

# 5<sup>th</sup> Annual Symposium

October 2, 2015  
BioScience Research Collaborative

Organizers:

Behnaam Aazhang, Ph.D., Rice University  
Nitin Tandon, M.D., University of Texas Health Science Center at Houston  
Valentin Dragoi, University of Texas Health Science Center at Houston  
Dora Angelaki, Ph.D., Baylor College of Medicine  
Rob Raphael, Ph.D., Rice University  
Caleb Kemere, Ph.D., Rice University  
Jacob Robinson, Ph.D., Rice University  
Melissa S. Thompson, Ph.D., Gulf Coast Consortia

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## 5<sup>th</sup> Annual NeuroEngineering Symposium

Friday, October 2, 2015  
BioScience Research Collaborative (BRC)

*Unless otherwise noted, proceedings will take place in the Auditorium.*

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9:00 AM	<i>Welcome and Introduction</i>
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9:05 AM	<u>Keynote Address I</u> Session Chair: Jacob Robinson, Rice University <b><i>The Novel Neurotechnologies</i></b> Rafael Yuste, Columbia University
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10:05 AM	<i>Poster Session I: Odd Poster Numbers (Event Space)</i>
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	<u>Short Talks, Session I</u> Session Chair: Caleb Kemere, Rice University
10:50 AM	<b><i>How you can get lost in your own backyard with a bad map: Impaired engagement of positional memory following chemogenetic disruption of place field stability</i></b> Joanna Jankowsky, Baylor College of Medicine
11:25 AM	<b><i>Opto-Analytical Sensing, Imaging and Stimulation (OASIS)</i></b> Wei-Chuan Shih, University of Houston
12:00 PM	<b><i>Hippocampal Replay Correlates with Memory Retrieval in Inhibitory Avoidance Task</i></b> Chun-Ting Wu, Baylor College of Medicine
<hr/>	
12:15 PM	<i>Lunch (Event Space)</i>
<hr/>	
	<u>Short Talks, Session II</u> Session Chair: Nitin Tandon, University of Texas Health Science Center at Houston
1:15 PM	<b><i>Population Inference for Functional Brain Connectivity</i></b> Genevera Allen, Rice University
1:50 PM	<b><i>Seizure Detection via Autonomic Signatures of Epilepsy: Closing the Loop</i></b> Shivkumar Sabesan, Cyberonics
2:25 PM	<b><i>It's about time</i></b> Harel Shouval, University of Texas Health Science Center at Houston
3:00 PM	<b><i>The Social Networks of Neural Progenitor Cells</i></b> Arun Mahadevan, Rice University
<hr/>	
3:15 PM	<i>Poster Session II: Even Poster Numbers (Event Space)</i>
<hr/>	
4:00 PM	<u>Keynote Address II</u> Session Chair: Valentin Dragoi, University of Texas Health Science Center at Houston <b><i>Tools for Mapping and Fixing the Brain</i></b> Ed Boyden, Massachusetts Institute of Technology
<hr/>	
5:00 PM	Closing Remarks and Awards
5:15 PM	Reception (Event Space)



**Rafael Yuste, M.D., Ph.D.**

Professor, Department of Biological Sciences and Department of Neuroscience  
Investigator, Howard Hughes Medical Institute  
Co-Director, Kavli Institute for Brain Science  
Columbia University and Columbia University Medical Center

The goal of our laboratory is to understand the function of the cortical microcircuit. The cortex constitutes the larger part of the brain in mammals. In humans it is the primary site of mental functions like perception, memory, control of voluntary movements, imagination, language and music. No accepted unitary theory of cortical function exists yet; nevertheless, the basic cortical microcircuitry develops in stereotyped fashion, is similar in different cortical areas and in different species, and has apparently not changed much in evolution since its appearance. At the same time, the cortex participates in apparently widely different computational tasks, resembling a "Turing machine".

Because of this, it is conceivable that a "canonical" cortical microcircuit may exist and implement a relatively simple, and flexible, computation.

We attempt to reverse-engineer the cortical microcircuit using brain slices from mouse neocortex as our experimental preparation. The techniques applied are electrophysiology, anatomy, and a variety of optical methods, including infrared-DIC, voltage- and ion-sensitive dye imaging with confocal, two-photon and second harmonic microscopy. We also use laser uncaging, biolistics, electroporation, electron microscopy and numerical simulations, and make extensive use of genetically modified mouse strains.

We focus on two major questions:

(1) What is the function of dendritic spines? Spines are an essential element in cortical circuits and are still poorly understood. Two-photon microscopy has enabled functional studies of dendritic spines and has shown that they compartmentalize calcium because of their morphological features and local calcium influx and efflux mechanisms. Recent data indicates that spines can serve as electrical compartments and that can linearize input summation, indicating that cortical circuits could be essentially linear networks. Also, spines exhibit rapid morphological plasticity, raising the possibility that the function of the spine, or the synapse, is equally dynamic.

(2) What are the multicellular patterns of activity under spontaneous or evoked activation of the circuit? It is still unknown if adult cortical neurons respond individually, or if there are multicellular units of activation that may represent a functional state of the circuit, such as an attractor. Optical imaging of populations of cells make it possible to visualize circuit dynamics, deduce its potential circuit architecture and explore if canonical microcircuits exist. We are also interested in understanding how epileptic seizures can recruit apparently normal cortical circuits.

Rafael Yuste was born in Madrid, where he attended the Ramiro de Maeztu High School and studied Medicine at the Universidad Autonoma and the Fundacion Jimenez Diaz Hospital. After a brief period in Sydney Brenner's group at the LMB in Cambridge, he did his Ph.D. work with Larry Katz in Torsten Wiesel's laboratory at Rockefeller University in New York. He then moved to Bell Labs, where he was a postdoctoral student of David Tank and also worked with Winfried Denk. In 1996 he joined the Department of Biological Sciences at Columbia University, where he is currently a tenured professor. In 2005 he became an HHMI Investigator and co-director of the Kavli Institute for Brain Circuits at Columbia. Since 1997 he has also been a visiting researcher in Javier DeFelipe's laboratory at the Cajal Institute in Madrid. Yuste is responsible for the introduction of calcium imaging as a method to monitor the activity of neuronal circuits and is interested in the structure and function of cortical circuits, the biophysical properties of dendritic spines, and the pathophysiology of epilepsy.



**Ed Boyden, Ph.D.**

Leader, Synthetic Neurobiology Group  
Associate Professor and AT&T Chair, MIT Media Lab and McGovern Institute,  
Departments of Biological Engineering and Brain and Cognitive Sciences  
Co-Director, MIT Center for Neurobiological Engineering  
Massachusetts Institute of Technology

Complex biological systems like the brain present a challenge: their molecular building blocks are organized with nanoscale precision, but support physiological processes and computations that occur over macroscopic length scales. To enable the understanding and fixing of such complex systems, we are creating tools that enable molecular-resolution maps of large scale systems, as well as technologies for observing and controlling information processing in such systems. First, we have developed a method for imaging large 3-D specimens with nanoscale precision. We embed a specimen in a swellable polymer, which upon exposure to water expands isotropically in size, enabling conventional diffraction-limited microscopes to do large-volume nanoscopy. Second, we have collaboratively developed strategies to image fast physiological processes in 3-D with millisecond precision, and used them to acquire neural activity maps throughout small organisms. Third, we have collaboratively developed robotic methods to automate single cell analysis in living mammalian brain. Finally, we have developed a set of genetically-encoded reagents, known as optogenetic tools, that when expressed in specific neurons, enable their electrical activities to be precisely driven or silenced in response to millisecond timescale pulses of light. In this way we aim to enable the systematic mapping, dynamical observation, and control of complex biological systems like the brain.

Ed Boyden is a professor of Biological Engineering and Brain and Cognitive Sciences at the MIT Media Lab and the MIT McGovern Institute. He leads the Synthetic Neurobiology Group, which develops tools for analyzing and repairing complex biological systems such as the brain, and applies them systematically to reveal ground truth principles of biological function as well as to repair these systems. These technologies, created often in interdisciplinary collaborations, include expansion microscopy, which enables complex biological systems to be imaged with nanoscale precision, optogenetic tools, which enable the activation and silencing of neural activity with light, and optical, nanofabricated, and robotic interfaces that enable recording and control of neural dynamics. He has launched an award-winning series of classes at MIT that teach principles of neuroengineering, starting with basic principles of how to control and observe neural functions, and culminating with strategies for launching companies in the nascent neurotechnology space. He also co-directs the MIT Center for Neurobiological Engineering, which aims to develop new tools to accelerate neuroscience progress.

His group has hosted hundreds of visitors to learn how to use neurotechnologies, and he also regularly teaches at summer courses and workshops in neuroscience, and delivers lectures to the broader public (e.g., TED (2011); World Economic Forum (2012, 2013)). Ed received his Ph.D. in neurosciences from Stanford University as a Hertz Fellow, where he discovered that the molecular mechanisms used to store a memory are determined by the content to be learned. Before that, he received three degrees in electrical engineering, computer science, and physics from MIT. He has contributed to over 300 peer-reviewed papers, current or pending patents, and articles, and has given over 300 invited talks on his group's work.



**Joanna L. Jankowsky, Ph.D.**

Assistant Professor, Department of Neuroscience, Baylor College of Medicine

Neurophysiological studies over the last 40 years have elucidated a complex network of spatially-tuned neurons spanning the temporal lobe. Despite this remarkable progress, the field has yet to demonstrate a functional relationship between these place-responsive neurons and spatial learning or recall. We used a novel chemogenetic silencing system to test how interrupting transmission between entorhinal cortex and downstream hippocampal neurons would impact spatial coding in CA1 and behavioral performance in a spatial recall task. Acute silencing of superficial entorhinal cortex and neighboring pre- and parasubiculum caused global remapping and temporal instability of previously established CA1 place fields. Behavioral testing revealed substantial decay of positional memory after CA1 remapping. Our findings suggest that even in a familiar setting, the neural map provided by spatial tuning of hippocampal neurons remains critical for navigation.

Highlights:

- Transgenic model for temporospatial controlled neuronal silencing via systemic ligand
- Acute silencing of entorhinal cortex causes global disruption of CA1 spatial tuning
- Entorhinal-induced CA1 remapping degrades reference memory in water maze
- Navigation even in a familiar setting appears to require a stable reference map

Dr. Joanna Jankowsky obtained her undergraduate degree in biology from Amherst College (1991) and her Ph.D. in Cellular and Molecular Neuroscience from Caltech (1999). Joanna pursued postdoctoral training in Neuropathology at Johns Hopkins School of Medicine, where she learned to create and characterize mouse models of neurodegenerative disease. In 2003, Joanna returned to Caltech - along with her mice - to study Neurophysiology as a Senior Research Fellow. She won the NIH New Innovator Award in 2007 to create a transgenic system for selective neuronal silencing, based on the idea that this approach would inform understanding of circuit dysfunction in Alzheimer's disease. In 2008, she joined the Department of Neuroscience at Baylor College of Medicine, where her laboratory uses the mouse models she's created to elucidate the basic biology of Alzheimer's disease and to explore new therapeutic possibilities. Joanna has been fortunate to have the support of many outstanding scientists in these studies and the work she presents today results from an ongoing collaboration with BCM colleague Daoyun Ji.



**Wei-Chuan Shih, Ph.D.**

Associate Professor, Departments of Electrical and Computer Engineering, Biomedical Engineering and Chemistry, University of Houston

Light-matter interaction can provide rich constitutional information in tissue, cells, and molecules. Our laboratory has developed a broad range of opto-analytical sensing, imaging and stimulation (OASIS) technologies with core innovations in material, device, and instrumentation. In this talk, I will first report some of the light-based technologies and their potentials. I will next present a novel multi-modal neural probe which has the potential to become a platform for light-based techniques to be applied in the deep brain region. Currently, the neural probe has both optical and electrical channels, and is dubbed University of Houston Optrode (UHO). I will discuss the design and fabrication of UHO and show preliminary modeling and experimental results.

Wei-Chuan Shih earned his Ph.D. from MIT Spectroscopy Laboratory/NIH Laser Biomedical Research Center under laser physicist Michael S. Feld, developing novel optical spectroscopy techniques for non-invasive chemical/biomedical sensing and disease diagnosis. He also worked extensively on MEMS design and fabrication. Prior to joining the University of Houston, he was a Schlumberger research fellow, developing optical analysis of hydrocarbon fluids and optical offshore oil spill monitoring. Dr. Shih is an Associate Professor of Electrical & Computer Engineering, Biomedical Engineering, and Chemistry at the University of Houston. He was a MIT Martin Fellow, and received NSF CAREER Award in Biophotonics (2012), inaugural NASA Early CAREER Faculty Award in

Environmental Sensing (2012), UH Award for Excellence in Research and Scholarship (2013), and UH Cullen College of Engineering Faculty Research Excellence Award (2015). His recent PhD graduate was the Best Dissertation Award winner by the Cullen College of Engineering (2014). He has published more than 60 articles in books, journals and conference proceedings, including ~40 peer-reviewed journal papers. He has more than 10 patents, one of which has been licensed. His recent invention, DotLens<sup>SM</sup> Smartphone Microscopy, has been featured on CNBC, HoustonPBS, UH Moment and numerous other media outlets. Besides NSF and NASA, his research is also supported by NIH, DOI, and GoMRI.



**Genevera Allen, Ph.D.**

Assistant Professor, Department of Statistics and Electrical and Computer Engineering, Rice University

Genevera Allen is the Dobelman Family Junior Chair and an Assistant Professor of Statistics and Electrical and Computer Engineering at Rice University. She is also a member of the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital and Baylor College of Medicine where she holds a joint appointment. Dr. Allen received her PhD in statistics from Stanford University (2010), under the mentorship of Prof. Robert Tibshirani, and her bachelors, also in statistics, from Rice University (2006).

Dr. Allen's research focuses on developing statistical methods to help scientists make sense of their 'Big Data' in applications such as high-throughput genomics and neuroimaging. Her work lies in the areas of modern multivariate analysis, graphical models, statistical machine learning, and data integration or data fusion. The recipient of several honors including the David P. Byar Young Investigator travel award and the International Biometric Society's Young Statistician Showcase award, she also represented the American Statistical Association at the Coalition for National Science Funding on Capitol Hill in 2013 and 2014, and has had her research highlighted on the House floor in a speech by Congressman McNerney (D-CA). In 2014, Dr. Allen was named to the "Forbes '30 under 30': Science and Healthcare" list. She is also the recipient of research grant awards from the Ken Kennedy Institute for Information Technology, the National Science Foundation (NSF), and joint initiatives between NSF and the National Institutes of Health. Dr. Allen also serves as an Associated Editor for the Electronic Journal of Statistics and Biometrics.

Outside of work, Dr. Allen is a patron of the Houston Symphony and Houston Grand Opera and is involved with several arts organizations throughout Houston. She also enjoys traveling, Texas craft beers, and practicing viola.



**Shivkumar Sabesan, Ph.D.**

Senior Principal Research Scientist, Group Lead, Cyberonics

Shivkumar (Shiv) Sabesan holds a Senior Principal Research Scientist position at Cyberonics where he directs the research, design and development of algorithms for diagnosis and closed-loop Neurostimulation therapy for epilepsy. He leverages 12+ years of experience in the area of devices and algorithms for neural engineering applications expanding Cyberonics' strategic focus beyond VNS Therapy to broader device-based solutions for epilepsy. Prior to joining Cyberonics, Shiv was a Research Assistant Professor in the Department of

Neurology at the Barrow Neurological Institute in Phoenix, Arizona, where his work focused on seizure detection/prediction/localization and closed-loop control of epilepsy and traumatic brain injury using vagus nerve stimulation (VNS) and deep brain stimulation (DBS). His work has resulted in over 60 publications and 10 patents. In addition, Shiv has also been a Co-Founder of two successful startup companies in the epilepsy space. A recognized expert in his field, Shiv serves as an active member of FDA's panel on model based medical device design and more recently, scientific reviewer for the NIH/DARPA BRAIN initiative grants. Shiv received his Ph.D. in electrical engineering from Arizona State University.

Epilepsy is the third most common neurological disorder after stroke and Alzheimer's and affects at least 50 million people worldwide. It is characterized by recurrent seizures. Seizures are associated

with a sudden development of synchronous firing in a massive group of neurons, and its duration can range from seconds to minutes. Seizures cause temporary disturbances in brain functions such as motor control, cognition, responsiveness. If seizures are untreated, permanent and extensive damage in the brain may occur. Patients with drug refractory epilepsy seek alternative solutions such as surgical resection, ketogenic diet and neuromodulation. Vagus nerve stimulation, or VNS Therapy®, is an FDA approved neuromodulation treatment that is used as an adjunctive therapy to pharmacology and has been demonstrated to reduce seizure frequency in a multicenter, randomized controlled trial as well as in subsequent single center trials. Recent developments in the area of closed-loop neuromodulation via detection of seizures using electrical activity of the brain have shown promise. In this context of closed-loop neuromodulation devices for epilepsy, seizure detection via detection of autonomic signatures in order to deliver therapy i.e. to close the loop provides a viable alternative to detection of abnormal electrical activity of the brain (w.r.t. low power hardware development and signal processing, long-term safety profile). This talk will discuss the design and development of automated seizure detection algorithms/sensors using autonomic signatures of epilepsy, their performance compared to brain-based seizure detection algorithms and the potential clinical benefit that such an approach may have for patients with epilepsy.



**Harel Shouval, Ph.D.**

Associate Professor, Department of Neurobiology and Anatomy, University of Texas Health Science Center at Houston

Animals and humans are able to intuitively compute interval times on scales from less than a millisecond to hours. The mechanisms for parts of this range are known, but not much is known about the mechanisms for computing temporal intervals at the range between hundreds of milliseconds to the several seconds. Recent surprising experimental results indicate that such computations might be present already in primary sensory cortex. But the circuit level mechanisms for representing and learning these temporal intervals have not been characterized.

On the basis of recent experimental results we have developed theory of how temporal intervals are calculated and learned in cortical circuits. We propose that interval time calculations are implemented in a recurrent network, and that such a network can learn temporal intervals that an order of magnitude larger than the intrinsic network time constants. I will describe both a stochastic spiking implementation of the network, and a one-dimensional dynamical mean-field theory that agrees well with the simulations. The mean-field theory provides intuition of how the network functions and what are its limitations.

Further, we propose that the network can learn these time constants using reinforcement based learning algorithm. I will describe two alternative models of the learning-rule and present very recent experimental evidence that supports one of these models.



## **Hippocampal Replay Correlates with Memory Retrieval in Inhibitory Avoidance Task**

Wu C-T<sup>1</sup>, Kemere C<sup>2</sup>, Ji D<sup>3</sup>

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2. Department of Electrical and Computer Engineering, Rice University, Houston, Texas
3. Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, Texas

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The hippocampus is intricately involved in the initial encoding and subsequent retrieval of episodic memories. Experiments involving recording the activity of ensembles of individual rodent hippocampal neurons have linked a particular pattern of activity – the expression of the place cell map – to the initial encoding process. However, how this neural ensemble expresses memory retrieval remains unclear. Recent data report that sequences of place cell activity exhibited while animals explore are subsequently reactivated in quiescent periods in a time compressed fashion. Such "awake replay" has been hypothesized as a neural substrate of memory retrieval. However, evidence to support the hypothesis that replay corresponds to the actual experience of remembering is limited, mainly because the reward-based tasks used in the past do not have a clear behavioral report of that memory retrieval has taken place. Here, after rats acquired fear memory by receiving mild foot shocks at a specific zone (shock zone) of a linear track, we analyzed hippocampal place cell activity when the animals were placed back to the track and displayed an apparent memory retrieval behavior: approaching and turning away from the shock zone. We found that before the animals turned away and avoid the shock zone, the place cells associated with the shock zone were reactivated. This reactivation occurred with awake replay of the place cell sequences representing the path ending around the shock zone. The result reveals the role of hippocampal place cells in contextual fear memory and provides strong evidence for the function of awake replay in memory retrieval. By demonstrating that hippocampal replay is a substrate for memory retrieval, we lay the foundation for therapeutic interventions that might target these neural patterns, either to dampen episodic memories, i.e., in PTSD, or to enhance them in cases of memory impairment. Rodent models provide a number of tools for neural circuit perturbation, and we are now developing tools to apply these perturbations with the high temporal precision required to target hippocampal replay representing specific memories.

Funding Sources:  
Simons Foundation  
NIH Grant EY020676

## **The Social Networks of Neural Progenitor Cells**

Mahadevan A<sup>1</sup>, Robinson JT<sup>1,2</sup>, Qutub AA<sup>1</sup>

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### **Objective**

Cell-cell communication among neural progenitor cells (NPCs) is essential for proper self-organization of the nervous system, a topic of great interest in regenerative medicine. Graph theory and network analysis have been used to study the functional connectivity of mature neuronal circuits but not developing networks, in which different modes of cell-cell communication dominate, and proximity of cell bodies plays a key role in neural cell fate. The objective of this study is to quantitatively describe the spatial organization of progenitor cell bodies at different stages of neuronal differentiation in order to uncover the role of cell-cell communication during neural network formation.

### **Methods**

hESC-derived neural progenitor cells were stimulated to differentiate through withdrawal of bFGF from culture medium and imaged continuously for up to 14 days. Time-lapse image sequences were processed using custom-written algorithms, and spatial proximity of cell bodies was used to create graph representations of NPC spatial topology. Numerous graph-based metrics such as clustering, modularity and motif counts were evaluated in NPC graphs in order to quantify the spatial organization of cells at different time points. Functional maturation of NPCs was analyzed using whole-cell patch clamp electrophysiology and immunocytochemistry.

### **Results**

We show that our graph-based metrics capture the characteristic geometric arrangement of cells in neural rosette-like structures seen at early time points of differentiation. We find that the cell bodies of NPCs self-organize into smaller, more tightly connected cliques during differentiation, and uncover relationships between network efficiency and modularity in the networks. Furthermore, our graph-based metrics distinguish cultures at different stages of functional maturation, which shows that spatial organization of cells is indicative of differentiation stage.

### **Conclusions**

Our results demonstrate the utility of graph theory-based analysis in studying the spatial organization of developing NPC communities. The insights gained from this study can be used to further our understanding of how progenitor cells self-organize into functional neural networks.

This work was supported by an NSF IGERT Neuroengineering Training Grant.

Morning Poster Session: Odd Poster Numbers  
Afternoon Poster Session: Even Poster Numbers

*(in alphabetical order by presenting author's last name)*

Poster  
No.

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## The Facilitation of Rapid Temporal Processing by Ion Channel Cooperativity Suggests Coordination through Membrane Electromechanics

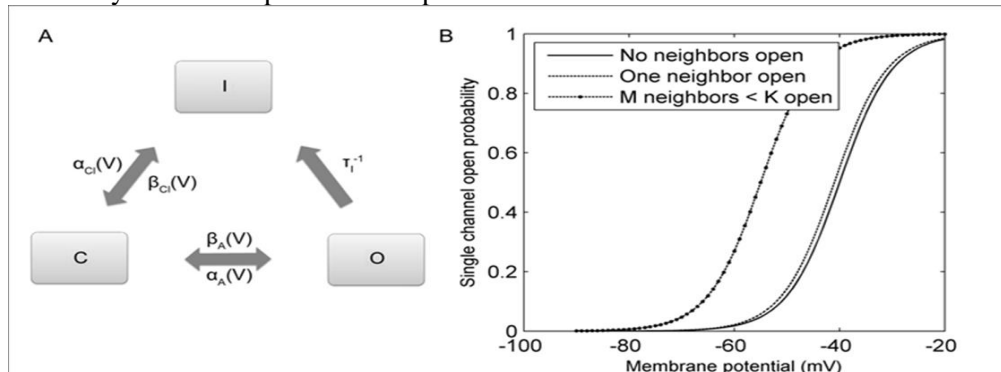
Mussie K. Araya<sup>1</sup> and William E. Brownell<sup>1,2</sup>

1 Molecular Physiology and Biophysics Baylor College of Medicine, Houston, Tx, USA

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The ability of neuronal populations to encode rapidly varying stimuli and respond quickly is crucial for basic neuronal computations, such as coincidence detection, grouping by synchrony, spike-timing-dependent plasticity and boosting the processing speed of neuronal networks. Theoretical analyses have linked these abilities to the fast-onset dynamics of action potentials (APs). While Hodgkin Huxley theory fails to explain the speed of AP onset, a computational analysis invoking cooperative activation of Na<sup>+</sup> ion channels at the axon initial segment (AIS) does. The near simultaneous gating of ion channels results in a hyperpolarized shift in the population activation curve producing a rapid AP initiation. State transition scheme of a single sodium channel and model results for inter-channel cooperativity are shown in figure 1. The biophysical basis for intra-channel coupling is unknown and Ca<sup>++</sup> or GTP based signaling is too slow. Axons show dimensional changes during the AP production and membrane tethers have been shown to generate electromechanical force at frequencies up to 10 kHz. It is also known that membrane mechanics modulate ion channel function. **We propose an electromechanical mechanism for cooperative gating of sodium channels at the AIS.** Specifically, the rapid modulation of membrane tension by membrane potential can provide a fast and direct mechanism for inter-channel coupling.



**Figure 1. A.** Gating scheme identified experimentally by Aldrich et al. suggests Na<sup>+</sup> channel has three states; open (O), closed (C) and inactivated (I). Transition from closed to open states and vice versa occur with rates  $\alpha_A(V)$  and  $\beta_A(V)$ . The transition from closed to inactivated states and vice versa occur with rates  $\alpha_C(V)$  and  $\beta_C(V)$ . The coupling between channels shifts the activation curve of each channel towards more hyperpolarized values. **B.** In the coupled model, the opening of neighboring channels shifts the single channel activation curve to more hyperpolarized potentials (by value proportional to the number of coupled neighboring channels M) such that the probability of channel opening at a given membrane potential is increased.

We combined optical tweezers and voltage clamp apparatus to pull membrane tethers from the cells in order to make precise measurement of membrane electromechanical force generation. We pulled membrane tethers from the soma and AIS of hippocampal pyramidal neurons to probe the membrane-cytoskeleton adhesion strength. We find stronger strength of membrane-cytoskeleton adhesion in the AIS suggesting ion channels are firmly anchored to the actin based cytoskeleton at AIS. Cooperative activation is highly dependent on the density of Na<sup>+</sup> channels. The clustering of Na<sup>+</sup> channels at the AIS by the actin cytoskeleton can set the stage for cooperative gating between ion channels (figure 1B). Once a tether is formed, the electromechanical force is measured by applying a sinusoidal voltage and measuring the tether pulling force. Testing for concomitant variation between electromechanical force and channel function to determine the membrane's role in ion channel gating will be discussed.

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## Micro-machined optical fiber with multiple stimulation sites for optogenetics applications

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Optogenetics is an emerging technique that can control genetically photosensitized neuron activity using visible light. Due to the excellent light guiding properties and simplicity, many existing demonstrations utilized optical fibers as the means of light delivery [1]. However, an optical fiber can only deliver light to the tip, limiting to a single stimulation site per fiber. Therefore, more fibers are needed for more stimulation sites. A number of approaches have been proposed to realize multi-site stimulation based on out-of-plane micro-waveguide arrays and in-plane micro-waveguide probes [2]. Although these designs are capable of providing multi-site stimulation, they do not change the fundamental aspect of single stimulation site per waveguide. Over the past few years, our group has developed simple light-guide integrated tetrode probes [3], as well as thin-film microelectrodes patterned directly on optical fiber [4], where the fundamental aspect of single stimulation site per light guide was not challenged. Here we present a new fabrication method to create multiple windows along a single optical fiber using laser micromachining. We show that individual oval shaped windows along the fiber can deliver >10% of the total power transmitted through the fiber. In addition, the orientation of the window can be easily controlled by rotating the fiber, thereby enables 3-dimensional light delivery using a single fiber. Monte Carlo modeling [5] is used to predict light delivery inside brain tissue for this fiber probe.

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## Sorting Cells Based on Electrophysiology: Challenges and Opportunities

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The brain's complex structures contain highly specialized cells of multiple types packed in close proximity. Because of this high degree of heterogeneity, studies of cell types, or exploration of subpopulations within a given region, must be performed with single-cell resolution. The selection of a small number of cells from a mixed population forms the basis of many exploratory genetic screens, as well as protein engineering efforts. Selecting small numbers of specific cells for such research most commonly involves the use of a resistance marker or a fluorescent tag. Such technologies are undoubtedly effective, but are unable to meet the needs of some experiments that involve primary cells and experiments looking for phenotypes with unknown genetic markers. Crucially, these techniques are unable to select cells based on dynamic features. Studies of neurons often require functional assays of one of neurons' most important attributes - their excitability. A neuron's electrical response to a given stimulus is unavoidably dynamic, and so screens for electrophysiological phenotypes are incompatible with common screening techniques. This leads to a need for electrophysiological assays well equipped for handling mixed populations of cells, with the added ability to link the electrophysiological phenotype of primary cells to a phenotype. By screening the responses of a population of olfactory neurons, for example, screening cells for electrical responses to certain odorants would permit the untangling of the many genes and proteins involved in the sense of smell. Demand for single cell analysis of this kind extends beyond the brain- electrical properties of cells are essential for cellular metabolism, communication, and controlling the action potentials generated by other excitable cells such as cardiomyocytes.

For over 40 years, most studies of electrical properties of single cells have relied upon measurements performed using manual patch clamp electrophysiology. Conventional patch clamp provides high fidelity recordings and precise control of membrane potential, but is time consuming and challenging, requiring specialized equipment and a trained experimentalist. As a result, studies requiring electrophysiology on many cells often resort to measurements using less accurate proxies for membrane potential, such as calcium imaging. Conductive nanowire electrodes have been shown to be able to record intracellular signals from cells, and electric field stimulation is commonly used to induce electrical activity in cells. To permit precise studies of electrical properties across many individual cells, or to isolate cells based on their electrophysiological traits for other tests, we have combined these technologies into a microfluidic chip to allow sorting of cells based on electrophysiology. We combine the flexibility of microfluidics with the scalability and precision provided by semiconductor fabrication techniques in a microfluidic chip. Our device incorporates suspended nanowire electrodes for electrical recordings and stimulation, along with planar electrodes for field stimulation when simultaneous stimulation and recording is desired. A cell of interest is guided using pressure-controlled flow to the electrode site, where it is held while the desired tests are performed. The cell can then be released and transported to an output well for postprocessing.

Starting from the mixed population in a tissue sample, evaluating single cells based on their electrophysiology permits discovery of specialized cell types, allows interrogation of difficult-to-isolate subpopulations, and provides information regarding population distributions in different brain regions.

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## Calibration of Visual Stimuli in a Virtual Reality System for Rodents

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Virtual reality systems provide a very flexible method of presenting visual stimuli and enable investigation of navigation in virtual spaces that are much larger than the actual space available in the laboratory. Using a virtual reality system to present visual stimulus to head-fixed animals also enables the use of neural recording and neural imaging systems that are difficult or impossible to use in freely moving animals. These neural monitoring systems enable the investigation of the neural representations of the physical world in awake, behaving animals that are engaged in complex navigational tasks. Virtual reality systems have long been used in neuroscientific experimentation to engage primates in navigational behavior, however, attempts to get rodents to navigate virtual reality environments were unsuccessful until a virtual reality system was designed which accounted for the much larger field of view of the murine visual system [1]. A rodent's visual field covers nearly the entire half sphere above the horizon and a large portion of the half sphere below it [2]. To design a virtual reality system that can cover such a large field of view, researchers resort to either the use of multiple displays or projectors or to the use of curved mirrors for increasing the visual field covered by a single projector. The difficulty in using multiple projectors lies in aligning them accurately and the use of multiple displays has in some cases resulted in behavior which suggests that the animal is navigating the real space occupied by the displays rather than the virtual space shown on them [1]. The use of non-planar mirrors to increase the coverage of a single projector results in distortion of the visual stimulus, which must be removed by modifying the projected image to account for the geometry of the projection system. The goal of this image modification is to produce viewing angles in the virtual reality system that are identical to those in the virtual world the researchers wish to create. In principle, image modification is the straightforward process of solving a 3-dimensional trigonometry problem to achieve identical viewing angles. In practice the geometry of the system must be known with sub-millimeter precision to achieve identical results. This is difficult to accomplish via measurement because some elements of the system, like the projector's focal point, are not directly observable. Multiple research groups have chosen to use curved mirrors in their murine virtual reality systems to cover the large visual field required [1,3], but none have published a comprehensive method for calibrating these systems or published metrics that quantify the viewing angle errors in their system.

In order to achieve a highly accurate reproduction of viewing angles in our murine virtual reality system, we have developed a camera-based calibration technique that harnesses the information about the geometry of the system contained in multiple photographs to calculate the geometry of the system with sub-millimeter accuracy. Additionally, this method can also be used to quantify the error in viewing angles at any location on our hemispherical display.

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## **Inferring Functional Connectivity of Neural Circuits Using Information Theoretic Causality Measures**

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Neural recording technologies such as voltage sensitive dyes (VSD) have enabled increasingly larger-scale simultaneous recording from neural networks, yet how signals recorded from individual neurons describe neural functions, plasticity and memory in a collective network is still poorly understood. In an attempt to tackle the aforementioned problem, we are applying and developing techniques to infer the underlying neural circuit by performing calculations of causal measures. Synthetic signals are generated by neural networks that are built using individual Hodgkin-Huxley neuronal models. Different estimation algorithms are compared and implemented to extract the stochastic properties of the neural signals. Using these stochastic properties directed information (DI), a causal connectivity measure, is calculated between each pair of neurons. Together with the connectivity, other biophysical properties, such as the sign of a synaptic connection (i.e., excitatory or inhibitory) can also be inferred. Our initial results from using context tree weighting (CTW) estimation combined with DI show that this approach is able of detecting direct connections, eliminating indirect connections, and identifying the types of the synapses and their strength in small-scale realistic neural networks. Once the algorithm is validated using various artificial networks generated by the Hodgkin-Huxley conductance-based neural models, it will be applied to larger-scale real data. The buccal ganglion of *Aplysia* will be used as a small brain test system. This method of combining large-scale recording techniques with signal processing tools to construct functional connectomes offers an automated tool to map a neural circuit and the ability to capture changes in synaptic strength due to learning or other behavioral modifications.

## Crossmodal Perceptual Adaptation Implies Neuronal Convergence of Auditory and Tactile Frequency Signals

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We perceive temporal frequency information by audition and touch. Because these modalities reciprocally influence each other in frequency perception, temporal frequency channels appear to be linked across audition and touch. Auditory and tactile perceptual channels may be tied explicitly if common neural populations support auditory and tactile frequency processing. Adaptation paradigms have been used previously to infer neural tuning properties in psychophysical experiments. In a series of psychophysical experiments, we employed a crossmodal frequency adaptation paradigm to test the hypothesis that a common frequency-tuned neural population processes auditory and tactile frequency signals. Participants (n = 20) each performed a tactile frequency discrimination task in 3 experiment sessions. Each session began with an auditory adaptation period (180s) during which the participant received prolonged auditory stimulation (adaptation conditions with bandpass noise stimuli centered at 200 Hz or 400 Hz) or silence (control condition). After initial adaptation, participants performed trials of a 2AFC tactile discrimination task in which they judged which of two vibrations presented sequentially to their finger was perceived as being higher in frequency. Vibration frequencies ranged from 100-300 Hz. We used a generalized linear mixed effects model (GLMM) to test whether auditory adaptation modulated tactile discrimination performance and whether this modulation was frequency-specific. Crossmodal adaptation significantly improved tactile frequency sensitivity when the spectral composition of the noise adaptor overlapped the tactile test frequencies. We implemented a simple and biologically plausible model that represents tactile frequency information with likelihood functions computed from a population of sensory neurons. By allowing auditory adaptation to modify the model's sensory neuron response characteristics, our model reproduced the frequency-specific crossmodal aftereffects. These psychophysical and modeling results support the hypothesis that auditory and tactile signals converge on a common frequency-tuned neural population.

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## Nanoscale Electrophysiology in Intact Small Organisms

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Small animals like *Caenorhabditis elegans* are vital model organisms for understanding fundamental biology. To facilitate versatile, high-throughput experiments in these animals, researchers have made technological advances in areas such as microscopy and microfluidics to provide novel platforms for behavioral and anatomical assays. However, electrophysiological measurements in these tiny animals remain slow with little versatility. Conducting patch clamp electrophysiology currently requires a highly invasive and difficult dissection protocol to expose muscle cells and neurons. Therefore, electrical measurements are limited to one or two cells within individual worms that die within a few minutes. A scalable technology that allows for tailored measurements would set a new paradigm for how electrophysiology is conducted in small model organisms.

To create a new platform for electrophysiology in intact small animals, we developed **nanoscale Suspended Electrode Arrays** (nano-SPEARS). These platinum electrodes (4  $\mu\text{m}$  wide, 3  $\mu\text{m}$  long, 0.08  $\mu\text{m}$  high) horizontally protrude into a microfabricated channel on a silicon chip. By integrating this chip with a microfluidic interface, we flush small organisms into the silicon chamber and tightly immobilize them against the nano-SPEARS. With this method, we circumvent the dissection process and have shown that nano-SPEARS measure body-wall muscle action potentials in completely intact *C. elegans*. In fact, animals remain viable following recordings and we have made the first electrophysiological recordings in *C. elegans* on multiple days.

nano-SPEARS offer two major advantages over conventional electrophysiology methods: scalability and versatility. Scalability has the potential to revolutionize fields currently in need of high-throughput electrophysiology, such as the study of human neurological diseases. To demonstrate how nano-SPEARS can facilitate our understanding of diseases, we made the first phenotypic profiles based on electrophysiology of *C. elegans* models for Amyotrophic Lateral Sclerosis and Parkinson's disease. We also showed that a known neuroprotective drug, clioquinol, rescues healthy electrophysiology in Parkinson's models. Because nano-SPEARS can be used to record from several worms simultaneously, our microchips provide a platform for high-throughput analyses of neurological diseases and potential drug treatments. Finally, nano-SPEAR electrophysiology is highly versatile and can be tailored perform previously impossible experiments. For example, using multiple electrodes, we recorded from multiple sites along the same worm and measured electrical signal propagation down the length of *C. elegans*.

Using nano-SPEARS, we have demonstrated multiple new experimental abilities not possible with conventional electrophysiology. These results firmly establish that nano-SPEAR microchips are the technological advance necessary for adding electrophysiology to the wealth of assays available for small model organisms.

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## Task Learning Promotes Interneuron Circuit Plasticity in the Olfactory Bulb

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Deciphering wiring diagrams of neural circuits is one of the most significant challenges facing neuroscience. In the olfactory bulb circuitry, principle neurons (mitral/tufted cells) make reciprocal connections with local inhibitory interneurons, including granule cells and EPL interneurons. However, our current understanding of the functional patterns of connectivity between these cell types, as well as experience-dependent plasticity of their connectivity maps remains incomplete. By combining acousto-optic deflector based scanning microscopy and genetically targeted expression of Channelrhodopsin-2, we mapped components of olfactory bulb circuitry connectivity in a cell type-specific manner. We found that EPL interneurons receive broader and stronger mitral cell input than granule cells, and that both of these interneuron types exhibit distinct patterns of local connectivity onto mitral cells. Using an olfactory associative learning paradigm, we found that each of these circuits displayed distinct features of experience-dependent plasticity. Whereas the reciprocal connectivity between mitral cells and EPL interneurons were stereotyped, the connections between granule cells and mitral cells were dynamic and adaptive. Together, we show that different interneuron types form distinct connectivity maps and distinct experience-dependent plasticity in the brain circuitry, which may reflect, or determine their functional roles in information processing.

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## Evidence accumulation in dynamic environments

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Decision making through evidence accumulation is a fundamental operation of organisms and ecological groups. Classic experiments explore the decision making process using two-alternative forced-choice tasks, where the truth does not change during a trial. However, the natural world constantly changes. Thus, we study how an optimal observer accumulates evidence when the correct option changes in time. Using sequential analysis, we derive a recursive system for the likelihood of each choice, showing an ideal observer discounts prior evidence at a rate determined by the volatility of the environment. For two choices, nondimensionalization can be used to describe the evidence accumulation process with a single parameter, the information gained over the expected time between switches. For a continuum of options, likelihoods evolve according to a stochastic integrodifferential equation, which can be scaled to represent a probability density function. A key observation is that, for fixed decision interrogation times, observers cannot obtain arbitrarily high accuracy, as one can in the case of an unchanging environment. Developing a neural population model that performs optimal evidence accumulation, we found populations tuned to each option should be coupled by mutual excitation, as opposed to the mutual inhibitory models that perform classic tasks.

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## Information Efficiency of Linear Recurrent Networks

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Brains are replete with recurrent connections, yet attempts to relate neural activity to behaviour have been based mostly on network models that feature minimal interaction between brain areas. In order to understand the implications of recurrent connections for information processing, we assessed the steady-state performance of two recurrently connected populations of neurons in a fine discrimination task using time-invariant stimuli and temporally uncorrelated noise. We considered a simple class of models in which the connectivity matrix was parametrised by a single variable  $k$  that represented the ratio of coupling strength between a pair of neurons from different populations to that from the same population. We found that the performance of the network exhibited a highly nonlinear dependence on the coupling strength  $k$ . Whereas the total information of the network was comparable to that within the individual populations in the weakly coupled regime, there was nearly a ten-fold gain for larger coupling strengths. This increase in information was a direct consequence of an increase in the effective time constant of integration as reflected in the eigenspectrum of the connectivity matrix, thus allowing the network to integrate the incoming signal over longer time periods. In contrast, when response covariance was held fixed, the network information remained independent of coupling strength by construction. The effect of coupling in this latter scenario was instead revealed when the network activity was disrupted by obliterating either of the two populations. Even for networks with only moderately large couplings, the information content of the surviving population exceeded that of the full network: suppressing the activity of one of the populations improved performance! This improvement was once again attributable to a favourable change in the network time constant following withdrawal of inputs from the suppressed population. The above results highlight some key properties of information flow in linear recurrent networks and provide useful tools for interpreting experimental data pertaining to selective inactivation of brain areas commonly carried out in behaving animals.

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## Mechanisms of Seizure Identified from Causal Connectivity Inferred using Directed Information

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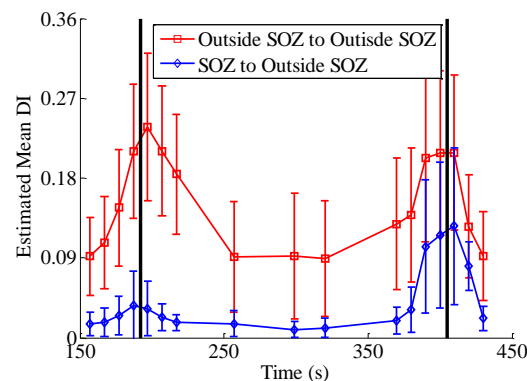
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Epilepsy is a common neurological disorder affecting nearly 1% of the world's population. The current treatments for epilepsy based on medication and surgical resection are not effective. Learning how seizures originate is crucial to develop next generation treatments for epilepsy. We analyzed the changes in causal connectivity over time in five epileptic patients to improve our understanding of seizures. The causal connectivity between electrodes implanted in an epileptic patient is estimated from electrocorticographic (ECoG) recordings using directed information (DI) from multiple shifted time-windows. Figure 1 plots the results of our analysis from a seizure of patient P1. The solid vertical black lines in Figure 1 represent the seizure start and end times as determined by neurologist. In addition, there is no significant seizure activity between 250s and 350s in this seizure. The mean and standard deviation of the average strength of the outgoing connections from all channels outside seizure onset zone (SOZ) and all channels in SOZ to the channels outside SOZ is plotted in Figure 1. The red and blue curves correspond to the connections from electrodes outside SOZ and within SOZ, respectively. It is clear from this figure that the electrodes outside SOZ become more synchronous during seizures implying that seizures occur when the regions outside SOZ become sufficiently hyper synchronous. We also observed a 'trigger' pulse (two small spikes in the blue curve) from the electrodes in SOZ to those outside at the beginning of the seizure activity. These trends are broadly observed in the remaining patients as well. In addition, we present the connections between the inferences made from our dynamic connectivity analysis in human patients and the seizure generation mechanisms observed in animal models of epilepsy. This could be the first step towards development of novel treatments for epilepsy.



**Figure 1: Dynamic causal connectivity of patient 1 inferred using directed information**

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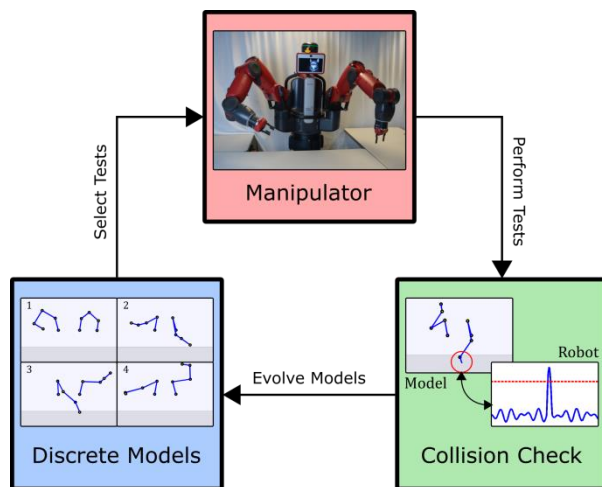
## On Body Schema Acquisition in Traditional Manipulators: Utilizing Collision Predictions and Discrete Model Spaces

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Robots typically need body schema, a representation of the body used during motion, in order to meaningfully interact with the world. From both practical and biological standpoints, it would be desirable if the robot could autonomously acquire any unknown body schema information. To date, a variety of techniques have been proposed which yield some degree of kinematic knowledge; however, these methods involve redundancy or additional sensors, and as such cannot be straightforwardly applied to generic manipulators. In this paper, we specifically address body schema acquisition in rigid serial chains while requiring only joint position measurements. Instead of modifying the robot's structure or sensing capabilities, we leverage collision predictions to direct our search through the discrete space of potential models. Evolutionary algorithms are modified to solve the ensuing combinatorial optimization problem, and a novel test selection algorithm is introduced to improve performance while accounting for joint errors. The resultant process is validated through simulations using a Baxter robot, where two specific applications are considered



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## EEG Source Localization Constrained by Time Varying Functional MRI

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Despite a plethora of research centering on visual stimulus and motor responses, a detailed pathway that links these two has yet to be sufficiently explored. We propose an EEG source imaging approach that utilizes high spatial resolution fMRI in a time-variant, spatially selective manner, to explore the spatial and temporal details of this multiple sequential event-related potential pathway.

During a visual stimulus/motor response EEG/fMRI experiment, a male participant was shown a series of visual stimuli, each belonging to one of two categories: pleasant faces (control, n = 36) and unpleasant faces (target, n = 38). Each stimulus was shown for a period of 10 seconds followed by a 50-second green screen used as a base-line. The subject was asked to squeeze a rubber ball with his right hand for the entire duration the stimulus image was shown only if he preserved the presented face as unpleasant. EEG recording was performed with a sampling rate of 5 kHz with a 64-channel EEG recording system. fMRI scanning was performed separately with the same experimental paradigm. A subject specific Boundary Element Model was created from a T1 MR image. In the present study, we proposed a strategy for EEG source localization using time-variant partial fMRI activation map as constraints. An fMRI activation map was divided into multiple sub-maps, modeled as prior source distributions. Following the frame work of variational free energy [1], EEG data in a given time window was used to select the best fit source priors from the fMRI BOLD mapping. Subsequently, the calculated fMRI prior was used in an fMRI-informed EEG source localization that employed a  $l_2$ -norm minimum norm estimate scheme [2].

The fMRI BOLD activation map showed statistically significant regions of cortical activity during the visual-motor task when the subject responded to the unpleasant-face stimulus (see Figure 1a). The predominantly activated regions were found to be the left motor cortex, bilateral visual cortices, fusiform face areas, supplementary motor areas, and posterior cingulate cortices. More time-specific, localized brain activity was found using the proposed spatiotemporal variant fMRI constraint method when compared to the previous time-invariant fMRI constraint method. The estimated cortical activity matched well with the expected visual and motor brain areas.

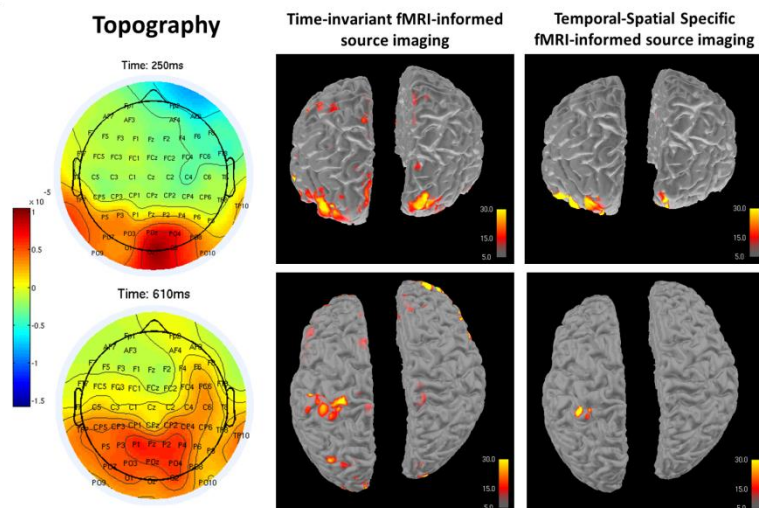


Figure 1. Source reconstruction results for time #1 (top) and time #2 (bottom) using traditional time-invariant fMRI-constraint method (middle); and the proposed temporal-spatial specific fMRI-constraint source localization method (far right). Color scale (arbitrary unit) show 70% activation level as full yellow, and 30% as full red.

## An altered divisive normalization model of autism

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Autism is a neurodevelopmental disorder marked by a diverse set of symptoms including perceptual, social, and cognitive atypicalities. This heterogeneity presents a significant challenge to establishing a comprehensive characterization of the disorder. The widespread effect of the disorder on neural systems suggests that autism may broadly impact neural computations as opposed to isolated systems. As such, we hypothesize that alterations in canonical computations that occur throughout the brain may underlie the behavioral characteristics of autism. Here we focus on one computation in particular, divisive normalization, which balances a neuron's net excitation with inhibition reflecting the combined activity of a population of neurons. Divisive normalization inherently reflects the ratio of neural excitation to inhibition, which is believed to be abnormally elevated in autism. In the present work, we show that an altered divisive normalization signal which elevates the excitatory/inhibitory ratio can account for perceptual findings in autism. Specifically, we develop a neural network model of primary visual cortex (V1) in which individual units are selective for stimulus location and orientation. An increased E/I ratio is simulated in the model by reducing the strength of the inhibitory divisive normalization signal reflecting the population activity. To examine how this alteration might give rise to perceptual autism symptomatology, we simulate two perceptual studies comparing the behavior of typically developing controls and individuals with autism on tasks that strongly engage V1. The first, a motion discrimination task employing stimuli of different sizes and contrasts, revealed reduced surround suppression and overall better discrimination performance in autism for high contrast stimuli, but equivalent performance across the groups at low contrasts. The second, a feature detection task investigating the facilitating effect of an attentional cue, reported a sharper gradient of attention in autism than in controls. Interestingly, we find that the results of both studies could be accounted for by the same alteration in divisive normalization. Our results suggest that the divisive normalization framework can provide novel insights into the neural basis autism and generate hypotheses that are readily testable by psychophysics experiments. In future work, it should be possible to adapt this framework to other sensory modalities as well as more complex operations such as facial processing which require hierarchical processing.

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## Activation of Membrane Protein Piezo1 with Magnetic Nanoparticles

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A main challenge in neurobiology is to modulate specific populations of neurons in the brain with high temporal precision. Current techniques include electrode implantation or optogenetics, both of which involve invasive surgery. Moreover, electrode stimulation lacks specificity and optogenetics is limited in depth due to light scattering. However, magnetic fields can penetrate the brain without damaging any tissues.

Our approach is to engineer a magneto-sensitive channel combining the mechano-sensitive channel Piezo 1 with superparamagnetic iron oxide nanoparticles. We have found based on calculations and experiments in HEK293s that a DC magnetic field of only a few hundred mT creates enough force between nanoparticles to activate Piezo1. We have conjugated these nanoparticles with antibodies that can recognize c-Myc tag inserted in specific regions of the ion channel. We covalently attach nanoparticles functionalized with carboxyl groups to the amine groups of the antibody using carbodiimide reaction. We have inserted affinity tags in extracellular domains of the Piezo1 channel to which we can attach these functionalized nanoparticles. We have identified several binding sites on the Piezo1 protein that are accessible to magnetic nanoparticles and where the protein tag does not disrupt the gating mechanism. The activation of the nanoparticle-attached Piezo1 is assessed using patch clamp electrophysiology or calcium imaging. The magnetic field is generated by an electromagnet capable of generating fields up to 300mT.

By expressing Piezo1 in specific neurons, we aim to use this approach to wirelessly activate deeper structures of the brain for behavioral neuroscience. Future application for this technology includes treatment of Parkinson disease, epilepsy or PTSD.

## Stochastic Motion of Bumps in Planar Neural Fields

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We analyze the effects of spatiotemporal noise on stationary pulse solutions (bumps) in neural field equations on planar domains. Neural fields are integrodifferential equations whose integral kernel describes the strength and polarity of synaptic interactions between neurons at different spatial locations of the network. Fluctuations in neural activity are incorporated by modeling the system as a Langevin equation evolving on a planar domain. Noise causes bumps to wander about the domain in a purely diffusive way. Utilizing a small noise expansion along with a solvability condition, we can derive an effective stochastic equation describing the bump dynamic as two-dimensional Brownian motion. The diffusion coefficient can then be computed explicitly. We also show that weak external inputs can pin the bump so it no longer wanders diffusively. Inputs reshape the effective potential that guides the dynamics of the bump position, so it tends to lie near attractors which can be single points or contours in the plane. Perturbative analysis shows the bump position evolves as a multivariate Ornstein–Uhlenbeck process whose relaxation constants are determined by the shape of the input. Our analytical approximations all compare well to the statistics of bump motion in numerical simulations.

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## General Inference by Neural Population Codes

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Behavioral experiments on humans and animals suggest that the brain performs probabilistic inference to interpret its environment. We present a general-purpose, neurally plausible implementation of such inference operations. This implementation is based on distributed neural representations of probabilistic graphical models. A probabilistic graphical model is a representation of a joint probability distribution that uses a graph to express the conditional dependency structure between random variables. For general graphs of this sort, Loopy Belief Propagation (LBP) is a 'message-passing' algorithm that can be used to perform approximate inference. LBP uses local marginalization and integration operations to perform inference efficiently with local operations, even for complex models. In LBP, a message from one node to a neighboring node is a function of incoming messages from all other neighboring nodes, except the recipient. This exception renders it neurally implausible because neurons must send the same output to all target neurons. Interestingly, however, LBP can be reformulated as a sequence of Tree based Re-Parameterization (TRP) of the graphical model. Each iteration of TRP involves re-factorizing a portion of the probability distribution corresponding to an acyclic subgraph. This formulation still implicitly has the message exclusion problem, but this can be circumvented using a dynamical system with a separation of time-scales for certain variables. We show that a network of Probabilistic Population Codes (PPCs) can both represent the messages and synthesize the information they contain, so that they implement the TRP updates for inference on a general graph. PPCs are a statistically efficient neural representation of probability distributions that are capable of implementing marginalization and cue-integration in a biologically plausible way. Our simulations indicate that the performance of the PPC-based network implementation of TRP updates for probabilistic inference is comparable to the direct evaluation of LBP, and thus provides a compelling substrate for general inference in the brain.

## Characterization Of Light Adaptation Induced Alterations In Mouse Retinal Ganglion Cell Spatiotemporal Tuning

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**Objective:** Reverse correlation methods such as spike-triggered averaging consistently identify the spatial center in the linear receptive fields (RFs) of retinal ganglion cells (GCs). However, the spatial antagonistic surround observed in classical experiments has proven more elusive. Tests for the antagonistic surround have relied on models that make simplifying assumptions such as space-time separability and radial homogeneity/symmetry. We circumvented these, along with other common assumptions, and sought to develop a more accurate model which would account for the antagonistic surround and inseparability predicted to exist in GCs.

**Methods:** Flat-mount retinal preparation (N=16) from 12-14 week-old dark adapted C57/B6 mice were placed onto a multi-electrode array (MEA) for multicellular recording. Receptive fields (RFs) were mapped at both photopic and scotopic (3 orders of magnitude dimmer) mean light levels for 90 minutes using a binary white noise checkerboard stimulus with 50 micrometer checkerboard squares presented at 15 Hz. Spike-triggered averages (STA) were used to identify the average space-time stimulus preceding a spike for our population of GCs (N=805) at each light level. Subsequent model fitting allowed identification of properties for the space-time RF. Unless otherwise specified GCs were compared using a Wilcoxon rank sum test. To identify ON and OFF GCs we used principal components (PC) analysis of the temporal STA at the peak spatial location and clustered cells based on the first two PCs.

**Results:** We observed a linear antagonistic surround in 754 of 805 mouse GCs. By characterizing the RF's space-time structure, we found the overall linear RF's inseparability could be accounted for both by differences between the center and surround and differences within the surround. By using a model with five RF space-time subcomponents we were able to parameterize properties of the RGC while maintaining space-time inseparability. We then probed the space-time STA with a model prediction of the surround we identified considerable asymmetry in the RF surround.

**Conclusions:** We removed many common assumptions in characterization of mouse RGC space-time RFs and found the antagonistic surround was significant in the linear receptive field. Moreover, with a novel modeling approach we were able to characterize the properties of this surround. Using this characterize we identified inhomogeneity and asymmetry that up to now had not been known. This modeling approach allowed us to identify five different receptive field subcomponents that could represent distinct circuit components. Further studies need to be carried out to determine the anatomic correlates but these results shed new light on the spatiotemporal organization of GC linear RFs and highlight a major contributor to its inseparability.

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Research for Preventing Blindness

## Screening Mechanosensitive Ion Channels in Microfluidics

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Microfluidic devices can be used to test mechanical stresses on isolated cells in suspension provided the cells are expressing proteins that can respond to each of these stresses. We are mutating and functionalizing mechanosensitive channels to confer magnetic sensitivity to neurons. This will require rapidly testing large quantities of modified mechanosensitive channels, mainly mutations of the cation selective channel Piezo-1.

Using suspended cells expressing these mechanosensitive channels in combination with fluorescent calcium reporters, we are able to monitor calcium influx due to shear stress. This shear stress can be modulated with alterations to pressure, viscosity, and shape of microfluidic channels. By creating a converging-diverging microfluidic channel, we are able to expose the cell to a large shear stress force while observing the fluorescent response within a single field of view. Shear stress can be characterized with computational fluid dynamics and preliminary results show levels compatible with Piezo-1 activation. Cells transfected with Piezo-1 and GCaMP, a genetically encoded calcium indicator, have shown observable fluorescent responses within the microfluidic channel. We have also begun testing mutants of Piezo-1 containing c-Myc tags for magnetic functionalization.

In addition to testing known constructs and protein mutations made in the lab, microfluidics offer a unique advantage in that mixed populations of cells can be sorted based on the phenotype. Various areas of the brain have been reported to express mechanosensitive ion channels. We could therefore use our device to screen mixed populations of neurons isolated from the brain, sort according to response, and analyze expression to elucidate mechanosensitive cellular mechanisms.

This research was supported by funding from the Defense Advanced Research Projects Agency (DARPA).

## Phase Coupling as a Mechanism for Information Transfer Between the Superior Temporal and Visual Cortices During Speech Perception

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Speech perception is a multisensory process that uses both auditory information from the talker's voice and visual information from the talker's mouth. Wernicke's area, especially posterior superior temporal cortex, is known to be a critical brain region for both auditory and visual speech perception. How does visual speech information travel from occipital lobe to temporal cortex?

To answer this question, we recorded electrocorticographic (ECoG) data from patients with temporal lobe epilepsy implanted with grids and strips of subdural electrodes. Subjects were presented with audiovisual speech under two conditions: clear auditory and clear visual (AV) and clear auditory and noisy visual (AVn). Noise was introduced into the visual speech by blurring the image. To ensure attention, subjects reported the word spoken by the talker. Performance was the same in both conditions (98% for both AV and AVn).

To measure neural activity, we decomposed the ECoG response into different frequency bands. The spectral power in the high gamma band (70-150 Hz) for each electrode was used as an index of neural activity. Large increases in gamma power were observed in both visual and temporal cortex. To understand information transfer between the regions, we examined phase coupling of the ECoG response, as it measures coordinated firing between regions; low frequencies are thought to be especially important for coupling distant brain regions. We found significant phase coupling between visual and temporal cortex in the delta frequency band (1 – 4 Hz), significantly greater for clear than noisy speech (AV vs. AVn, 0.28 vs. 0.22,  $p = 0.0024$ , paired t-test).

Phase coupling was observed between visual cortex and superior temporal cortex during visual speech perception, suggesting that it may serve as a neural mechanism for information transfer. Phase coupling was higher when the stimulus contained more visual information (AV) and weaker when it contained less visual information (AVn). The increase in phase coupling preceded the high gamma activity that indicates single-neuron firing, suggesting that it serves to gate information transfer between distant brain regions.

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## Optimal Inference in Feedforward Networks

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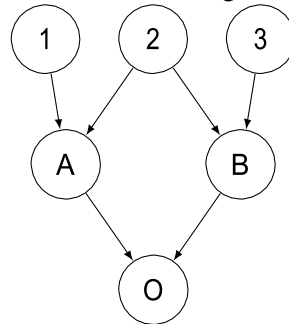
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We investigate optimal inference in a model of information propagation in a network of locally Bayes optimal agents. An example of such a network is given by



We assume that a subsets of agents in the top row make a measurement of a common parameter  $s$ . Each agent communicates their belief about the parameter to other agents in the network, according to the geometry. These agents then optimally combine this input information. Their belief about  $s$  is therefore the posterior distribution over  $s$  obtained from part of the network. For example, if the beliefs of agents in the first layer are described by Gaussian distributions, agents in the second layer perform a linear operation. Finally, the observer in the last layer integrates all information, accounting for all possible correlations due to redundancies in the information that has been received by agents upstream. Every agent has knowledge of the structure of the network and tries to make the best estimate possible.

We find that even if information is integrated in such a locally optimal way, agents in the final layer are not always able to obtain a globally optimal estimate of  $s$ . For example, in the case above, an observer who had access to all the agents in the first layer will generally make a better estimate than the last agent. We provide sufficient and necessary conditions so that the agents in such networks can make optimal estimates, and derive asymptotic results about when these conditions hold as network sizes diverge.

## Imaging Voltage Dynamics *In Vivo* With Improved Genetically Encoded Indicators

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Nervous systems encode information as spatiotemporal patterns of membrane voltage transients, so accurate measurement of electrical activity has been of long-standing interest. Recent engineering efforts have improved our ability to monitor membrane voltage dynamics using genetically encoded voltage indicators. In comparison with electrophysiological approaches, such indicators can monitor many genetically defined neurons simultaneously; they can also more easily measure voltage changes from subcellular compartments such as axons and dendrites. Compared with genetically encoded calcium indicators, voltage sensors enable a more direct, accurate, and rapid readout of membrane potential changes. However, several challenges remain for *in vivo* voltage imaging with genetically encoded indicators. In particular, current voltage sensors are characterized by insufficient sensitivity, kinetics, and/or brightness to be true optical replacements for electrodes *in vivo*.

As a first step towards addressing these challenges, we developed a new voltage indicator, ASAP2, that further improves upon the sensitivity of the fast voltage sensor Accelerated Sensor of Action Potentials 1 (ASAP1). We also describe here how ASAP2 can report stimulus-evoked voltage responses in axonal termini of the fly visual interneuron L2. In this system, ASAP sensors enabled the monitoring of neural activity with greater temporal resolution than three recently reported calcium and voltage sensors. Overall, our study reports novel voltage indicators with improved performance, illustrates the importance of sensor kinetics for accurately reporting neural activity, and suggests L2 as an *in vivo* platform for benchmarking neural activity sensors. We anticipate that ASAP2 will facilitate current and future efforts to understand how neural circuits represent and transform information.

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## Nanotube-Integrated Microfluidic Platform for High Throughput Single Cell Electrophysiology on Chip

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Cells regulate and maintain an electrical potential across the membrane, which allow neurons to integrate, process and propagate information. Current method for studying electrical properties of individual cells based on manual positioning of patch clamp pipettes provides high fidelity recordings of intracellular electrical activity, but is slow compared to other cellular interrogation methods such as gene sequencing. This low-throughput electrophysiology imposes an experimental bottleneck for studying large populations of cells.

To overcome this bottleneck, we propose a new scalable platform for single cell high through electrophysiology. Combining a series of state-of-art nanofabrication techniques, we are able to assemble suspended Al<sub>2</sub>O<sub>3</sub> nanotubes embedded on a microfluidic template. By controlling fluid flow in this device we can rapidly direct cells towards the nanotube where we can perform electrical measurements. The small size of this tube, roughly 200 nm in diameter, creates a minimally invasive interface with the cell of interest. After electrical interrogation, cells can be released from the tube and sorted based on the electrophysiology phenotype for further analysis if necessary.

Previous works have demonstrated intracellular electrical recordings of individual cells using metallic nanowires as probe. Although effective for recording, metallic probes cannot perform current or voltage clamp experiments due to the electrochemistry performed at the metallic surface. For example, it is desirable to shift and maintain the membrane potential away from the resting value, which requires charge transfer over several seconds. Electrochemical reactions at the metal surface often affect the local pH via hydrolysis. Nanotubes, on the other hand, allow for direct flow of ions through solution without altering the pH near the cell. By incorporating this novel probe, we open the possibility of reproducing standard patch clamp recording modes on chip, such as voltage clamp and current clamp, increasing the range of experiments that can be performed by integrated electrophysiology chips.

## Magnetolectric Materials for Noninvasive Neural Modulation

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The ideal tool for neural modulation is noninvasive and cell specific allowing for neurological studies in freely moving animals as well as lead to alternative treatments for neurological disorders. Methods currently used for neural modulation involve invasive procedures implanting electrodes into tissue where the resulting signal is attenuated by surrounding tissue and lacks specificity. Optogenetics offers an alternative that is cell specific, but the light is again attenuated over very short distances. However, magnetic fields can pass through tissue without attenuation. Using the magnetolectric coupling between a magnetosensitive and piezoelectric material we propose several geometries of magnetolectric materials that will allow for specific, non-invasive neural modulation by the application of an external magnetic field.

We first propose to use a two-layer film composed of Metglas (magnetostrictive) and polyvinylidene fluoride (piezoelectric) layers. Cells expressing voltage gated sodium channels will be grown on these films and an external alternating magnetic field will be magnetoelectrically converted into a voltage across the piezoelectric layer. At resonant frequencies and low magnetic field strengths, this voltage has been found to be up to 1.5 V, which is sufficient to capacitively stimulate voltage gated ion channels. Equivalent circuit modeling has shown these magnetolectric films to be capable of generating action potentials in neurons under the application of an external magnetic field. Patch clamp electrophysiology and calcium sensitive imaging will be used to test these magnetolectric films in vitro.

To create a magnetolectric mechanism compatible with specific in vivo preparations, future work will also investigate multiferroic nanoparticles with a magnetostrictive core (cobalt ferrite) and a piezoelectric shell (barium titanate). These magnetolectric nanoparticles will then be directly tethered to a voltage gated ion channel. Under an applied magnetic field, the core and the shell will interact to create an electric field sufficient to trigger gating of the channel.

This technology has potential future applications in many areas of neurological research as a noninvasive alternative to existing neural modulation techniques.

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## Complex Nonlinear Neural Codes and Redundancy

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Perception is hard because the relevant causal variables are generally ambiguous and rarely directly observable in sense data. Instead, sensory inputs are typically influenced by irrelevant variability, often called nuisance variables, that must be disentangled from the relevant variables. Removing nuisance variables requires the brain to transform its sense data and select the subset of task-relevant information. Most of these transformations require nonlinear computation (Yang et al., 2015).

Do we need to know the exact nonlinearity that the brain used in order to decode the stimulus successfully? Can we use an ‘effective’ nonlinearity to achieve the same decoding efficiency? Here we generalize the method of partial correlation analysis (Haefner et al., 2013) to infer the effective nonlinear computations. Our approach is akin to using a Taylor series expansion of the neural nonlinearities, to approximate the sufficient statistics that the brain assumes in decoding the stimulus.

For high-order statistics there are an enormous number of ways to combine neural responses. Naively one might expect that the information content in any one of these combinations would be tiny, and thus inaccessible to measure with reasonable amounts of data. However, in the presence of information-limiting noise (Moreno et al., 2014), the higher level responses will be highly redundant. We show that we can use this fact to identify particular subsets of nonlinear sufficient statistics that are required to predict the behavioral output. Thus we can determine the statistical power needed to successfully determine the effective nonlinearity the brain uses in decoding.

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## Three-Dimensional Innervation Zone Imaging from Multi-Channel Surface EMG Recordings

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**Objective** There is an unmet need to accurately identify the locations of innervation zones (IZs) of spastic muscles, so as to guide botulinum toxin (BTX) injections for the best clinical outcome. A novel 3D IZ imaging (3DIZI) approach was developed by combining the bioelectrical source imaging and surface electromyogram (EMG) decomposition methods to image the 3D distribution of IZs in the target muscles.

**Methods** Simultaneous surface EMG (128 channel) and intramuscular EMG were acquired from the bicep muscle with the Refa136 amplifier (TMSi, Enschede, The Netherlands). The 128-unipolar channels were employed for surface EMG measurements with two flexible 64-channel surface electrode arrays (TMSi, Enschede, The Netherlands). Realistic geometry upper arm models (Fig.1) were constructed from a general magnetic resonance (MR) image data set and modified to match the ultrasound images of the subjects' upper arms, then meshed into finite element models.

The surface IZ location was first obtained through the EMG decomposition using our newly developed K-means clustering and convolution kernel compensation (KmCKC) approach, which decomposed the surface EMG signals into their constituent MUAP trains. Bioelectrical source imaging accuracy was then performed with the surface IZ location used as a prior knowledge to estimate the depth of the IZ. The 3DIZI localization results were compared with intramuscular EMG recordings. Localization errors (LEs)

**Results** Fig. 1 shows the estimated IZ locations of two MUs within the bicep using the proposed 3DIZI approach. The overlap of the two IZs reconstructed from their MUAPs fully covers the position of the wire electrode inserted into the biceps, which validates the accuracy of the 3DIZI approach in localizing IZs in the 3D space of the target muscles.

**Conclusions** The experimental validation results demonstrate the high performance of the 3DIZI approach in accurately reconstructing the distributions of IZs and the dynamic propagation of internal muscle activities in the biceps from high-density surface EMG recordings.

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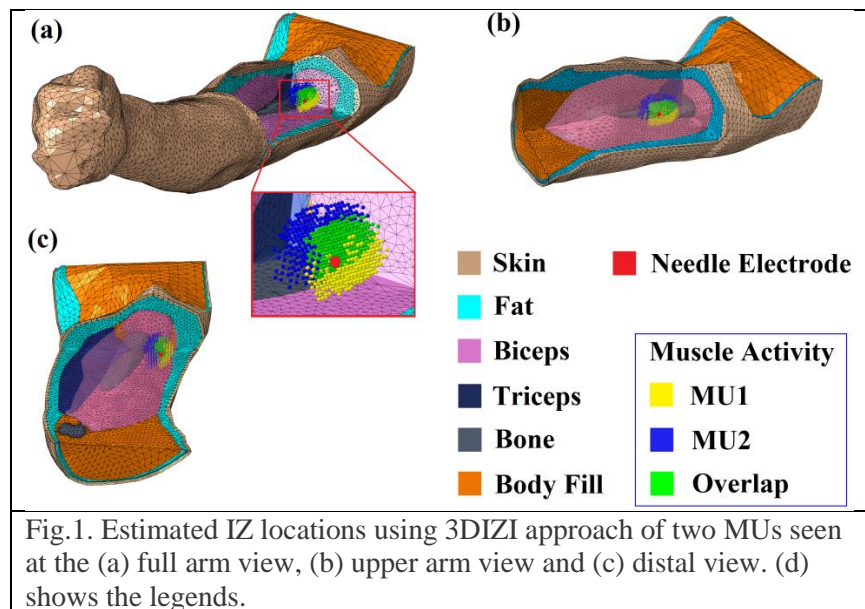


Fig.1. Estimated IZ locations using 3DIZI approach of two MUs seen at the (a) full arm view, (b) upper arm view and (c) distal view. (d) shows the legends.