to maintain suspended cells in the bioreactor and remove biologics from the bioreactor. However, it suffers from membrane fouling/clogging due to cells and cell debris. Moreover, product recovery efficiency becomes significantly low over cultivation time, resulting in low manufacturing efficiency.

Second, there is no robust online sensor for critical quality attributes, such as purity and binding affinity, during manufacturing to understand the real-time relationship between the critical quality attributes and bioprocesses. For example, sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), size exclusion chromatography (SEC), and capillary gel electrophoresis (CGE or CE-SDS) are commonly used to check protein purity, but they offer only at-line/offline discontinuous analysis.

In this context, we developed a novel micro/nanofluidic system to demonstrate continuous online monitoring of protein size distribution of cell culture supernatant during perfusion culture (Figure 1). The system consists of perfusion culture, online sample preparation, and detection of protein size distribution. To enable long-term perfusion culture, we used a membraneless microfluidic cell retention device. The cell retention is based on size-based cell sorting. Its high cell-concentration-capacity (>40E+6 cells/mL), scalability, long-term biocompatibility, and high product recovery efficiency have already been demonstrated. The online sample preparation consists of buffer-exchange, cell clarification, protein labeling, and denaturation. At the end of the system, the nanofluidic device continuously monitors protein size distribution. It has nanofilter array and supports continuous-flow size-based protein separation and concentration.



▲ Figure 1: The micro/nanofluidic system for continuous monitoring of protein size distribution of cell culture supernatant containing monoclonal antibodies (IgG1) during perfusion culture.

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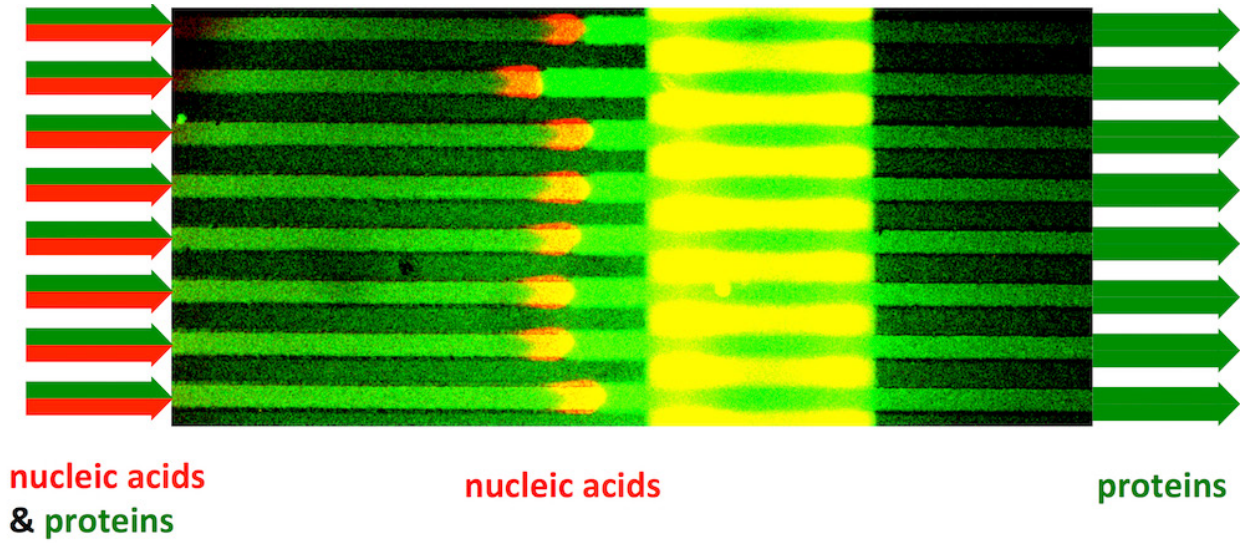
Electrokinetic Purification for DNA Analysis

W. Ouyang, J. Han
Sponsorship: NIH

Rapid detection of ultralow-abundance pathogenic DNAs in complex clinical samples, which are often as low as <100 copies/ml (~0.1 aM), is critical for early diagnosis of infectious diseases. Despite the unprecedented amplification capacity of the polymerase chain reaction (PCR), its detection sensitivity and specificity are limited by the ability to purify DNAs from clinical samples with minimal loss. Currently, DNA extraction relies on slow and labor-intensive spin column-based solid phase extraction, which introduces significant losses of DNAs during capture, elution, and final sampling, especially for ultralow-abundance samples.

Ion-concentration-polarization (ICP)-based electrokinetic trapping (ET) has attracted much attention in the past decade as a viable approach for the rapid concentration of DNAs and other biomolecules, with enrichment speeds of ten-thousand-fold in ~10 minutes. Based on this technique, we report the direct enrichment and purification of DNAs in complex biological samples by pressure-modulated selective electrokinetic trapping (PM-SET). We showcase the utility of PM-SET in human serum that contains 60–80 mg/mL total serum protein and perhaps represents one of the most complex backgrounds for molecular detection. Through modulating the hydrostatic pressure applied to the ICP-based ET device, we demonstrate the selective trapping of DNAs (of high electrophoretic mobility) while the majority of background proteins (of low electrophoretic mobility) are simultaneously removed (Figure 1), achieving an enrichment factor of >4800 in 15 minutes for DNAs.

With these advantages, we believe that PM-SET could potentially play an enabling role in developing lab-on-a-chip devices toward point-of-care diagnostics, on-site food and environment monitoring, and a variety of other applications in resource-limited settings.



▲ Figure 1: Selective electrokinetic concentration of DNAs (green) and simultaneous filtration of background proteins (red) in parallel microfluidic channels with induced ion depletion zones.

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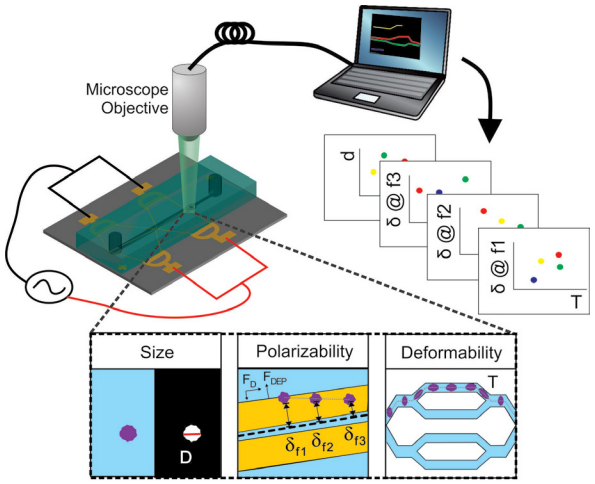
Multi-parameter Cell-tracking Intrinsic Cytometry for Characterization of Single Cells

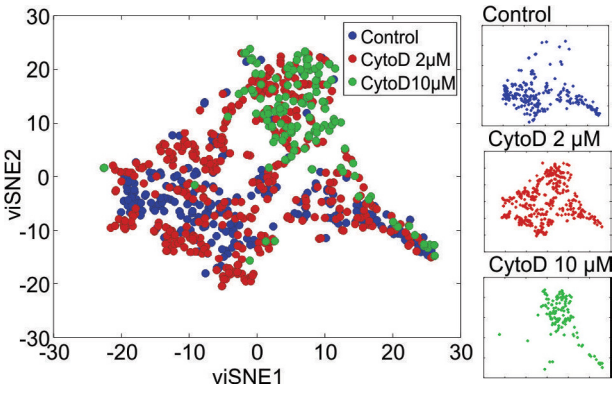
N. Apichitsopa, J. Voldman
Sponsorship: Bose Research Award

Cells possess biochemical properties that require extrinsic tags, e.g., fluorescent dyes, for detection and biophysical properties, e.g., morphological, mechanical, electrical, and optical properties, which are intrinsic and do not require any labels. While extrinsic labeling techniques are highly specific to cell states, analyses of label-free biophysical properties are more suitable for applications, which require quick turnaround, and for analysis where biochemical labels for targeting cell states are not known. Development of single-cell biochemical analysis techniques with high sensitivity, throughput, and multiplexing capability has advanced understanding of complex biological systems and has established their presence in biological research labs and clinical practice. In contrast, development of single-cell biophysical analysis techniques is often limited to proof-of-concept due to the low-specificity nature of the intrinsic markers and the lack of approaches to combine multiple biophysical assays for high-dimensional biophysical phenotyping of single cells.

To address this challenge, we propose a general approach to combine multiple biophysical measurements of single cells via optical tracking. To show specific implementation of this approach, we developed a microfluidic platform that measures up to five intrinsic markers of single cells, including size, deformability, and polarizability at three frequencies (Figure 1). We chose these intrinsic markers because each has been associated with important biological functions and proven useful for cell characterization, and they are rarely studied together. Cell tracking was demonstrated on the fully integrated platform, and multiple intrinsic markers of single cells were measured from cell samples treated with varying concentrations of actin polymerization inhibitor. An unsupervised dimensionality reduction technique, viSNE, was implemented to visualize the five-dimensional intrinsic marker measurements in two-dimensional visualization (Figure 2). Our analysis showed that an increase in number of intrinsic markers measured by our intrinsic cytometry platform resulted in an increase in classification accuracy of cell states induced by drug treatment.



▲Figure 1: System overview of the multi-parameter intrinsic cytometry, which measures up to five intrinsic markers of single cells, including size, polarizability at three frequencies, and deformability.



▲Figure 2: viSNE map of multi-parameter intrinsic measurements of HL60 cell line treated with different concentrations of Cytochalasin D, inhibitor of actin polymerization, colored by Cytochalasin D concentrations.

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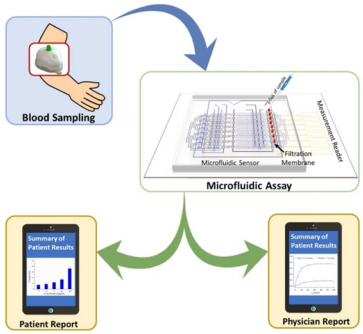
Point-of-Care Biomarker Detection through Electronic Microfluidics

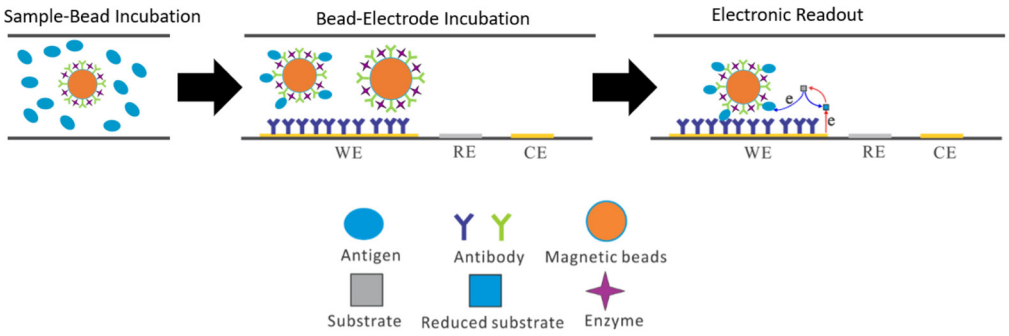
D. Wu, K. Kikkeri, J. Lee, J. Voldman
Sponsorship: Novartis

Identification of protein biomarkers is a vital step for numerous biomedical applications including clinical diagnostics, monitoring, and treatment. However, traditional blood analysis techniques require large sample volumes and centralized laboratories with trained technicians to perform tests. This translates to long wait times (~days) for patients and healthcare providers to receive testing results. Point-of-Care (PoC) devices have emerged as promising alternatives to these traditional blood assays as they are capable of rapid analysis (~mins) in non-laboratory settings. Thus, we are developing an integrated and electronically operated PoC platform for the rapid identification of protein biomarkers.

As shown in Figure 1, in principle, the PoC system is a blood-to-result platform that incorporates an interface for automated sample withdrawal from blood collection devices, an electrochemical assay, and an electronic readout. The electrochemical assay was developed as a bead-based electronic enzyme-linked immunosorbent assay (ELISA) to reduce assay time, lower required sample volume (~µL), and enable platform automation. The workflow of this bead-based electronic assay is shown in Figure 2. Following sample infusion, magnetic microbeads conjugated with antibodies and enzymes are introduced to the sample. Target biomarkers bind to antibodies on the surface of the microbeads and are then sent to electrodes for detection. Biomarker-bound beads then attach to capture antibodies coated on the electrodes. Following an incubation period, enzymes on the attached microbeads catalyze chemical reactions to generate current, which is measured electronically. Electrical readouts are then correlated with the target biomarker concentrations on the transducer. Results have indicated that this sensor has the sensitivity range required for clinically relevant concentrations of various biomarkers for a variety of biomedical applications. Furthermore, initial testing has shown that the platform produces rapid results (within 30 mins) using small volumes (~µL) of blood.



◀ Figure 1: Overview of platform operation. Blood samples are withdrawn from collection devices and infused into the microfluidic channels. An electrochemical assay is performed in the device, which is then measured electronically.



▲ Figure 2: Schematic of the bead-based electronic ELISA. The workflow of the assay, which includes incubation of sample with beads equipped with enzymes and antibodies, incubation of beads with antibody on electrodes, and electrochemical measurement.

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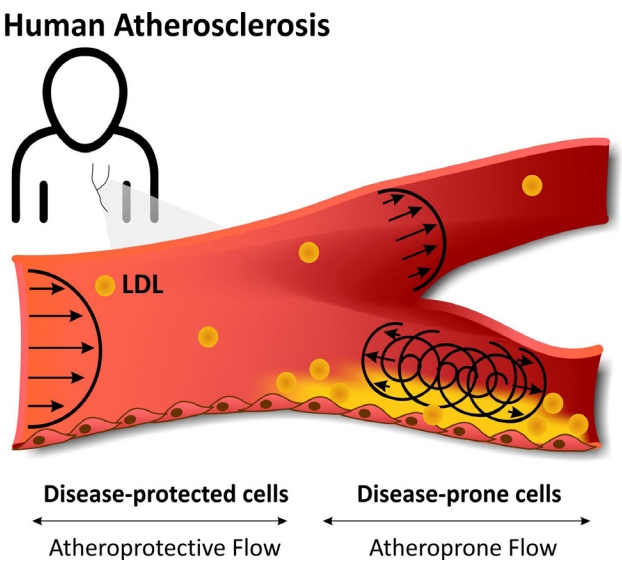
A Microfluidic System for Modeling Human Atherosclerosis and Pathophysiology

S. Varma, W. Liao, J. Voldman
Sponsorship: MIT-GSK Gertrude B. Elion Research Fellowship

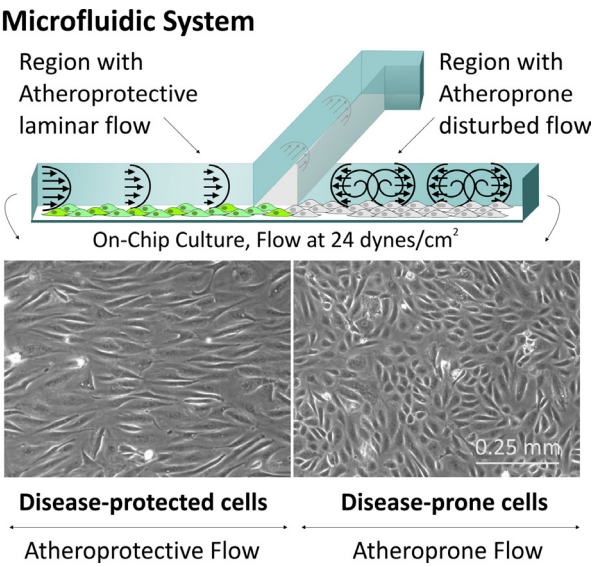
Hemodynamic flows and consequent fluid shear stresses (FSS) directly regulate endothelial function (EF), which in turn regulates atherosclerotic disease progression (atherogenesis). Laminar, helical flows with a high-magnitude pulsatile FSS waveform enhance EF (i.e., are atheroprotective), while multidirectional flows with a low-oscillatory FSS waveform impede EF (i.e., are atheroprone). Understanding atherogenesis requires a microenvironment with representative flows regulating EF (Figure 1). Current systems usually provide a single aspect of atheroprotective or atheroprone flows: high/low shear, oscillatory/unidirectional flow, uniform/pulsatile flow, etc., but do not recreate all the spatiotemporal flow features to mimic the complexity of physiological flows.

We have developed a microfluidic system that, for the first time, fully recapitulates in vivo-like spatiotemporal atheroprotective flow simultaneously with atheroprone flows, both with complex but programmable features. Applying these flows upon primary human endothelial cells (hECs), we can concurrently monitor maintenance of EF and the emergence of endothelial dysfunction in precise locations within a single cellular monolayer, as it occurs in vivo. We utilize on-chip valves to dynamically modulate flows—and hence FSS applied on cells—mimicking in vivo waveform dynamics and magnitude. Additionally, we utilize patterned grooves within the device to impart specific spatial profiles of flow, enabling us to recapitulate the complete spatiotemporal flow signatures found in vivo.

Our platform allows us to monitor hECs cultured under spatiotemporal flows and execute relevant biological assays for assessing EF. As an example, we observe cell alignment exclusively under atheroprotective flows compared to atheroprone flows, matching known in vivo morphology of functional hECs (Figure 2). Overall, with this highly relevant platform, we can, for the first time, systematically and simultaneously control unexplored hemodynamic flow parameters that condition hECs to regulate human disease susceptibility.



▲Figure 1: Human atherosclerosis disease progression is regulated by distinct endothelial phenotypes that are preconditioned to be either disease-protected or disease-prone, depending on the local spatiotemporal hemodynamic flows.



▲Figure 2: Our microfluidic system recapitulates the spatiotemporal hemodynamics and vascular regions relevant to atherosclerosis. Conditioning hECs with on-chip flows induces distinct phenotypic signatures in the two regions, e.g., flow alignment, similar to in vivo observations.

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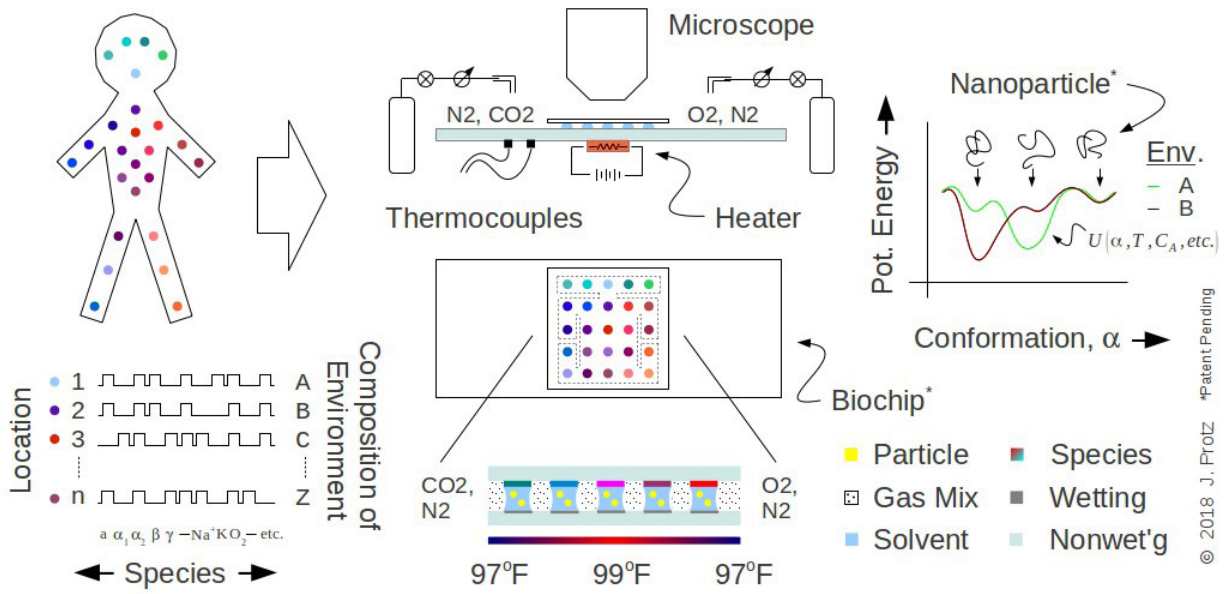
Biochip for Drug Delivery using TERCOM

J. Protz
Sponsorship: Protz Lab Group, BioMolecular Nanodevices, LLC

Targeted drug delivery has been an area of active investigation for several decades. Most approach target cell-borne receptors chemically or genetically. Some use external stimuli such as heat or radio waves to drive spatially-localized release. In one approach, particles estimate their own location within the body by correlating their sensed environment (e.g., temperature, pressure, salinity, sugar levels, pH, etc.) or its time history against a carried map and releases a charge of a drug based on this estimate. This eliminates external aids and is closely related to terrain contour matching (TERCOM) and scene correlation (DSMAC), techniques used in aircraft navigation.

Previous work by the PI and his group focused on the development of nanoparticles capable of sensing and retaining a memory of their environment with noisy DNA. Current efforts focus on the theory of estimating location within the body from vectors of sensed variables and on development of a SiO2 MEMS biochip (microarray) that can test or screen particles and molecules for such sensitivity. Preliminarily explored particle concepts have included liposomes and proteins (bottom-up fab) and thin films (top-down fab). A chip concept that implements a microarray with a half-toned chemical library and material data drawn from conventional surgical analogs has also been considered. The objective is to demonstrate a targeted nanoparticle that implements TERCOM- or DSMAC-like navigation in the body and a biochip that can evaluate its selectivity. The concept is outlined in Figure 1.



▲ Figure 1: Illustration of biochip screening for TERCOM functional nanoparticles.

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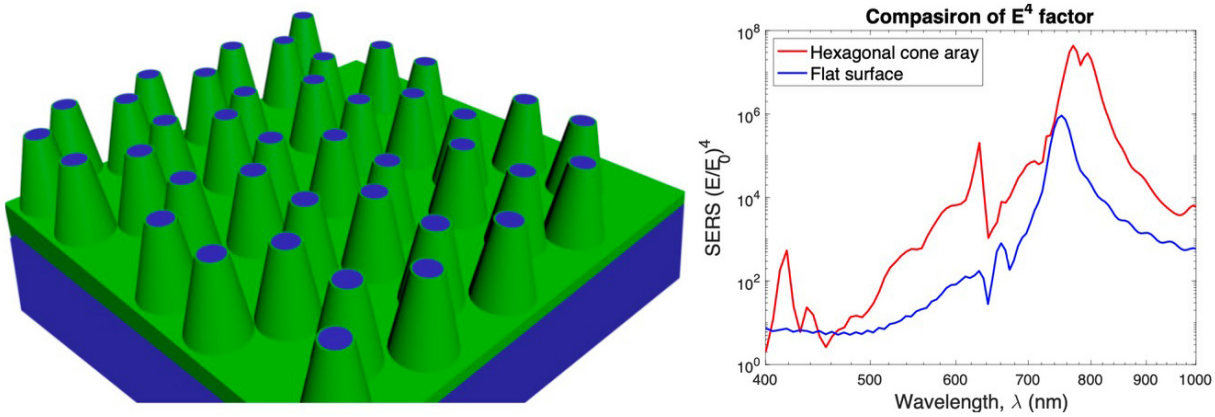
Nanocone-arrayed SERS Substrate for Rapid Detection of Bacterial Sepsis

N. Jia, S.-G. Kim
Sponsorship: Institute for Medical and Consultations

Rapid detection of bacteria is a very critical part of treating infectious disease. Sepsis kills more than 25 percent of its victims, resulting in as many as half of all deaths in hospitals before identification of the pathogen for patients to get the right treatment. Raman spectroscopy is a promising candidate in pathogen diagnosis, given its fast and label-free nature if the concentration of the pathogen is high enough to provide reasonable sensitivity. This work develops a new kind of surface-enhanced Raman spectroscopy (SERS) substrate that will provide high enough sensitivity and fast and close contact of the target structure to the hot spots for an immunomagnetic-based, bacteria-concentrating and -capturing technique.

The substrate uses an inverted cone structure array made of transparent PDMS to funnel the light to the top of the cones, where plasmonic nanorods are located. A high-reflective and low-loss layer is deposited on the outer surface of the cone. Given the geometry of the cone, photons are multi-reflected by the outer layer and thus the number density of photon increases by at least an order. After the pattern and geometric shape of the cones are optimized, the hot spots of the proposed SERS substrate could have an enhancement factor of 10^8 or higher, which could be high enough to detect immunomagnetically densified bacteria.



▲ Figure 1: The comparison of E^4 factor between hexagonal dense packing cone array and the flat surface.

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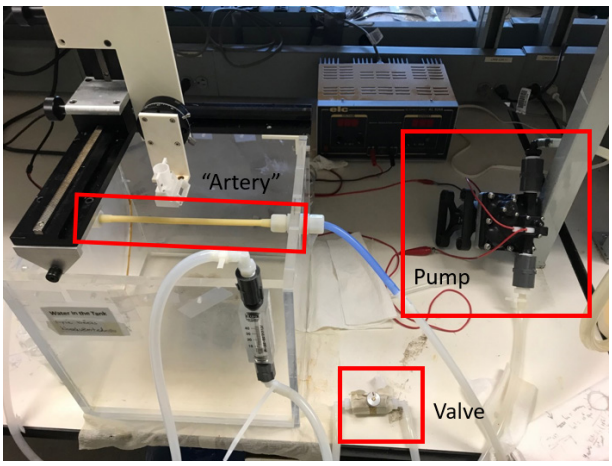
Arterial Blood Pressure Estimation using Ultrasound Technology and a Transmission Line Arterial Model

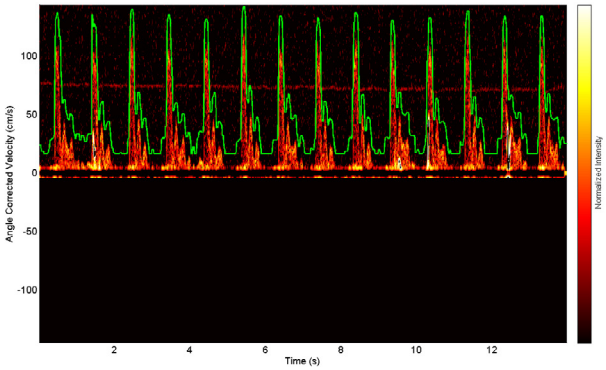
K. Beeks, C. G. Sodini
Sponsorship: MEDRC, Analog Devices

This work describes the application of a transmission line model to arterial measurements in order to derive useful cardiovascular parameters. Non-invasive ultrasound techniques are used to make these measurements, which has several benefits over invasive methods such as arterial catheterization. However, invasive methods are seen as the "gold standard" measurements and therefore the most accurate. Having accurate measurements performed non-invasively is very desirable for cardiologists to determine their patients' risk of developing cardiovascular disease.

This work details how to obtain the "blood" flow and pulse pressure waveforms with ultrasound transducers using a flow phantom with blood mimicking fluid (BMF) shown in Figure 1. Two transducers, one for imaging and one for Doppler, are used together to derive these pulse pressure waveforms from distension and "blood" flow velocity measurements. Unfortunately, the pulse pressure waveform does not contain diastolic pressure information. By decomposing the backward and forward pulse and flow waves and using the transmission line model, the diastolic pressure can be determined, yielding a complete arterial blood pressure waveform.



▲ Figure 1: The flow phantom experiment is designed to mimic the heart pumping blood through a single arterial segment. BMF is pulsing through a latex rubber tube.



▲ Figure 2: The fluid flow velocity of the BMF is measured using pulsed Doppler ultrasound.

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Human Subject Studies of Ultrasound for Continuous and Non-invasive Arterial Blood Pressure Waveform Monitoring

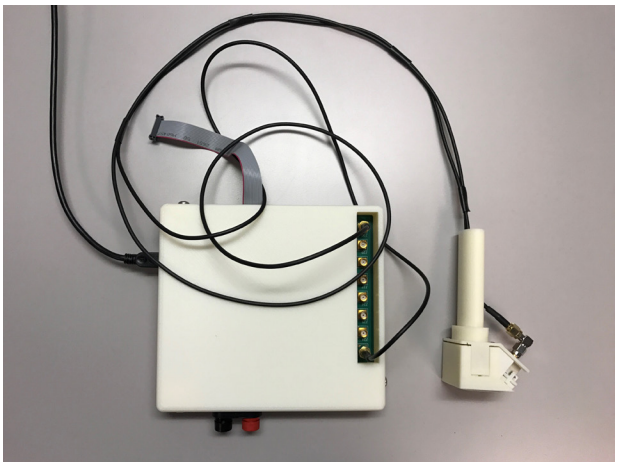
M. S. Feng, H.-S. Lee, C. G. Sodini
Sponsorship: MEDRC, Analog Devices, Inc.

Arterial blood pressure (ABP) is a key physiological parameter for evaluating the circulatory system of patients. The ABP reflects the pathophysiologic states of the cardiovascular system. Currently, the ABP waveform is usually obtained via an arterial line (A-line) in intensive care settings; while considered the gold standard, the A-line is invasive. Thus, our goal is to develop a reliable, continuous, and non-invasive ABP waveform estimation system. Ultrasound is an ideal imaging modality to achieve this goal due to its low cost and portability. Two human subject studies are in progress using prototype ultrasound devices to develop this ABP waveform estimation system.

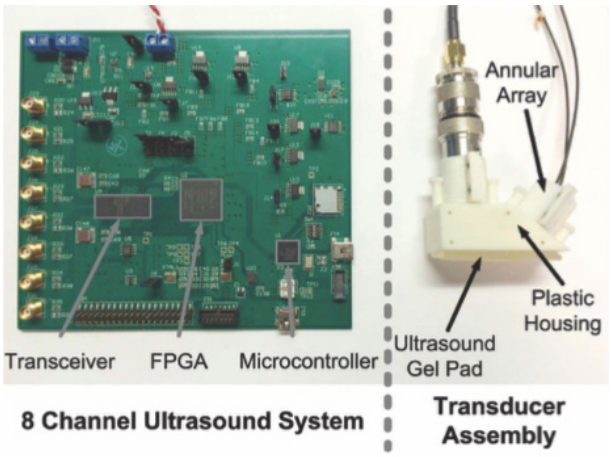
The first human subject study is being done in collaboration with the Boston Medical Center to compare the measured ABP waveform on patients with A-lines with the pulse pressure waveform measured with the Flow Method we developed at the carotid artery. In the Flow Method, the blood flow is measured with pulsed Doppler using a single ultrasound transducer while the arterial area and distention are measured by using M-mode imaging with a second single ultrasound transducer

A drawback of the Flow Method is that it provides only the pulse pressure waveform rather than the absolute ABP waveform. Thus, a transmission line model of the arterial blood flow system is being developed to make an estimation of the diastolic pressure, which provides the baseline for the absolute ABP waveform. The pulse pressure waveform on its own gives no information on diastolic blood pressure. However, the transmission line model suggests that the waveform may contain information regarding the patient's vascular resistance. By decomposing the waveform into the forward and backward traveling waves, we can derive the reflection coefficient. The reflection coefficient provides an estimate of the vascular resistance, which is multiplied with the measured diastolic blood flow to yield the diastolic pressure.

The second human subject study is underway in collaboration with Massachusetts General Hospital to compare the measured ABP waveform on patients with A-lines with mean arterial pressure (MAP) calculated by the transmission line model at the brachial arteries.



▲Figure 1:The prototype ultrasound system and transducer assembly. The system is capable of sufficient data rate to display blood flow and arterial pulsation simultaneously.



▲Figure 2: The prototype ultrasound system and transducer assembly. Ultrasound gel pad is utilized to achieve acoustic coupling between the transducer surface and the skin.

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- K. A. Beeks, "Arterial Blood Pressure Estimation using Ultrasound Technology and Transmission Line Model," Master's Thesis, Massachusetts Institute of Technology, Cambridge, 2019.
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- J. Seo, S. J. Pietrangelo, C. G. Sodini, and H.-S. Lee, "Motion Tolerant Unfocused Imaging of Physiological Waveforms for Blood Pressure Waveform Estimation using Ultrasound," *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 65, no. 5, pp. 766-779, Mar. 2018.

Measuring Saccade Latency using Smartphone Cameras

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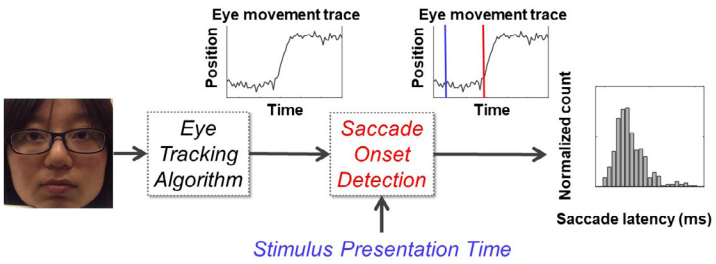
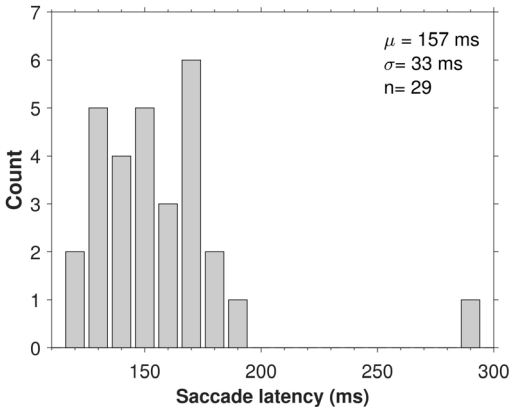
Sponsorship: SenseTime

With current clinical techniques, it is difficult to accurately determine the condition of a patient with a neurodegenerative disease (e.g., Alzheimer's disease). The most widely used metrics are qualitative and variable, exposing the need for a quantitative, accurate, and non-obtrusive metric to track disease progression. Clinical studies have shown that saccade latency--an eye movement measure of reaction time--can significantly differ between healthy subjects and patients. We propose a novel system that measures saccade latency outside the clinical environment using videos recorded with a smartphone camera. This is challenging, given the absence of infrared illumination and high-speed cameras, adverse lighting conditions, and the instability of the tracking device.

To overcome these challenges and therefore enable tracking of saccade latency in large cohorts of subjects, we combined a deep convolutional neural network (CNN) for gaze estimation with a model-based approach for saccade onset determination that provides automated signal-quality quantification and artifact rejection (Figure 1). A variant of the iTracker gaze estimation CNN and a hyperbolic tangent model resulted in mean saccade latencies and associated standard deviations on iPhone recordings that were essentially the same as those obtained from recordings using a high-end, high-speed camera. With our system, we recorded over 19,000 latencies in 29 self-reported healthy subjects and observed significant intra- and inter-subject variability, which highlights the importance of individualized disease tracking (Figure 2). Our framework shows that unobtrusive, individualized tracking of neurodegenerative disease progression is possible.



▲ Figure 1: Saccade latency measurement system. An iPhone 6 video is processed using an eye-tracking algorithm. Saccade latency values are estimated by estimating the saccade onset using a hyperbolic tangent model.



▲ Figure 2: Distribution of the mean saccade latencies from 29 subjects. Notice the wide range of mean saccade latency values across healthy subjects.

FURTHER READING

- H.-Y. Lai, G. Saavedra-Peña, C. Sodini, V. Sze, and T. Heldt, "Measuring Saccade Latency using Smartphone Cameras," *J. of Biomedical and Health Informatics (JBHI)*, doi: 10.1109/JBHI.2019.2913846, 2019.
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A Simplified Design for Modeling Coronary Capillary Fluid Transport in a PDMS Model

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Myocardial injury is the leading cause of adult mortality in the United States. Despite the tremendous scientific interest in modeling the cardiac capillary damage that is characteristic of this event, few platforms exist to model in-vivo fluid dynamics, especially capillary interactions, accurately. Tissue-interface-mimicking microfluidic devices are the few in-vitro models for studying the critical behavior of capillaries, but frequently used models require single micrometer resolution photolithography tools. This study examines and evaluates an accessible alternative design that employs centimeter-resolution photolithography to achieve similar flow properties. Although fundamental fluid dynamics properties of the new design are in accordance with expectations, some suggestions are made to improve the applicability of the new design for modeling cross-membrane diffusion in capillaries.