

Poster Number	Abstract Title and Authors
1	The Facilitation of Rapid Temporal Processing by Ion Channel Cooperativity Suggests Coordination through Membrane Electromechanics <u>Araya MK</u> and Brownell WE
2	Micro-machined Optical Fiber with Multiple Stimulation Sites for Optogenetics Applications <u>Arnob MP</u> , <u>Hoang N</u> , Shih WC
3	Sorting Cells Based on Electrophysiology: Challenges and Opportunities <u>Bell MA</u> , Vercosa D, Avants B, and Robinson JT
4	Calibration of Visual Stimuli in a Virtual Reality System for Rodents <u>Bridgewater JW</u> , Fang RH, Angelaki DE, and Pitkow XS
5	Inferring Functional Connectivity of Neural Circuits Using Information Theoretic Causality Measures Cai Z, Aazhang B, and Byrne JH
6	Crossmodal Perceptual Adaptation Implies Neuronal Convergence of Auditory and Tactile Frequency Signals <u>Crommett LE</u> , Perez-Bellido A and Yau JM
7	Nanoscale Electrophysiology in Intact Small Organisms <u>Gonzales DL</u> , Badhiwala KN, Vercosa DG, Avants BW, Liu Z, Zhong W and Robinson JT
8	Task Learning Promotes Interneuron Circuit Plasticity in the Olfactory Bulb <u>Huang L</u> , Garcia I, Quast KB, Cordiner K, Saggau P, and Arenkiel BR
9	Evidence Accumulation in Dynamic Environments Veliz-Cuba A ¹ , <u>Kilpatrick ZP</u> [*] , and Josic K
10	Information Efficiency of Linear Recurrent Networks <u>Lakshminarasimhan KJ</u> , Angelaki DE, and Pitkow X
11	Mechanisms of Seizure Identified from Causal Connectivity Inferred using Directed Information <u>Malladi R</u> , Kalamangalam G, Tandon N, and Aazhang B
12	On Body Schema Acquisition in Traditional Manipulators: Utilizing Collision Predictions and Discrete Model Spaces <u>McDonald CG</u> , Losey D, and O'Malley M
13	EEG Source Localization Constrained by Time Varying Functional MRI Nguyen TT, Potter T, Karmonik C, Grossman R, and <u>Zhang Y</u>
14	An Altered Divisive Normalization Model of Autism <u>Patterson JS</u> , Rosenberg A, and Angelaki DE
15	Activation of Membrane Protein Piezo1 with Magnetic Nanoparticles <u>Polali S</u> , Duret G, Murphy DB, and Robinson JT
16	Stochastic Motion of Bumps in Planar Neural Fields <u>Poll DP</u> , and Kilpatrick ZP
17	General Inference by Neural Population Codes <u>Raju RV</u> , and Pitkow X
18	Characterization of Light Adaptation Induced Alterations in Mouse Retinal Ganglion Cell Spatiotemporal Tuning Sabharwal JS, Cowan CS, and Wu SM
19	Screening Mechanosensitive Ion Channels in Microfluidics <u>Sebesta CE</u> , Duret G, and Robinson JT

20	Phase Coupling as a Mechanism for Information Transfer Between the Superior Temporal and Visual Cortices During Speech Perception <u>Sertel MO</u> , Yoshor D, and Beauchamp MS
21	Optimal Inference in Feedforward Networks <u>Stolarczyk SP</u> , and Josić K
22	Imaging Voltage Dynamics <i>In Vivo</i> with Improved Genetically Encoded Indicators <u>St-Pierre F</u> , Yang HH, Pan MM, Ding X, Yang Y, Clandinin TR ⁴ , and Lin MZ
23	Nanotube-Integrated Microfluidic Platform for High Throughput Single Cell Electrophysiology on Chip <u>Vercosa DG</u> , Bell MA, Avants BW, and Robinson JT
24	Magnetolectric Materials for Noninvasive Neural Modulation <u>Wickens AL</u> , Chen R, Ajayan PM, and Robinson JT
25	Complex Nonlinear Neural Codes and Redundancy Yang Q and Pitkow X
26	Three-Dimensional Innervation Zone Imaging from Multi-Channel Surface EMG Recordings <u>Zhang C</u> , Liu Y, Peng Y, Li S, Zhou P, and Zhang Y
27	Characterizing the Variability of Hippocampal Neural Activity using Hidden Markov Models (HMMs): A Principled Framework for Exploring Sequential Neural Reactivation Ackermann ER, and Kemere CT
28	Micro-scale Real-time Decoding and Closed-loop Modulation of Human Language Yellapantula, S

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

Araya MK¹ and Brownell WE^{1,2}

1 Molecular Physiology and Biophysics Baylor College of Medicine, Houston, TX

2 Otolaryngology – H&N Surgery Baylor College of Medicine, Houston, TX

Corresponding author: Mussie K. Araya Molecular Physiology and Biophysics Baylor College of Medicine, Houston, TX araya@bcm.edu

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⁺ 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⁺⁺ 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.

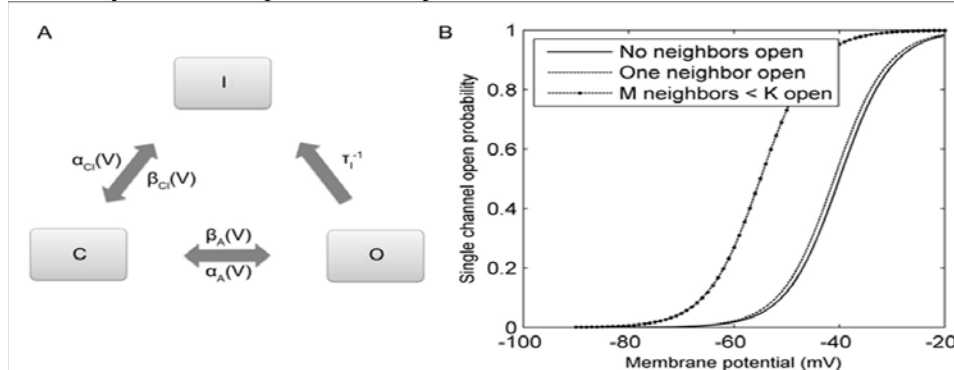


Figure 1. A. Gating scheme identified experimentally by Aldrich et al. suggests Na⁺ channel has three states; open (O), closed (C) and inactivated (I). Transition from closed to open states and vice versa occur with rates $\alpha_A(V)$ and $\beta_A(V)$. The transition from closed to inactivated states and vice versa occur with rates $\alpha_{Cl}(V)$ and $\beta_{Cl}(V)$. 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⁺ channels. The clustering of Na⁺ 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.

Research Support: **R01**-Electromechanics of the cochlear outer hair cell NIH/NIDCD

Micro-machined Optical Fiber with Multiple Stimulation Sites for Optogenetics Applications

Arnob MP¹, Hoang N², Shih WC^{1, 3, 4}

1. Department of Electrical & Computer Engineering, University of Houston, Houston, TX 77204
2. Department of Material Science & Engineering, University of Houston, Houston, TX 77204
3. Department of Biomedical Engineering, University of Houston, Houston, TX 77204
4. Department of Chemistry, University of Houston, Houston, TX 77204

Corresponding author: Shih WC, Department of Electrical & Computer Engineering, Department of Biomedical Engineering, Department of Chemistry, University of Houston, Houston, TX 77204. Email: wshih@uh.edu

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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Wei-Chuan Shih acknowledges the National Institute of Health (NIH) Grant (NIH 1R21NS084301-01A1) and National Science Foundation (NSF) CAREER Award (CBET-1151154).

Sorting Cells Based on Electrophysiology: Challenges and Opportunities

Martin Bell A.^{1,2} Vercosa D,^{1,2} Avants B,² and Robinson JT,^{2,3,4}

¹Applied Physics Program, Rice University, Houston, TX

²Department of Electrical and Computer Engineering, Rice University, Houston, TX

³Department of Bioengineering, Rice University, Houston, TX

⁴Department of Neuroscience, Baylor College of Medicine, Houston, TX

Corresponding author: Martin Bell, Applied Physics Program, Electrical and Computer Engineering, Rice University, Houston, Texas, amb6@rice.edu.

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.

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

Calibration of Visual Stimuli in a Virtual Reality System for Rodents

Bridgewater JW¹, Fang RH¹, Angelaki DE^{1,2}, and Pitkow XS^{1,2}

1. Department of Neuroscience, Baylor College of Medicine, Houston, TX

2. Department of Electrical and Computer Engineering, Rice University, Houston, TX

Corresponding author: Bridgewater JW, james.bridgewater@bcm.edu

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.

This work was supported by NSF IOS-1450923, the Simons Foundation, and the McNair Foundation.

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Inferring Functional Connectivity of Neural Circuits Using Information Theoretic Causality Measures

Cai Z¹, Aazhang B¹, Byrne JH²

1. Electrical and Computer Engin., Rice University, Houston, TX

2. Neurobio. and Anat., The University of Texas Medical School at Houston, Houston, TX

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

Crommett LE¹, Perez-Bellido A¹, Yau JM¹

1. Department of Neuroscience, Baylor College of Medicine, Houston, TX

Corresponding author: Crommett LE, Dept. of Neuroscience, Graduate School of Biomedical Science, Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030, Email: crommett@bcm.edu

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.

Funding: Rice University/ Baylor College of Medicine Neuroengineering IGERT

Nanoscale Electrophysiology in Intact Small Organisms

Gonzales DL^{1,2}, Badhiwala KN³, Vercosa DG^{1,2}, Avants BW², Liu Z³, Zhong W³, Robinson JT^{1-3,5}

1. Applied Physics Program, Rice University, Houston, TX
2. Electrical and Computer Engineering, Rice University, Houston, TX
3. Bioengineering, Rice University, Houston, TX
4. BioSciences, Rice University, Houston, TX
5. Neuroscience, Baylor College of Medicine, Houston, TX

Corresponding author: Jacob T. Robinson, Electrical and Computer Engineering, Rice University, Houston, TX, jtrobinson@rice.edu.

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 μm wide, 3 μm long, 0.08 μm 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.

Funding sources. This work is funded by the DARPA Young Faculty Award D14AP00049 (JTR), National Institutes of Health grant DA018341 (WZ), and the Hammill Foundation (JTR & WZ). DG is funded by the National Science Foundation (NSF) Graduate Research Fellowship Program 0940902 and a training fellowship from the Keck Center of the Gulf Coast Consortia on the NSF IGERT: Neuroengineering from Cells to Systems 1250104.

Task Learning Promotes Interneuron Circuit Plasticity in the Olfactory Bulb

Huang L¹, Garcia I^{2,3}, Quast KB¹, Cordiner K⁴, Saggau P^{4,5}, Arenkiel BR^{1,2,4,6}

1. Department of Molecular & Human Genetics, Baylor College of Medicine, Houston, TX
2. Program in Developmental Biology, Baylor College of Medicine, Houston, TX
3. Medical Scientist Training Program, Baylor College of Medicine, Houston, TX
4. Department of Neuroscience, ^{Baylor} College of Medicine, Houston, TX
5. Allen Institute for Brain Science, Seattle, WA
6. Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital, Houston, TX

Corresponding author:

Benjamin R. Arenkiel, Ph.D

Assistant Professor and McNair Scholar

Departments of Molecular & Human Genetics and Neuroscience

Baylor College of Medicine

Jan and Dan Duncan Neurological Research Institute

Houston, TX 77030

arenkiel@bcm.edu

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.

This work was supported by the McNair Medical Institute, NINDS grant R01NS078294 to B.R.A., and NIH IDDRC grant U54HD083092.

Evidence Accumulation in Dynamic Environments

Veliz-Cuba A, Kilpatrick ZP*, and Josic K*

Department of Mathematics, University of Houston, Houston TX

*equal contribution

Corresponding Author: Zachary P. Kilpatrick, Department of Mathematics, University of Houston, Houston TX (zpkilpat@math.uh.edu)

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.

This work was supported by NSF-DMS-1311755 (ZPK); NSF/NIGMS-R01GM104974 (AV-C and KJ); and NSF-DMS-1122094 (KJ).

Information Efficiency of Linear Recurrent Networks

Lakshminarasimhan KJ¹, Angelaki DE^{1,2}, Pitkow X^{1,2}

1. Department of Neuroscience, Baylor College of Medicine, Houston, TX
2. Department of Electrical and Computer Engineering, Rice University, Houston, TX

Corresponding author:

Lakshminarasimhan KJ, Department of Neuroscience, Baylor College of Medicine
1 Baylor Plaza, Houston, TX 77030, USA, E-mail: jlakshm@bcm.edu

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.

This work was supported by grant EY017566 to DEA and grant from McNair Foundation to XP.

Mechanisms of Seizure Identified from Causal Connectivity Inferred using Directed Information

Malladi R¹, Kalamangalam G², Tandon N³, Aazhang B¹

1. Department of Electrical and Computer Engineering, Rice University, Houston, TX

2. Department of Neurology, University of Texas Health Science Center, Houston, TX

3. Department of Neurosurgery, University of Texas Health Science Center, Houston, TX

Corresponding Author: Rakesh Malladi, ECE Department, Rice University, Houston, TX,
rm17@rice.edu.

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.

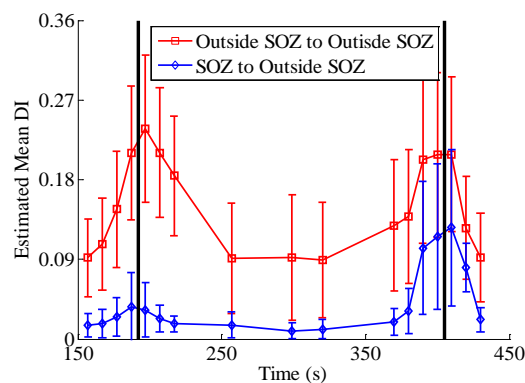


Figure 1: Dynamic causal connectivity of patient 1 inferred using directed information

Acknowledgement - This work is funded by a grant from National Science Foundation. This work will be presented at Society for Neuroscience (SfN) 2015.

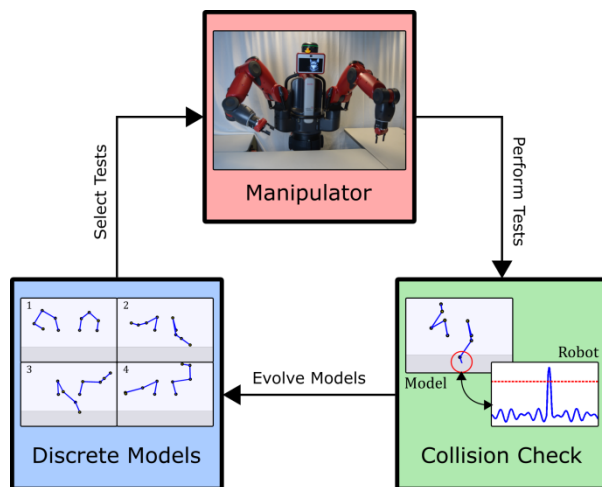
On Body Schema Acquisition in Traditional Manipulators: Utilizing Collision Predictions and Discrete Model Spaces

McDonald CG, Losey D, O'Malley M

Department of Mechanical Engineering, Rice University, Houston, TX

Corresponding Author: McDonald C. G., Dept. of Mechanical Engineering, Graduate Student, Rice University, 6100 Main St., MS-321, Houston, TX 77005, E-mail: cgm4@rice.edu

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



Acknowledgements: This work is supported by NSF IGERT grant number 1250104.

EEG Source Localization Constrained by Time Varying Functional MRI

Nguyen TT¹, Potter T¹, Karmonik C², Grossman R², Zhang Y¹

1. University of Houston, Houston, TX

2. The Methodist Hospital Neurological Institute, Houston, TX

Corresponding author: Yingchun Zhang, Department of Biomedical Engineering, University of Houston, Houston, TX 77204 USA. (phone:713-743-6127; Fax: 713-743-0226; e-mail: yzhang94@uh.edu).

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.

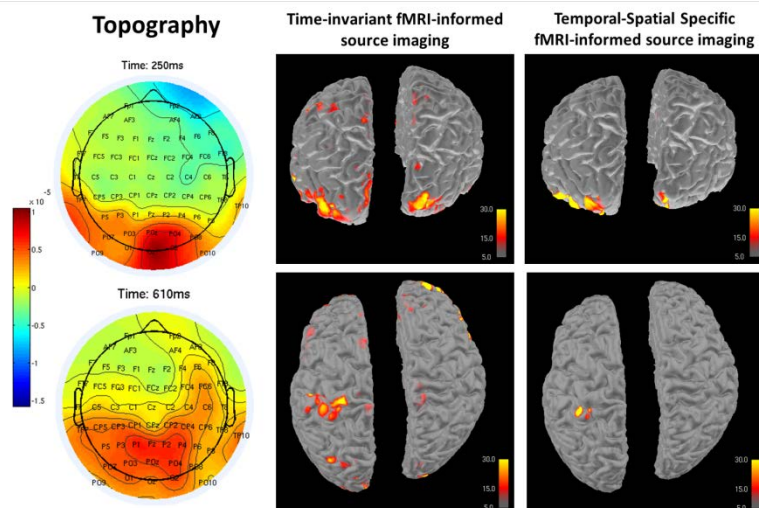


Figure 1. Source reconstruction results for time #1 (top) and time #2 (bottom) using traditional time-invariant fMRI-constraint method (middle); and the proposed temporal-spatial specific fMRI-constraint source localization method (far right). Color scale (arbitrary unit) show 70% activation level as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

An altered Divisive Normalization Model of Autism

Patterson JS¹, Rosenberg A², Angelaki DE¹

1. Department of Neuroscience, Baylor College of Medicine, Houston, TX
2. Department of Neuroscience, University of Wisconsin - Madison, Madison, WI

Corresponding author: Jaclyn Sky Patterson, Department of Neuroscience, Baylor College of Medicine, Houston, TX, jspatter@bcm.edu.

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.

This work was supported by Integrative Graduate Education and Research Traineeship Training Grant 43413-I (to J.S.P.) and Simons Foundation Autism Research Initiative 247992 (to D.E.A.).

Activation of Membrane Protein Piezo1 with Magnetic Nanoparticles

Polali S^{1,2}, Duret G¹, Murphy DB^{1,2}, and Robinson JT^{1,3,4}

1. Electrical and Computer Engineering, Rice University, Houston, TX
2. Applied Physics, Rice University, Houston, TX, USA
3. Bioengineering, Rice University, Houston, TX, USA
4. Neuroscience, Baylor College of Medicine, Houston, TX

Corresponding Author: Sruthi Polali, sp25@rice.edu

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

Poll DP¹, Kilpatrick ZP²

1. Department of Mathematics, University of Houston, Houston, TX
2. Department of Mathematics, University of Houston, Houston, TX

Corresponding author: Kilpatrick ZP, Department of Mathematics, Assistant Professor, University of Houston, Houston, TX, zpkilpat@math.uh.edu

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.

General Inference by Neural Population Codes

Raju RV¹, Pitkow X^{1,2}

1. Electrical and Computer Engineering, Rice University, Houston, TX
2. Department of Neuroscience, Baylor College of Medicine, Houston, TX

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

Sabharwal JS¹, Cowan CS¹, Wu SM^{1,2}

1. Neuroscience, Baylor College of Medicine, Houston, TX
2. Ophthalmology, Baylor College of Medicine, Houston, TX

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.

Funding:

NRSA - 1F30EY025480

Vision Core Grant – EY002520

NEI Training Grant – EY007001

Retina Research Foundation

Research for Preventing Blindness

Screening Mechanosensitive Ion Channels in Microfluidics

Sebesta CE,¹ Duret G,² and Robinson JT^{1,2,3}

¹Department of Bioengineering, Rice University, Houston, TX

²Department of Electrical and Computer Engineering, Rice University, Houston, TX

³Department of Neuroscience, Baylor College of Medicine, Houston, TX

Corresponding author: Charles Sebesta, Department of Bioengineering, Rice University, Houston, Texas,
ces13@rice.edu

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

Sertel MO¹, Yoshor D², Beauchamp MS²

1. Neurobiology and Anatomy, University of Texas Health Science Center in Houston, Houston, TX
2. Neurosurgery, Baylor College of Medicine, Houston, TX

Corresponding author: Muge Ozker Sertel, Neurobiology and Anatomy, University of Texas Health Science Center in Houston, Houston, TX, muge.o.sertel@uth.tmc.edu

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.

Optimal Inference in Feedforward Networks

Stolarczyk SP¹, Josić K¹

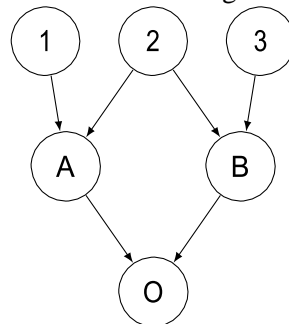
1. Department of Mathematics, University of Houston, Houston, TX

Corresponding author:

Simon Stolarczyk, Department of Mathematics, University of Houston,
3551 Cullen Blvd., Suite 641 PGH, Houston, TX 77204-3008

Email: spstolar@math.uh.edu

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

St-Pierre F^{1,2}, Yang HH⁴, Pan MM^{3,4}, Ding X⁵, Yang Y^{3,4}, Clandinin TR⁴, Lin MZ^{3,4}

1. Department of Neuroscience, Baylor College of Medicine, Houston, TX
2. Department of Electrical and Computer Engineering, Rice University, Houston, TX
3. Department of Bioengineering, Stanford University, Stanford, CA
4. Department of Neurobiology, Stanford University, Stanford, CA
5. Department of Bioengineering, California Institute of Technology, Pasadena, CA

Corresponding author: François St-Pierre, stpierre@bcm.edu, mailing address: Department of Neuroscience, Baylor College of Medicine, One Baylor Plaza, MS: BCM 295, Suite S636A, Houston, TX 77030

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.

Funding sources: This work was supported by National Science Foundation grant 1134416 (F.S.-P., M.Z.L.), DARPA grant W911NF-14-1-0013 (M.Z.L.), NIH Brain Initiative Grant 1U01NS090600-01 (M.Z.L.), and NIH grants R01 HL12652701 (J.C.W.), R01 EY022638 (T.R.C.), and R21 NS081507 (T.R.C.). H.H.Y. is supported by a Stanford Graduate Fellowship and a Stanford Bio-X Graduate Fellowship. Y.Y. is supported by The Walter V. and Idun Berry Postdoctoral Fellowship. M.Z.L. receives funding from the Rita Allen Foundation and the Burroughs Wellcome Fund.

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

Vercosa DG^{1,2}, Bell MA^{1,2}, Avants BW², Robinson JT^{2,3}

1. Applied Physics, Rice University, Houston, TX
2. ECE Department, Rice University, Houston, TX
3. Bioengineering Department, Rice University, Houston, TX

Corresponding author: Daniel Vercosa, Applied Physics, Rice University, Houston, TX
dgvercosa@rice.edu

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 Al₂O₃ 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.

Magnetoelectric Materials for Noninvasive Neural Modulation

Wickens AL,^{1,2} Chen R,³ Ajayan PM,^{3,4,5} Robinson JT^{2,6,7}

1. Applied Physics Program, Rice University, Houston, TX
2. Electrical and Computer Engineering Department, Rice University, Houston, TX
3. Chemistry Department, Rice University, Houston, TX
4. Materials Science and NanoEngineering Department, Rice University, Houston, TX
5. Chemical and Biomolecular Engineering Department, Rice University, Houston, TX
6. Bioengineering Department, Rice University, Houston, TX
7. Department of Neuroscience, Baylor College of Medicine, Houston, TX

Corresponding Author: Amanda Wickens, alw12@rice.edu

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 magnetoelectric coupling between a magnetosensitive and piezoelectric material we propose several geometries of magnetoelectric 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 magnetoelectric 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 magnetoelectric films in vitro.

To create a magnetoelectric 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 magnetoelectric 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.

This work is supported by an IGERT training grant under NSF Award DGE-1250104.

Complex Nonlinear Neural Codes and Redundancy

Yang Q,¹ and Pitkow X^{1,2}

¹Rice University, Department of Electrical and Computer Engineering, Houston, TX

²Baylor College of Medicine, Department of Neuroscience, Houston, TX

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

Zhang C¹, Liu Y¹, Peng Y¹, Li S², Zhou P², Zhang Y¹

1. Department of Biomedical Engineering, University of Houston, Houston, TX
2. Department of Physical Medicine and Rehabilitation, University of Texas Health Science Center, Houston, TX

Corresponding author: Yingchun Zhang, Department of Biomedical Engineering, University of Houston, Houston, TX, yzhang94@uh.edu

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.

Funding sources: This work was supported in part by NIH K99DK 082644, NIH R00DK082644 NIH R24HD050821 and the University of Houston.

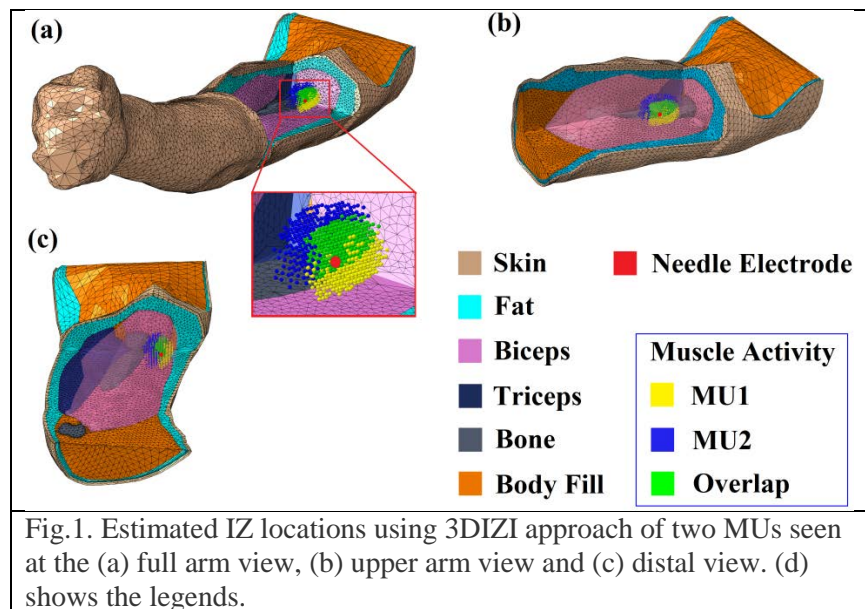


Fig.1. Estimated IZ locations using 3DIZI approach of two MUs seen at the (a) full arm view, (b) upper arm view and (c) distal view. (d) shows the legends.

Characterizing the Variability of Hippocampal Neural Activity using Hidden Markov Models (HMMs): A Principled Framework for Exploring Sequential Neural Reactivation

Ackermann ER¹, Kemere, CT^{1,2}

1. Department of Electrical and Computer Engineering, Rice University, Houston TX
2. Department of Neuroscience, Baylor College of Medicine, Houston TX

Corresponding author: Etienne Ackermann, Department of Electrical and Computer Engineering, Rice University, Houston TX, era3@rice.edu

Populations of neurons in the rodent hippocampus (HP) have been shown to accurately encode information about the animal's location in its environment. Several computational models have been developed in an attempt to uncover this neural representation of spatial topology at the behavioral timescale, including the recent use of latent variable models to infer the hippocampal population codes during spatial navigation [1]. However, understanding the population code of so-called “replay” sequences—along with a satisfactory interpretation thereof—remain more elusive.

Short bursts of increased neural activity are commonly observed in the HP, co-occurring with sharp-wave ripples (SWRs), and some of these events are usually classified as replay events—that is, sometimes time-compressed sequences are observed that look “similar” to sequences of neural activity that had previously been experienced by the animal. The question then naturally arises: if some of these SWR events correspond to previously experienced activity—the replay events—then what do all the rest of the neural activity during SWRs mean?

Here we develop and use hidden Markov models (HMMs) to characterize the variability of sequential neural activity in the rodent hippocampus on both the behavioral and the replay timescales. Such an approach is attractive because it provides a principled (and probabilistic) framework on which to study and explore sequential neural activity (including replay), which is in contrast to the heuristic approaches (such as template matching) that have been used thus far to classify events as either being replay, or not. Moreover, even though the stimuli are necessarily unobserved (latent), the use of HMMs enable us to uncover sequential activity in those events that have traditionally been classified as non-replay—or simply as noise—and we anticipate that a closer look at these “non-replay” events will deepen our understanding of SWRs, replay, and their potential role in decision making and memory consolidation.

[1] Linderman SW, Johnson MJ, Wilson MA, and Chen Z, “A Nonparametric Bayesian Approach to Uncovering Rat Hippocampal Population Codes During Spatial Navigation”

Funding sources: This work was funded by an NSF CAREER award (CBET-1351692) and a HFSP Young Investigator's award (RGY0088).

Micro-scale Real-time Decoding and Closed-loop Modulation of Human Language

Yellapantula, S

Department of Electrical and Computer Engineering, Rice University, Houston TX

Corresponding author:

Sudha Yellapantula, Rice University, Electrical & Computer Engineering, 6100 Main St., Houston, TX
77005-1827

Humans produce language, which is a defining characteristic of our species and our civilization. We can select words precisely out of a large lexicon with remarkably low error rates. It is perhaps not surprising that the complex speech production system is easily affected by disease. It has been reported that brain damage induced language disorders affect millions, and with little hope of remediation. Research on the anatomical, physiological, and computational bases of speech production has made important strides in recent years but has been limited by a glaring lack of information on the dynamics of the process. This is a limitation that pertains to the low spatio-temporal resolution of available tools to collect data and the effectiveness of the current tools for analysis.

The driving vision is to develop an unparalleled understanding of cortical representation and fine-grained connectivity in the human language system. Our team has expertise in signal decoding of the processes of cued word production with intracranial recording techniques, as well as using cortical stimulation to modulate the system. FDA-approved arrays are used to perform closed-loop decoding of sensorimotor processes during speech production and transient neuromodulation of the language system in patients with epilepsy undergoing intracranial electrode placement for the localization of seizures. However, the fine-grained representation of sensorimotor loops in the language system necessitates the development of ultra-small, energy efficient and wireless detectors to enable expanding of the knowledge gained in this exploratory project to eventual application in patients who have sustained neurological injuries that have resulted in pervasive language impairments. This integrative project brings innovative microelectronics technologies together with state of the art large data analysis techniques to develop a first of its kind system to remediate language disorders.

Our project objective is to make two fundamental advances in hardware and analysis in two major steps. First, we will perform recordings in humans at a more standard scale level using existing micro-ElectroCorticoGraphy arrays and use the data to infer optimal parameters for real time language signal decoding and modulation. Second, we will use this insight, for the design of an innovative wireless recording and modulation system in humans with unprecedented temporal and spatial resolution.

[The above extract is taken from the proposal with the same name]