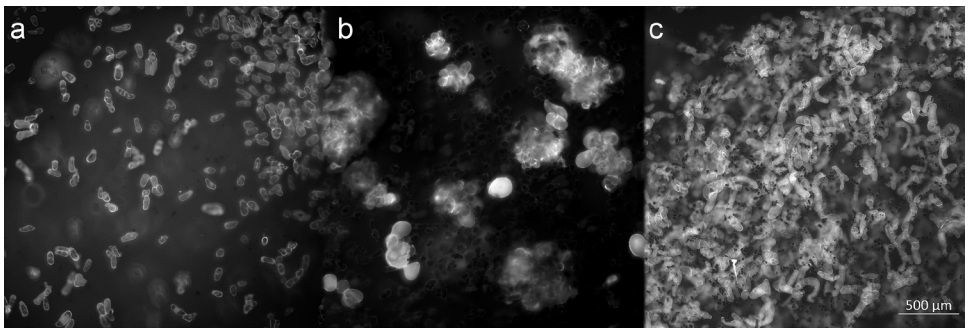
Biological, Medical Devices, and Systems

Tuning Plant Cell Culture Parameters for Improved Model Physiologies

A. L. Beckwith, J. T. Borenstein, L. F. Velásquez-García
Sponsorship: Texas Instruments

In vitro plant culture models provide valuable insights into factors governing plant growth and development. Improved understanding of genetic and biochemical pathways in plants has facilitated advancements in a variety of industries —from guiding the development of more robust crops, to enabling increased biofuel yields by tuning biomass genetics. Despite the utility of plant culture models, translation of cellular findings to the plant-scale is hindered in current culture systems. These limitations are, in part, because culture systems fail to recapitulate physical aspects of the natural cellular environment. This work investigates the role of extra-cellular mechanical and chemical influences such as scaffold stiffness, hormone concentrations, media pH, and cell density on cell development and growth patterns. Early results indicate that tuning of biomechanical and biochemical cues leads to cell growth which deviates from typical culture morphologies and better resembles natural plant tissue structures.

New analytical methods and measurement metrics were developed to monitor cell enlargement, elongation, and differentiation in response to altered culture conditions. Through factorial design of experiments, optimal conditions for maintenance of long-term cell viability or elevated differentiation rates have been identified. Maps of cell response over a range of extracellular conditions allows for tuning of plant cell models to allow for the exhibition of desired physiological compositions. With the aid of these new data maps, plant tissues which are traditionally difficult to access or study in real-time can be better replicated for study in the laboratory setting.



▲ Figure 1: Zinnia elegans cells (a) shortly after isolation from leaves; cells exposed to varied growth conditions may grow into patterns of (b) bulbous, cell aggregates, or (c) uncoordinated, elongated cells.

FURTHER READING

- A. L. Beckwith, J. T. Borenstein, and L. F. Velásquez-García, "Monolithic, 3D-printed Microfluidic Platform for Recapitulation of Dynamic Tumor Microenvironments," *J Microelectromech Syst.*, DOI: 10.1109/JMEMS.2018.2869327.
- A. L. Beckwith, L. F. Velásquez-García, and J. T. Borenstein, "Microfluidic Model for Evaluation of Immune Checkpoint Inhibitors in Human Tumors," *Advanced Healthcare Materials*, DOI: 10.1002/adhm.201900289.

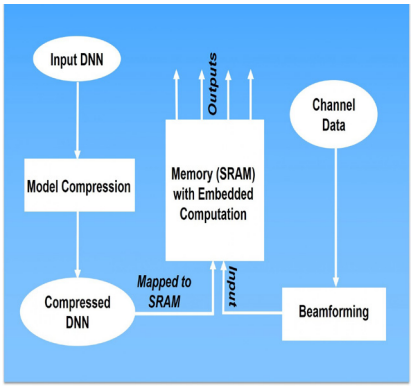
Conformable Ultrasound Patch with Energy-efficient In-memory Computation for Bladder Volume Monitoring

K. Brahma, L. Zhang, V. Kumar, A. P. Chandrakasan, C. Dagdeviren, A. E. Samir, Y. C. Eldar
Sponsorship: Texas Instruments

Continuous monitoring of urinary bladder volume aids management of common conditions such as post-operative urinary retention. Urinary retention is prevented by catheterization, an invasive procedure that greatly increases urinary tract infection. Ultrasound imaging has been used to estimate bladder volume as it is portable, non-ionizing, and low-cost. Despite this, ultrasound technology faces fundamental challenges limiting its usability for next generation wearable technologies. (1) Current ultrasound probes cannot cover curved human body parts or perform whole-organ imaging with high spatiotemporal resolution. (2) Current systems require skilled manual scanning with attendant measurement variability. (3) Current systems are insufficiently energy-efficient to permit ubiquitous wearable device deployment.

We are developing an energy-efficient body contour conformal ultrasound patch capable of real-time bladder volume monitoring. This system will incorporate (1) deep neural network- (DNN) based segmentation algorithms to generate spatiotemporally accurate bladder volume estimates and (2) energy-efficient static random-access memory (SRAM) with in-memory dot-product computation for low-power segmentation network implementation. We aim to develop platform technology embodiments deployable across a wide range of health-monitoring wearable device applications requiring accurate, real-time, and autonomous tissue monitoring.

We are training a low-precision (pruned and quantized weights) DNN for accurate bladder segmentation. DNNs are computation-intensive and require large amounts of storage due to high dimensionality data structures with millions of model parameters. This shifts the design emphasis towards data movement between memory and compute blocks. Matrix vector multiplications (MVM) are a dominant kernel in DNNs, and In-Memory computation can use the structural alignment of a 2D SRAM array and the data flow in matrix vector multiplications to reduce energy consumption and increase system throughput.



▲ Figure 1: The flowchart of an energy-efficient system implementing a compressed segmentation network using SRAM designed for in-memory dot product computation.

FURTHER READING

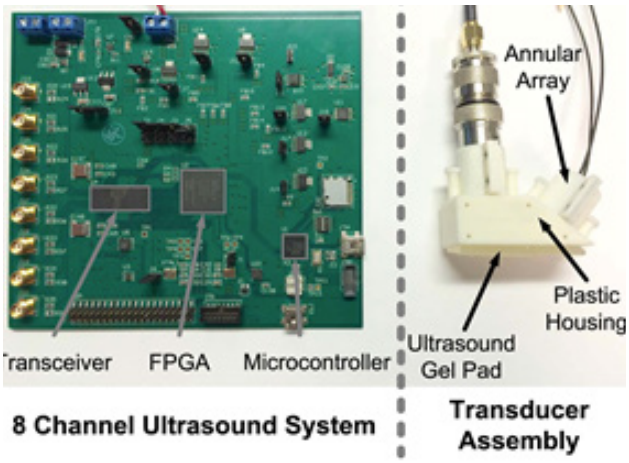
- C. M. W. Daft, "Conformable Transducers for Large-volume, Operator-independent Imaging," *2010 IEEE International Ultrasonics Symposium*, pp. 798-808, 2010.
- R. J. V. Sloun, R. Cohen, and Y. C. Eldar, "Deep Learning in Ultrasound Imaging," arXiv, vol. 1907, p. 02994, 2019.
- A. Biswas and A. P. Chandrakasan, "Conv-RAM: An Energy-efficient SRAM with Embedded Convolution Computation for Low-power CNN-based Machine Learning Applications," *2018 IEEE International Solid - State Circuits Conference - (ISSCC)*, pp. 488-490, 2018

Arterial Blood Pressure Estimation Using Ultrasound Technology

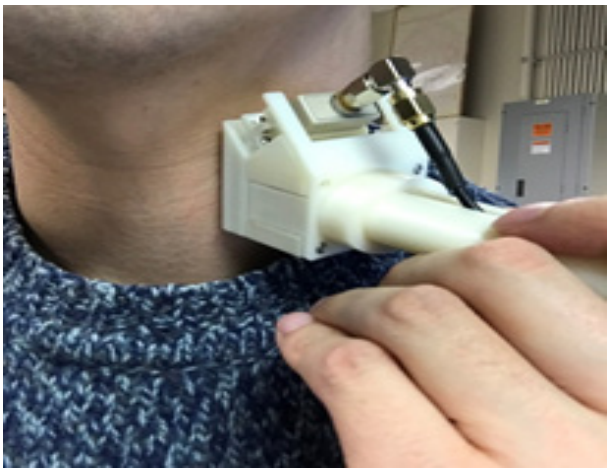
A. Chandrasekhar, C. G. Sodini, H.-S. Lee
Sponsorship: MEDRC-Philips, MIT J-Clinic, CICS

Hypertension, or high blood pressure (BP), is a major risk factor for cardiovascular diseases. Doctors prefer monitoring BP waveforms of ICU patients as the morphology and absolute values of these signals help to assert the cardiovascular fitness of the patient. At present, doctors use invasive radial catheters to record these waveforms. Invasive transducers are inconvenient and can be painful and risky to the patient. Hence, we are developing an algorithm to estimate BP waveforms using non-invasive ultrasound measurements at the brachial and carotid arteries.

Ultrasound probes are a commonly used sensing modality for non-invasive cardiovascular imaging. For instance, doctors use a linear array transducer to image superficial blood vessels like the brachial or the carotid artery. These multifunctional probes can record the lumen area waveform of these arteries and measure the velocity of the blood. In this project, we will record the aforementioned signals with a commercial ultrasound probe and a custom-designed probe (see Figure 1) and use the physics of the arterial pulse wave transmission to estimate the shape and absolute values of the pressure waveform. The pressure waves originating from the heart traverse the arterial wall with a velocity commonly referred to as pulse wave velocity (PWV). According to the physics of the arterial pulse wave transmission, we can calculate PWV from the ultrasound signals. Compliance and pulse pressure of the pressure waves in the artery may be obtained using the Bramwell-Hill equation. Finally, absolute values of the pressure will be derived using a combination of a transmission line model of the artery and machine learning algorithms.



▲Figure 1: Final design of the ultrasound based probe.



▲Figure 2: Ultrasound transducer placed above the carotid artery.

FURTHER READING

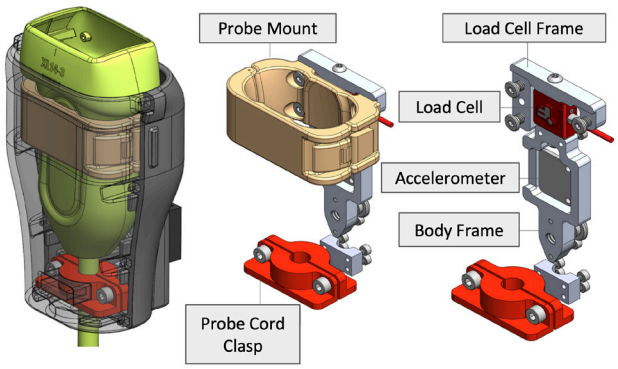
- J. Seo, "Noninvasive Arterial Blood Pressure Waveform Monitoring using Two-element Ultrasound System," *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, vol. 62, no. 4, pp. 776-784, 2015.

Superficial Blood Vessel Lumen Pressure Measurement with Force-coupled Ultrasound Image Segmentation and Finite-element Modeling

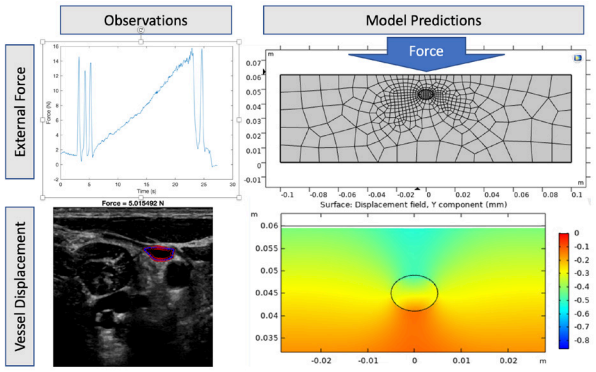
A. Jaffe, I. Goryachev, B. Anthony
Sponsorship: MEDRC-Philips

Blood pressures of arteries and veins are valuable indicators of cardiovascular health. Systolic and diastolic arterial pressure can be obtained in vivo noninvasively and accurately with a blood pressure cuff on one of the limbs. However, no noninvasive means to evaluate lumen pressure in veins exists other than visual assessment of the internal jugular vein, which often requires ample skill to execute despite its inaccuracy. What is more, venous pressure is constantly evaluated in the context of congestive heart failure in determining diuretic treatment. Heart failure cardiologists face the difficult decision between ordering an invasive test with plenty of inherent risk or noninvasively but inaccurately evaluating jugular venous pressure.

Our group has developed a force-coupled ultrasound probe attachment, providing the ability to measure the force applied by an ultrasound probe for each image obtained. We can segment a superficial blood vessel of fewer than 5 cm of depth and without bone between it and the skin to track its deformation in response to external force applied by the ultrasound probe. Furthermore, we can create a forward finite-element model of a blood vessel cross section to predict vessel deformation in response to the known force applied. We can nest this forward model into a combined iterative inverse model with the observed force and vessel deformation to optimize over the lumen pressure by comparing predicted deformation to observed deformation. This method has the potential to noninvasively and accurately derive sampled arterial and venous pressure waves.



▲Figure 1: CAD modeling of the casing made for the Philips XL14-3 xMATRIX ultrasound transducer. The surface of the ultrasound probe contacts the skin, where the force is translated to the load cell.



▲Figure 2: Top left: Force recording as a function of time by the force-coupled ultrasound probe. Bottom left: Segmented internal jugular vein image under ~ 5 N of force. Top right: Finite element mesh of a simple vein and surrounding tissue forward model. Bottom right: Y-component of distributed displacement in millimeters including the vein in the center.

FURTHER READING

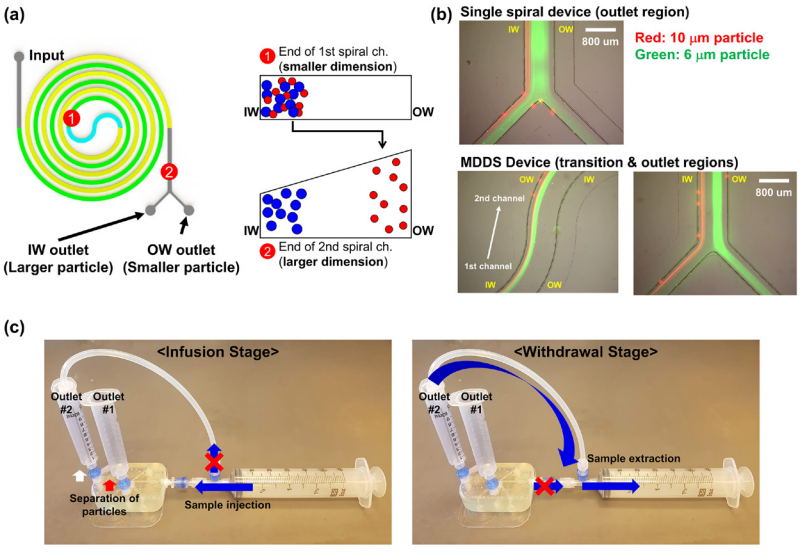
- M. W. Gilbertson and B. W. Anthony, "Force and Position Control System for Freehand Ultrasound," *IEEE Transactions on Robotics*, vol. 31, no. 4, pp. 835-49, Jun. 2015.
- A. M. Zakrzewski, A. Y. Huang, R. Zubajlo, and B. W. Anthony, "Real-time Blood Pressure Estimation from Force-measured Ultrasound," *IEEE Transactions on Biomedical Engineering*, vol. 65, no. 11, pp. 2405-16, Oct. 2018.

Development of Fully-automated and Field-deployable Sample Preparation Platform Using a Spiral Inertial Microfluidic Device

H. Jeon, J. Han
Sponsorship: NIH, Ohana Bioscience

Sample separation is a key step in sample preparation to isolate target analytes from interferents in the biofluid sample for a particular analysis. As the current standard, centrifugation and affinity-based (labeling) methods or their combination are used for sample separation. Although those methods themselves are straightforward, they are labor-, energy-, and time-intensive and require large volumes of sample (on the order of 1 mL) and well-trained operators; expensive labeling reagents should be employed for the labeling methods. More importantly, the centrifugation process and cell labeling can cause damage of sample (e.g., ex vivo cell activation), which leads the challenges in assessing the host's immune response or leukocyte functions correctly.

To overcome these limitations, we propose a new type of spiral cell-sorting process using a multi-dimensional double spiral (MDDS) device, where particles are concentrated through a first smaller-dimensional spiral channel and subsequently separated through a second, larger-dimensional spiral channel (Figure 1a). Because of the initial focusing in the first spiral channel, particle dispersion can be significantly decreased, and smaller particles can be effectively extracted into the outer-wall side of the channel, resulting in increase of separation resolution (Figure 1b). To obtain a more purified and concentrated output, we also developed a new recirculation platform based on a check-valve that allows only one-way flow. In the platform, the separated output can be extracted back into the input syringe by the withdrawal motion of a syringe pump and processed again through the MDDS device by the infusion motion of a syringe pump, resulting in higher purity and concentration (Figure 1c). The developed platform can be operated in a fully-automated or even hand-powered manner with a great separation performance. Therefore, we expect that the developed platform could provide an innovative sample preparation solution for point-of-care analyses and diagnostics.



▲ Figure 1: (a) Schematic diagram of operation of the MDDS device. (b) Movement of particles having 6- and 10-μm diameters in the MDDS device compared to the single spiral device. (c) Check-valve-based recirculation method.

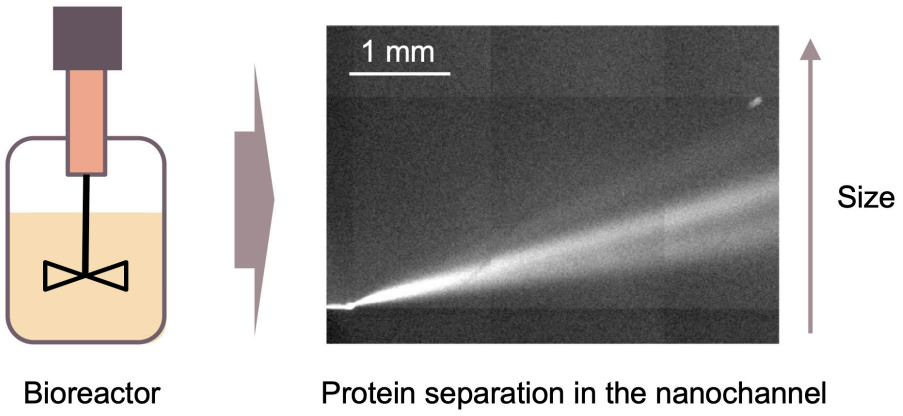
Nanofluidic Monitoring of the Quality of Protein Drugs During Biomanufacturing

T. Kwon, Z. Sun, J. Han
Sponsorship: U.S. Food and Drug Administration, SMART

Biologics are drugs produced from any biological source (e.g., mammalian cells, bacteria, yeast). Biologics include recombinant therapeutic proteins, vaccines, monoclonal antibodies, and other living cells. Because of their high effectiveness and reduced complications, biologics can be used to treat many complex conditions, such as cancers and autoimmune disorders, and are transforming modern medicine. Biologics are typically produced through a biomanufacturing process including large-scale bioreactor cultivation, purification, and quality checks. Quality checking is critical during this process; quality deviation can significantly compromise drug efficacy and safety.

To ensure the quality of biologics, quality control laboratories at manufacturing sites routinely use conventional analytical technologies, such as liquid chromatography and mass spectroscopy. Most analytical technologies require (1) labor intensive manual sample preparation, (2) large sample volume, and (3) technical expertise from scientists/technicians. In addition, these techniques have limited data throughput due to offline and discontinuous analysis. To overcome these limitations, micro/nanofluidics can be used to monitor critical quality attributes during biomanufacturing. With the advantages of easy automation, continuous-flow, and small sample volume, micro/nanofluidic technologies can produce a large amount of quality data for improved quality control and understanding of biologics. Previously, our group introduced a new nanofluidic device for continuous-flow multi-parameter quality analytics. Recently, this nanofluidic device was integrated with continuous biomanufacturing to monitor protein size in a fully automated, continuous, online manner (Figure 1).

We are expanding the capability of our nanofluidic device to monitor other critical quality attributes such as binding affinity and glycosylation of monoclonal antibodies during biomanufacturing. With optimization of the monitoring system, we aim to achieve "real-time" and "multi-modal" quality analytics. This nanofluidic analytics is expected to improve the safety and efficiency of biomanufacturing in the future.



▲ Figure 1: The example of protein quality monitoring using the nanofluidic device during biomanufacturing. The proteins produced from the bioreactor can be fed into the device after protein labeling and denaturation and separated based on size continuously.

FURTHER READING

- S. H. Ko, D. Chandra, W. Ouyang, T. Kwon, P. Karande, and J. Han, "Nanofluidic Device for Continuous Multiparameter Quality Assurance of Biologics," *Nature Nanotechnology*, vol. 12, no. 8, pp. 804–812, May 2017.
- T. Kwon, S. H. Ko, J.-F. P. Hamel, and J. Han, "Continuous Online Protein Quality Monitoring during Perfusion Culture Production Using an Integrated Micro/Nanofluidic System," *Analytical Chemistry*, vol. 92, no. 7, pp. 5267–5275, Mar. 2020.

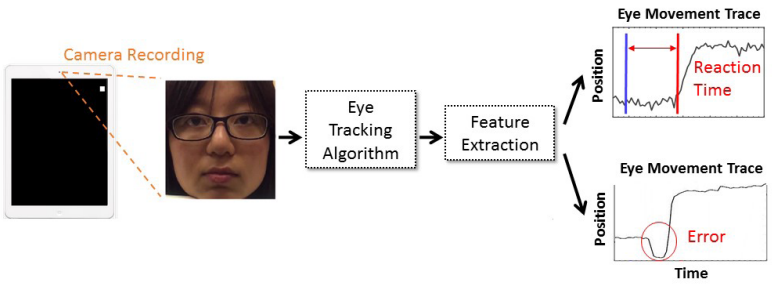
Measuring Eye Movement Features Using Mobile Devices to Track Neurodegenerative Diseases

H.-Y. Lai, G. Saavedra-Peña, C. G. Sodini, T. Heldt, V. Sze
Sponsorship: MIT Quest for Intelligence (SenseTime), MIT-IBM Watson AI Lab

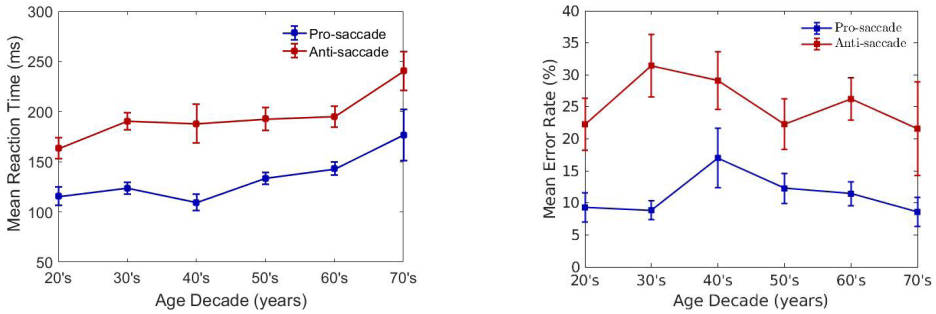
Current clinical assessment of neurodegenerative diseases (e.g., Alzheimer's disease) requires trained specialists, is mostly qualitative and is commonly done only intermittently. Therefore, these assessments are affected by an individual physician's clinical acumen and by a host of confounding factors, such a patient's level of attention. Quantitative, objective and more frequent measurements are needed to mitigate the influence of these factors.

A promising candidate for a quantitative and accessible diseases progression monitor is eye movement. In the clinical literature, an eye movement is often measured through a pro/anti-saccade task, where a subject is asked to look towards/away from a visual stimulus. Two features are observed to be significantly different between healthy subjects and patients: reaction time (time difference between a stimulus presentation and the initiation of the corresponding eye movement) and error rate (the proportion of eye movements towards the wrong direction). However, these features are commonly measured with high-speed, IR-illuminated cameras, which limits the accessibility. Our goal is to develop a novel system that measures these features outside of the clinical environment.

Previously, we showed we can accurately measure reaction time using iPhone cameras, by combining a deep convolutional neural network (CNN) for gaze estimation with a model-based approach for saccade onset determination. We showed that there is significant intra- and inter-subject variability in reaction time, which highlights the importance of individualized tracking. We have since developed an app to facilitate data collection and include error rate measurement. With a large amount of data, we can validate the effect of age on these features and identify confounding factors, leading to a better understanding of relationship between eye movement features and disease progression. By facilitating repeat measurements, our framework opens the possibility of quantifying patient state on a finer timescale in a broader population than previously possible.



▶ Figure 1: Eye movement features measurement pipeline. We record the subject with the frontal camera of an iPad. We process the video with an eye tracking algorithm and calculate reaction time and error rate.



▲ Figure 2: Relationship between age and eye movement features.

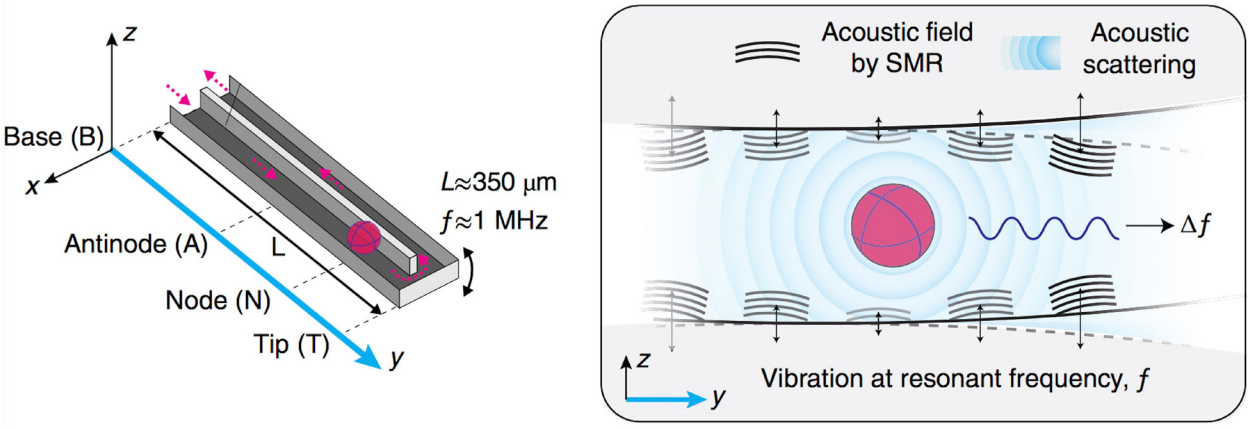
FURTHER READING

- H.-Y. Lai, G. Saavedra-Peña, C. G. Sodini, V. Sze and T. Heldt, "Measuring Saccade Latency Using Smartphone Cameras," in *IEEE Journal of Biomedical and Health Informatics*, vol. 24, no. 3, pp. 885-897, 2020.
- H.-Y. Lai, G. Saavedra-Peña, C. G. Sodini T. Heldt, and V. Sze, "Enabling Saccade Latency Measurements with Consumer-grade Cameras," in *Proceedings of the IEEE International Conference on Image Processing (ICIP)*, pp. 3169-3173, 2018.
- G. Saavedra-Peña, H.-Y. Lai, V. Sze, and T. Heldt, "Determination of Saccade Latency Distributions Using Video Recordings from Consumer-grade Devices," in *Proceedings of the IEEE Engineering in Medicine and Biology Conference (EMBC)*, pp. 953-956, 2018.

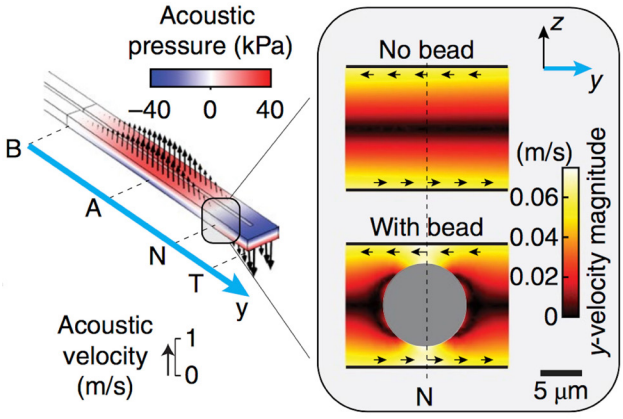
Noninvasive Monitoring of Single-cell Mechanics by Acoustic Scattering

J. H. Kang, T. P. Miettinen, L. Chen, S. Olcum, G. Katsikis, P. S. Doyle, S. R. Manalis
Sponsorship: NCI

The monitoring of mechanics in a single cell throughout the cell cycle has been hampered by the invasiveness of mechanical measurements. Here we quantify mechanical properties via acoustic scattering of waves from a cell inside a fluid-filled vibrating cantilever with a temporal resolution of < 1 min. Through simulations, experiments with hydrogels, and the use of chemically perturbed cells, we show that our readout, the size-normalized acoustic scattering (SNACS), measures stiffness. To demonstrate the noninvasiveness of SNACS over successive cell cycles, we used measurements that resulted in deformations of < 15 nm. The cells maintained constant SNACS throughout interphase but showed dynamic changes during mitosis. Our work provides a basis for understanding how growing cells maintain mechanical integrity and demonstrates that acoustic scattering can be used to noninvasively probe subtle and transient dynamics.



▲ Figure 1: Schematic of the suspended microchannel resonator (SMR) with a particle flowing through the embedded fluidic channel. Acoustic scattering causes a resonant frequency shift at the node of an SMR.



▲ Figure 2: Acoustic pressure (color-coded according to the key) and acoustic velocities (arrows) in the SMR from simulations. The zoomed-in schematic on the right shows magnitudes of y-acoustic velocities with and without a polystyrene bead at the node. Black arrows indicate the directions of y-acoustic velocities.

FURTHER READING

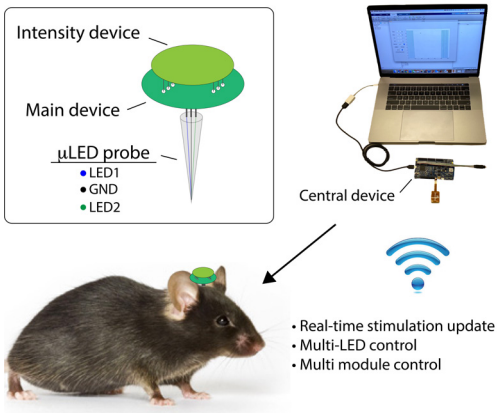
- J. H. Kang, T. P. Miettinen, L. Chen, S. Olcum, G. Katsikis, P. S. Doyle, and S. R. Manalis. "Noninvasive Monitoring of Single-cell Mechanics by Acoustic Scattering," *Nature Methods*, vol. 16, no. 3, pp. 263-269, 2019.

Modular Optoelectronic System for Wireless, Programmable Neuromodulation

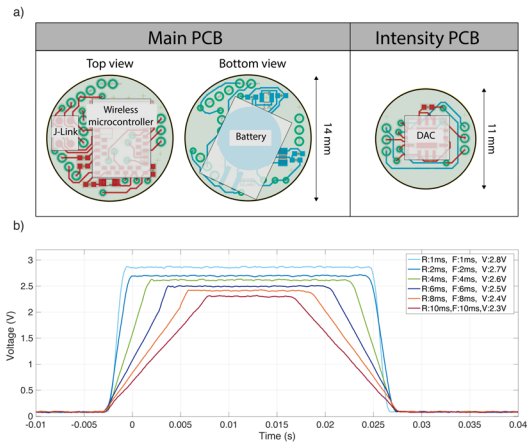
S. Orguc*, J. Sands*, A. Sahasrabudhe, P. Anikeeva, A. P. Chandrakasan
Sponsorship: Delta Electronics

Optogenetics is a technique that uses visible light stimulation to activate or inhibit neurons genetically modified to express light-sensitive proteins from the microbial rhodopsin family. It offers light-sensitive opsin proteins to the region of interest and provide advantages such as cell type specificity, millisecond temporal precision, and rapid reversibility. Furthermore, compared to the electrical stimulation, it causes negligible electrical perturbation to the environment, which enables simultaneous electrical recording while stimulating a region of interest. The stimulation of the targeted neurons can be achieved using lasers, light-emitting diode (LED)-coupled optical fibers, or wireless μLEDs.

This work presents a modular, light-weight head-borne neuromodulation platform that achieves low-power wireless neuromodulation and allows real-time programmability of the stimulation parameters such as the frequency, duty cycle, and intensity. This platform is composed of two parts: the main device and the optional intensity module (Figure 1). The main device is functional independently; however, the intensity control module can be introduced on demand (Figure 2). The stimulation is achieved through the use of LEDs directly integrated in the custom-drawn fiber-based probes. Our platform can control up to 4 devices simultaneously, and each device can control multiple LEDs in a given subject. Our hardware uses off-the-shelf components and has a plug-and-play structure, which allows for fast turnover time and eliminates the need for complex surgeries. The rechargeable, battery-powered wireless platform uses Bluetooth Low Energy (BLE) and is capable of providing stable power and communication regardless of orientation. This platform presents a potential advantage over the battery-free, fully implantable systems that rely on wireless power transfer, which is typically direction-dependent, requires sophisticated implantation surgeries, and demands complex experimental apparatuses. Although the battery life is limited to several hours, this is sufficient to complete the majority of behavioral neuroscience experiments. Our platform consumes 0.5 mW and has a battery life of 12 hours.



▲ Figure 1: System overview. The platform communicates with the central device for stimulation updates.



▲ Figure 2: a) The PCB design of the main device and the intensity device. b) Programmable intensity control demonstration.

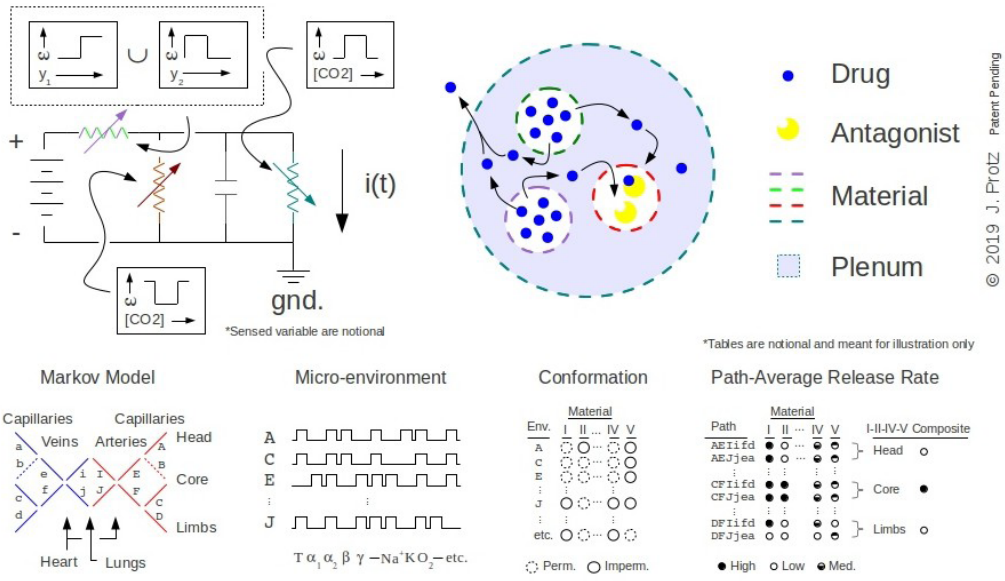
FURTHER READING

- O. Yizhar, L. E. Fenno, T. J. Davidson, M. Mogri, and K. Deisseroth, "Optogenetics in Neural Systems," *Neuron*, vol. 71, no. 1, pp. 9–34, 2011.
- Y. Jia, W. Khan, B. Lee, B. Fan, F. Madi, A. Weber, W. Li, and M. Ghovanloo, "Wireless Opto-electro Neural Interface for Experiments with Small Freely Behaving Animals," *Journal of Neural Engineering*, vol. 15, no. 4, p. 046032, 2018.
- P. Gutruf, V. Krishnamurthi, A. Vazquez-Guardado, Z. Xie, A. Banks, C.-J. Su, Y. Xu, C. R. Haney, E. A. Waters, I. Kandela, "Fully Implantable Optoelectronic Systems for Battery-free, Multimodal Operation in Neuroscience Research," *Nature Electronics*, vol. 1, no. 12, pp. 652–660, 2018.

Nanoparticle for Drug Delivery Using TERCOM

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

Targeted drug delivery has been an area of active investigation for many decades. Some approaches target cell-borne receptors; others use external stimuli such as heat or radio waves to drive spatially-localized release. In this work, particles estimate their own location within the body by correlating their sensed fluid environment (e.g. temp., press., salinity, sugar, pH, etc.) against an embodied map and release on the basis of this estimate; the approach is related to terrain contour matching (TERCOM), a technique used in air navigation. Preliminarily explored particle concepts have included liposomes and proteins (bottom-up fab) and thin films (top-down fab). As envisioned, a mixture of drug-laden and empty permeable vessels, each with a different environmental response, interconnect through a capacitive volume separated from the surroundings by a permeable film. In another envisioned approach, the monomer sequence of polypeptides or other polymers is selected to provide the greatest activity in preferred capillaries, the sequence of experienced environments affecting the conformation. In both, using item response theory, the mixture's or particle's composition is tailored to deliver a larger dose or greater activity to preferred capillaries. 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 as a means of screening candidate compositions for the desired spatial sensitivity. Overall, the work builds on a past effort by the PI and his group to develop nanoparticles which record their experience in DNA. Current efforts focus on the theory of estimating location within the body from vectors of sensed variables and on the development of concepts for particles and chips. The ultimate objective is to demonstrate a nanoparticle that implements TERCOM- or DSMAC-like navigation in the body and a chip that can evaluate its selectivity. The concept is outlined in Figure 1.



▲ Figure 1: Illustration of concept; environmentally sensitive vessels release differentially more drug to capillaries when traveling along preferred paths.

FURTHER READING

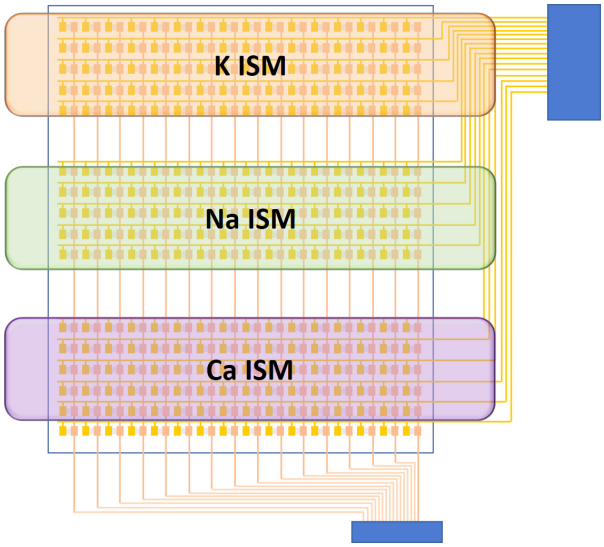
- J. Protz, "Methods and Compositions for Drug Targeted Delivery," (WO/2019/217601) International Patent Application PCT/US2019/031395, May 8, 2019 and "Nano Particle and Apparatus with Targeting," U.S. Provisional Patent Application, June 2, 2020.
- J. Protz, "Biochip for Drug Delivery Using TERCOM," *Massachusetts Institute of Technology, Cambridge, MA, 2019, Microsystems Technology Laboratories Annual Research Report*, 2019, p. 37.
- M. Tanner, E. Vasievich, and J. Protz, "Experimental Demonstration of Lossy Recording of Information into DNA," *Proc. SPIE 7679, Micro- and Nanotechnology Sensors, Systems, and Applications II*, 767920, doi: 10.1117/12.858775; https://doi.org/10.1117/12.858775, May 5, 2010.

Multiplexed Graphene Sensors for Detection of Ions in Electrolyte

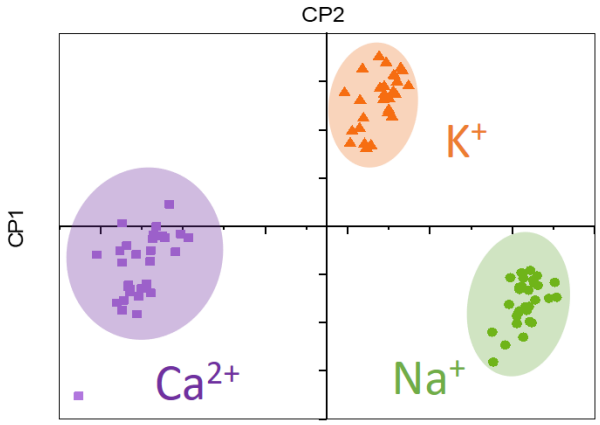
M. Xue, Y. Luo, T. Palacios
Sponsorship: MIT-ARL ISN, NSF CIQM

Nowadays wearable electronics such as sweat sensors targeting key biomarkers have been heavily investigated. However, these electronics typically contain only one sensor for each type of analyte and the performance is evaluated and optimized separately. When applied to real-world application with complex environment, the reproducibility and the reliability of such device is questionable. Here we present a platform technology for multiplexed, large-area sensing array for more reliable measurement. Graphene is used as signal transducer because of its high surface-to-volume ratio and excellent electrical properties. By utilizing a material jetting 3D printer, we can deposit different types of functionalization on specific regions of the array to achieve multiplexed sensing. Here we demonstrate a fully integrated sensing array with three types of ion-selective membranes (ISMs) to achieve detection of sodium, potassium and calcium(see Figure 1). Each types of functionalization covers over 70 working devices and in total more than 200 devices are functional in one array.

The sensor array is first tested with various concentration of solutions contain pure K, Na or Ca ions. All three types of sensors show excellent Nernstian sensitivity towards their target ion and moderate level of sensitivity towards other two types of ions. Using Principle Component Analysis, we can cluster and identify the type of ion as shown in Figure 2. The sensor array is also tested with a set of mixture solutions that are prepared by fixing the concentration of interfering ions while varying concentration of a specific type of ions. Similar clusters are observed indicating the sensor array's ability for identifying which type of ion concentration is changing within a complex mixture solution. This work demonstrates the possibility of achieving highly reliable multiplexed sensing array that can be deployed in complex environments. By collecting data from a statistically significant sample size, we would be able to apply more sophisticated statistical methods or machine learning models to further associate complex mixtures for real-world applications.



▲ Figure 1: Schematics for the sensor array. Three types of ion-selective membranes are deposited to achieve multiplex sensing



▲ Figure 2: Principle component analysis of the sensor array with pure solution of potassium, sodium or calcium ions

FURTHER READING

- C. Mackin et al., "Chemical Sensor Systems Based on 2D and Thin Film Materials," *2D Mater.*, Jan. 2020.
- M. F. Snoeij, V. Schaffer, S. Udayashankar, and M. V. Ivanov, "Integrated Fluxgate Magne-tometer for Use in Isolated Current Sensing," *IEEE J. Solid-State Circuits*, vol. 51, no. 7, pp. 1684–1694, Jul. 2016.
- J. Kim, A. S. Campbell, B. E. F. de Ávila, and J. Wang, "Wearable Biosensors for Healthcare Monitoring," *Nature Biotechnology*, vol. 37, no. 4. Nature Publishing Group, pp. 389–406, Apr. 25, 2019.

Analytical and Numerical Modeling of Microphones for Fully Implantable Assistive Hearing Devices

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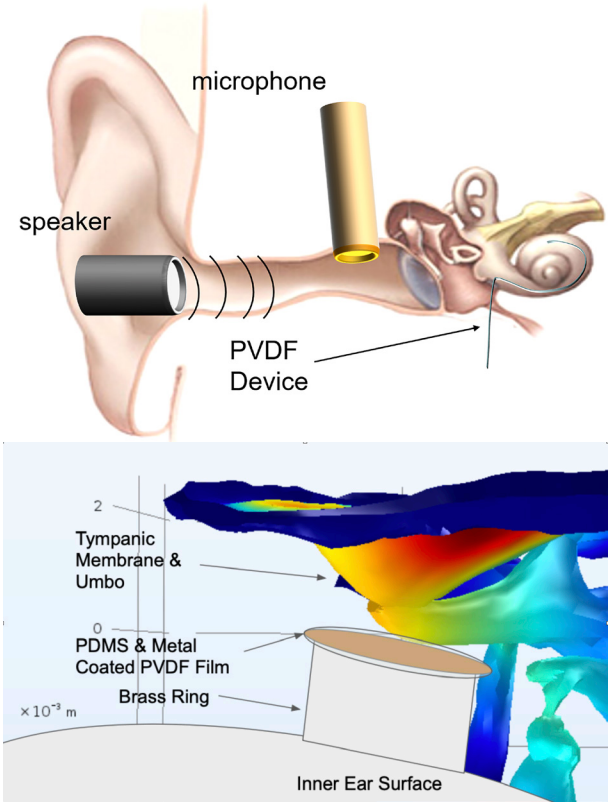
Sponsorship: NIH

Fully implantable cochlear implants (CIs) could take advantage of the natural enhancement of pressure and binaural cues afforded by the outer ear. They would also allow for hearing 24/7 and mitigate the limitations and inconvenience of an external device. To enable a fully implantable CI, we are developing two piezoelectric implantable microphones to be embedded inside a cochlear implant electrode array or the middle ear cavity as shown in Figure 1. The first type senses pressure along the CI array and has a form factor similar to conventional CI arrays. It will not sense at the base of the cochlea where unwanted noise can originate and scarring and bony growth occurs. The latter sits adjacent to the eardrum and senses any umbo displacement. We have built prototypes of such piezoelectric microphones made with polyvinylidene fluoride (PVDF), a piezoelectric film. We have inserted these prototype microphones inside the scala tympani through the round window and in the middle ear cavity. Preliminary tests show promise for achieving good sensitivity, low noise, and wide bandwidth with this structure.

Our approach combines analytical models for design guidance, numerical models for design verification, and bench-test experiments for validation. Analytical modeling is driven by the differential equations of solid mechanics and piezoelectricity. Numerical modeling is enabled by the COMSOL Multiphysics software where we have created simulations of the piezoelectric sensor and use ear mechanics measurements to choose the appropriate boundary conditions.

Progress has been made to advance both prototypes into a practical implantable microphone. We have created a platform for system optimization and started the iterative design process. In the near future we will begin sensing circuit design which will modify the system's overall sensitivity. We will verify numerical model parameters, conduct bench testing imitating cochlear conditions, develop surgical implantation methods, and generate device manufacturing processes



▲Figure 1: Implanted location of the PVDF devices within the cochlea and the middle ear cavity. Top image shows intracochlear experiment with the cochlear hydrophone carried out with prototype devices by S. Park et al. Bottom image shows finite element model of the middle ear with the drum microphone.

FURTHER READING

- P. Z. X. Li, Z. Zhang, S. Karaman, and V. Sze, "High-throughput Computation of Shannon Mutual Information on Chip," *Robotics: Science and Systems (RSS)*, Freiburg, Germany, 2019.
- Z. Zhang, T. Henderson, S. Karaman, and V. Sze, "FSMI: Fast Computation of Shannon Mutual Information for Information-theoretic Mapping," *International Conference on Robotics and Automation (ICRA)*, Montreal, Canada, 2019.