2014 Collaborative Research in Computational Neuroscience (CRCNS) PI Meeting

CRCNS PI Meeting

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Tempe Mission Palms Hotel and Conference Center

Tempe, AZ

Abstracts

Plenary Abstracts

Anton Arkhipov, Allen Institute for Brain Science

High-throughput Experimental and Computational Exploration of the Cortex

The Allen Institute for Brain Science has, over the past ten years, produced a series of brain atlases (www.brain-map.org). These are large (3 TB, >1 million slides) public resources that integrate genome-wide gene expression and neuroanatomical data across the entire brain for developing and adult humans, non-human primates and mice, and are complemented by high-resolution, cellular-based anatomical connectivity data of several thousand mice. It is the single largest integrated neuroscience database world-wide. Anyone can freely access this data without any restrictions.

We are embarked on an ambitious 10-year initiative to understand the structure and function of the neocortex and associated satellite structures in humans and mice. We are setting up high throughput pipelines to exhaustively characterize the morphology, electrophysiology, and transcriptome of cell types as well as their synaptic interconnections in the human neocortex (via a combination of fetal, neurosurgical and post-mortem tissues & human stem cells differentiated into forebrain neurons) and in the laboratory mouse. We are building brain observatories to image the activities of neurons throughout the cortico-thalamic system in behaving mice, to record their electrical activities, and to analyze their connectivity at the ultra-structural level. These experimental activities are synergistically complemented by efforts focused on developing computer simulations of the cortex at several levels of resolution. We use biophysically detailed models to take into account neuronal morphology and biophysical properties and to obtain a physically realistic description of cortical tissue at the level of local circuits. Point-neuron models are used to study larger cortical networks. At yet higher level of description, we employ population-statistics simulations to investigate overall information processing capabilities of the cortico-thalamic system. An integral part of all these efforts is the development of tools for processing and analysis of experimental data, as well as preparation, simulation, and visualization of computational models. In keeping with the Allen Institute for Brain Science's core value of open science, all data, knowledge and tools from this initiative will be shared with the broader scientific community.

Christiane Linster, Cornell University

Pre-processing of Sensory Information for Cortical Associative Learning: Distinct Roles for Nicotinic and Muscarinic Cholinergic Receptors

The olfactory bulb (OB) and piriform cortex receive dense cholinergic projections from the basal forebrain. Cholinergic modulation within the piriform cortex has long been proposed to serve important functions in olfactory learning and memory, whereas cholinergic modulation in the olfactory bulb is thought to regulate contrast and synchrony of odor representations. Using a combination of experimental and computational approaches, we here investigate how cortical discrimination learning is regulated by cholinergic modulation of the OB inputs to the piriform cortex. Our results suggest that muscarinic and nicotinic receptors serve complementary roles in regulating coherence and sparseness of the OB network output, which in turn differentially regulate the strength and overlap in cortical odor representations. Each of these leads to specific impairments in cortical learning, evidenced behaviorally via impairments in specific types of odor discrimination. Muscarinic receptor blockade in the OB results in a bona fide learning impairment that may arise because cortical neurons are activated less often, whereas impairments due to nicotinic receptor blockade may not be due to the inability of the cortex to learn, but rather arise because the cortex is unable to resolve highly overlapping input patterns.

Stephen Macknik, SUNY Downstate Medical Center

Sleights of Mind

Illusions are perceptual experiences that do not match the physical reality. Our perception of the outside world is generated indirectly by brain mechanisms, so all sensory perception is illusory to some extent. The study of illusions is critical to understanding the basic brain mechanisms of sensory perception, as well as to cure various neural diseases. The illusion community includes visual scientists, ophthalmologists, neurologists, painters, sculptors, mathematicians, graphic designers, and even magicians – each use a variety of methods to unveil the underpinnings of illusory perception. Magic tricks were cognitive illusions that fool us because humans have hardwired processes of attention and awareness that are hackable – a good magician uses your mind's own intrinsic properties against you in a form of mental jujitsu. The insights that magicians have gained over centuries of informal experimentation have led to new discoveries in the cognitive sciences, and they also reveal how our brains work in everyday situations.

Workshop Abstracts

Richard Gerkin, Arizona State University

Introduction to the Workshop Themes

Researchers spend billions of dollars and million of hours producing data and models for consumption and evaluation by our peers. However, many of these efforts are launched "from scratch", without integrating with, extending, or properly engaging the research efforts that preceded it. This is partly due to the challenges of building a computational or analytical edifice on top of others' research output, which can be difficult for an outsider to locate, interpret, or operate. An emerging solution to this challenge centers on standards, reproducibility, model and data-sharing infrastructure, and transparent methods to evaluate the scope and validity of previous work. This workshop will present progress towards this solution along numerous fronts, and how this progress has already begun allowing researchers to answer specific scientific questions more quickly, inexpensively, and reliably.

Yoonsuck Choe, Chul Sung, Jinho Choi, Manisha Srivastava, Wenjie Yang, Jaewook Yoo, John Keyser, and Louise C. Abbott, Texas A&M University

Open Web Atlas for High-resolution 3D Mouse Brain Data

Rapid advances in high-throughput, high-resolution, high-volume microscopy techniques in recent years have enabled the acquisition of extremely large volumes of neuroanatomical data (on the order of several terabytes). Examples of such techniques include Knife-Edge Scanning Microscopy (KESM) and other physical sectioning microscopy methods such as Array Tomography, Two-Photon Tomography, All-Optical Histology, Automatic Tape-Collecting Ultra-Microtome, Serial Block-Face Electron Microscopy, etc. Organizing, visualizing, analyzing, and disseminating such large data sets pose a serious challenge. In this abstract, we will present our work on a web-based, lightweight mouse brain atlas called the Knife-Edge Scanning Microscope Brain Atlas (http://kesm.org). The atlas serves several whole mouse brain data sets (Golgi for neuronal morphology, India ink for vasculature, and Nissl for cell bodies; voxel resolution = 0.6 um x 0.7 um x 1.0 um; data size ~ 1.5 TB per brain). The main design of the web-based atlas involves the use of mapping APIs such as the Google Maps API to render 3D volume data using an image overlaying technique. However, for a truly open and extensible system, we adopted the Open Layers API, an open source mapping API. Furthermore, we introduced several new components to the atlas to facilitate discovery: (1) all three orientations (coronal, sagittal, and horizontal) supported, (2) registration to the Allen Reference Atlas, (3) annotation facility, (4) integrated unit-volume viewer using WebGL for fully interactive viewing of small sub-volumes. These enhanced functions in the KESMBA are expected to greatly increase the use of the KESM data. The general atlas framework is also broadly applicable to other forms of biological data (not just brain data), and the software is available for download at http://sourceforge.net/projects/kesmba/.

Shreejoy Tripathy, University of British Columbia

NeuroElectro.org: Making the World's Neurophysiology Data Available for Reuse

The behavior of neural circuits is determined largely by the electrophysiological properties of the neurons they contain. Understanding the relationships of these properties requires the ability to first identify and catalog each property. However, information about such properties is largely locked away in decades of closed-access journal articles with heterogeneous conventions for reporting results, making it difficult to utilize the underlying data. We solve this problem through the NeuroElectro project: a Python library, RESTful API, and a web application (at http://neuroelectro.org) for the extraction, visualization, and summarization of published data on neurons' electrophysiological properties. Information is organized both by neuron type (using neuron definitions provided by NeuroLex) and by electrophysiological property (using a newly developed ontology). We discuss strategies for how to best combine, normalize and organize data collected across different labs and recording conditions. NeuroElectro is a valuable resource for experimental physiologists attempting to supplement their own data, for computational modelers looking to constrain their model parameters, and for theoreticians searching for undiscovered relationships among neurons and their properties.

Mitra Hartmann, Northwestern University

The Digital Rat: Tools for Modeling the Vibrisso-Tactile Natural Scene

I will describe The Digital Rat, a set of software tools that aim to enable anatomically and mechanically accurate modelling of the rat head and vibrissal (whisker) array. We aim for a simulation environment that can be used to model the spatiotemporal patterns of mechanical input to vibrissae during the rat's vibrisso-tactile exploratory behaviors. We anticipate soon expanding this model to the mouse.

Lydia Ng, Allen Institute for Brain Science

Overview of the Allen Brain Atlas Data, Tools, and API

The Allen Brain Atlas portal (brain-map.org) contains a growing collection of data and software that integrates gene expression and connectivity with neuroanatomy. There are currently seven major gene expression and connectivity atlases that span across species and developmental time points and three additional data sets focused on gene expression in sleep, diversity of gene expression across mouse strains and gene expression profile of glioblastoma in humans. This workshop presentation will focus on two of the large-scale mouse atlases: the Allen Mouse Brain Atlas and the Allen Mouse Brain Connectivity Atlas. The inaugural project of the Allen Institute for Brain Science, the Allen Mouse Brain Atlas is a genome-wide 3D atlas of gene expression in the adult mouse brain. The atlas consists of over half a million high resolution *in situ* hybridization images of the C57Bl/6J P56 mouse. The Allen Mouse Brain Connectivity Atlas examines longer range mesoconnectivity of neural connections in the mouse brain. When completed, the atlas will contain axonal projections mapped from ~300 anatomical regions and diverse neuronal population defined by ~100 transgenic Cre-driver lines to target specific cell types.

Fully automated pipelines have been developed to process the image data into a standard common coordinate framework based upon the Allen Reference Atlas. The availability of a comprehensive spatially mapped quantitative database enables integration into brain models and simulations and discovery of relationships in a data-driven manner. All data and services can be accessed via the Allen Brain Atlas API (api.brain-map.org) to foster community use and analysis of this dataset.

Friedrich Sommer, University of California, Berkeley

The NeuroData Without Borders Project and the CRCNS.org Repository

The Neurodata Without Borders (NWB) – Neurophysiology initiative is a one-year project to produce a unified data format for cellular-based, neurophysiology data based on representative use cases initially from four laboratories – the Buzsaki group at NYU, the Svoboda group at Janelia Farm, the Meister group at Caltech, and the Allen Brain Institute. The goal is to develop a common, integrated data format, which is sufficiently flexible and extensible to incorporate present and future electrophysiological and optical physiology data (i.e., cellular imaging) and to include complex metadata related to stimuli and behavior. I will describe the use cases of NWB, the project strategy and the community input that NWB is seeking. The second part of this talk will provide an update about the status and future plans of CRCNS.org, a web repository for sharing neurophysiology data.

Stephen Larson, OpenWorm.org

OpenWorm: Open Collaboration in Computational Neuroscience Focused on C. elegans

The *C. elegans* connectome (White et al., 1986; Varshney et al., 2011) is currently the most detailed connectome data set at the neuronal circuit level that is publicly available. Represented as a network graph, it consists of edges that distinguish between gap junctions and chemical synapses, weighted by synapse count, with nodes that represent neurons whose identities are unambiguous and well known. Within the OpenWorm project (Palyanov et al., 2012), we have previously transformed this data set into NeuroML as the foundation for a computational simulation framework for *C. elegans* (Busbice et al., 2012).

In an open and collaborative manner online, the OpenWorm project has been building infrastructure around this neuronal representation into a complete digital representation of the *C. elegans*. In this tutorial, I will explain the motivations, methods, and results of the OpenWorm project to date.

References

Busbice, T., Gleeson, P., Khayrulin, S., Cantarelli, M., Dibert, A., Idili, G., Palyanov, A., Larson., S. (2012) The NeuroML C. elegans Connectome, Neuroinformatics 2012 Abstract Book, September 11, 2012. http://g.ua/WNuf

Palyanov, A., Khayrulin, S., Larson, S. D., & Dibert, A. (2012). Towards a virtual C . elegans : A framework for simulation and visualization of the neuromuscular system in a 3D physical environment. *In Silico Biology*, *11*, 137–147. doi:10.3233/ISB-2012-0445

White, J. G., Southgate, E., Thomson, J. N., & Brenner, S. (1986). The Structure of the Nervous System of the Nematode Caenorhabditis elegans. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences (1934-1990)*, *314*(1165), 1–340. doi:10.1098/rstb.1986.0056

Varshney, L. R., Chen, B. L., Paniagua, E., Hall, D. H., & Chklovskii, D. B. (2011). Structural Properties of the Caenorhabditis elegans Neuronal Network. *PLoS Computational Biology*, *7*(2), e1001066. doi:10.1371/journal.pcbi.1001066

Sharon Crook, Arizona State University

Collaborative Modeling with NeuroML and the Open Source Brain Project

Computational models based on detailed neuroanatomical and electrophysiological data have been used for many years as an aid for understanding the function of the nervous system. NeuroML is an international, collaborative initiative to develop a language for describing and sharing detailed, multiscale models of neural systems [1]. The project focuses on the key objects that need to be exchanged among software applications used by computational neuroscientists. Examples of these objects include descriptions of neuronal morphology, the dynamics of ion channels and synaptic mechanisms, and the connectivity patterns of networks of model neurons. This modular approach brings additional benefits: not only can entire models be published and exchanged in this format, but each individual object or component, such as a specific calcium channel or excitatory synapse, can be shared and re-implemented in a different model. The use of a standardized description language based on XML also facilitates the development of tools that promote simulator interoperability.

Open Source Brain (OSB) [2] is a resource for sharing and collaboratively developing computational models of neural systems, where use of NeuroML is encouraged to ensure transparency, modularity, accessibility, and cross simulator portability. OSB provides advanced facilities to analyze, visualize, and transform models and to connect researchers interested in models of specific neurons, brain regions, and disease states.

We will provide an introduction to these resources and provide examples of how they can be used to accelerate model development and ensure model reproducibility.

[1] Gleeson P, Crook S, Cannon R, Hines M, Billings G, Farinella M, Morse TM, Davision A, Ray S, Bhalla U, Barnes SR, Dimitrova YD, Silver RA: NeuroML: a simulator-independent language for describing data-driving models of neurons and networks with a high degree of biological realism. *PLoS Computational Biology* 2010, 6: e1000815.

[2] Gleeson P, Piasini E, Crook S, Cannon R, Steuber V, Jaeger D, Solinas S, D'Angelo E, Silver RA: The Open Source Brain Initiative: enabling collaborative modeling in computational neuroscience. *BMC Neuroscience* 2012, 13(Suppl 1):O7.

Richard Gerkin, Arizona State University

SciUnit: Data-driven Validation of Models for Neuroscience

Rigorously validating a quantitative scientific model requires comparing its predictions against an unbiased selection of experimental observations according to sound statistical criteria. Developing new models thus requires a comprehensive and contemporary understanding of competing models, relevant data and statistical best practices. Today, developing such an understanding requires an encyclopedic knowledge of the literature. Unfortunately, in rapidly growing fields like neuroscience, this is becoming increasingly untenable, even for the most conscientious scientists. For new scientists, this can be a significant barrier to entry.

Software engineers seeking to verify, validate, and contribute to a complex software project rely not only on volumes of human documentation, but on suites of simple executable tests, called "unit tests''. Drawing inspiration from this practice, we have developed SciUnit, an easy-to-use framework for developing "model validation tests'' – executable functions, here written in Python. These tests generate and statistically validate predictions from a specified class of scientific models against one relevant empirical observation to produce a score indicating agreement between the model and the data. Suites of such validation tests, collaboratively developed by a scientific community in common repositories, produce up-to-date statistical summaries of the state of the field. Here we aim to detail this test-driven workflow and introduce it to the neuroscience community. As an initial example, we describe NeuronUnit, a library that builds upon SciUnit and integrates with several existing neuroinformatics resources to support validating single-neuron models using data gathered by neurophysiologists.

Main Meeting Speakers (Friday)

Jonathan Pillow, Princeton University & University of Texas at Austin
Kenneth Latimer, University of Texas at Austin
Jacob Yates, University of Texas at Austin
Miriam Meister, University of Washington
Alex Huk, University of Texas at Austin

Ramping vs. Stepping: Continuous and Discrete Latent Dynamical Models of Decision Signals Underlying Spike Trains in Parietal Cortex

The firing rates of neurons in the macaque lateral intraparietal (LIP) area exhibit gradual ramping that is commonly believed to reflect the accumulation of evidence during decision making. However, ramping that appears in trial-averaged spike responses does not necessarily indicate that spike rates ramp on single trials: ramping averages could also arise from instantaneous steps in spike rate that occur at different times on each trial. In this talk, I will describe an approach to this problem based on explicit statistical latent-dynamical models of spike trains. We examined responses recorded during sensory decision-making using a model with either ramping "accumulation-to-bound" dynamics or discrete "stepping" dynamics. In contrast to previous findings, we report that two thirds of choice-selective neurons in LIP are better explained by a model with stepping dynamics. We show that the stepping model provides an accurate description of LIP spike trains, allows for accurate decoding of decisions, and reveals decision-related structure that is hidden by conventional stimulus-aligned spike train rasters.

Eric Shea-Brown, University of Washington
Joel Zylberberg, University of Washington
Jon Cafaro, University of Washington
Max Turner, University of Washington
Fred Rieke, University of Washington

Signal and Noise in the Retina's Population Code for Direction

Information about sensory stimuli is often represented in the noisy activity of neural populations. How this noise is coordinated (or correlated) across the population determines the fidelity of the sensory representation, but there is considerable debate about whether and how this coordination occurs. We investigate this question for the ensemble activity of populations of direction selective retinal ganglion cells, and find a ~100% improvement in coding fidelity due to correlated activity. Dual-cell intracellular recordings lead to a mechanistic circuit model, which shows the origin of the effect. Here, excitation and inhibition conspire to separate signal and noise, via a simple statistical property we refer to as "radial variance" and which may generalize to other neural circuits.

Clarissa Shephard, Georgia Tech & Emory University
Christian Waiblinger, University of Tubingen
Cornelius Schwarz, University of Tubingen
Garrett B. Stanley, Georgia Tech& Emory University

How Dynamic is Encoding? State-dependent Feature Selectivity in Tactile Sensing

We live in a dynamically varying sensory world, and yet our fundamental understanding of how the brain processes sensory information is based on static models of encoding. Utilizing the rodent vibrissa pathway as a model system, in this collaborative project we have directly investigated dynamic encoding in the context of thalamocortical electrophysiology and behavior. Beyond acting as a simple relay, the thalamus acts as a gate for the peripheral signals, controlling what does and does not get transmitted to cortex. Furthermore, this gating is dynamic, and can be influenced through both bottom-up sensory influence, and top-down mechanisms related to wakefulness and attention. In one line of investigation, we explored the bottom-up effect of stimulus adaptation on the encoding of features in the whisker thalamocortical circuit of the anesthetized rat using a signal-in-noise paradigm. We recorded single unit activity in the ventral posterio-medial (VPm) region of the thalamus, and found that bottom-up adaptation regulated the degree of thalamic bursting, and that this subsequently regulated the balance between detectability and discriminability of the sensory signals. Biophysical modeling of the encoding suggests that the background noise serves to modulate the underlying membrane resting potential, which in turn regulates thalamic bursting and detectability/discriminability balance. In a parallel behavioral investigation, we set out to investigate which aspects of the signal are transmitted by thalamus and used to generate the animal's percept, and to further test whether this transmission is adaptive, i.e. is influenced by presenting different sensory environments. We trained head-fixed rats to detect precise whisker stimuli that mimic natural signatures (tagged 'slip-like events') embedded in broadband noise. Analyzing reaction times we found that rats extract whisker slips of different shape and direction based on the amplitude relative to the background.

Zhe Chen, New York University
Scott Linderman, Harvard University
Matthew A. Wilson, Massachusetts Institute of Technology

A Nonparametric Bayesian Approach to Uncovering Rat Hippocampal Population Codes During Spatial Navigation

Rodent hippocampal population codes represent important spatial information about the environment during navigation. Several computational methods have been developed to uncover the neural representation of spatial topology embedded in rodent hippocampal ensemble spike activity. Here we extend our previous work and propose a nonparametric Bayesian approach to infer rat hippocampal population codes during spatial navigation. To tackle the model selection problem, we leverage a nonparametric Bayesian model. Specifically, to analyze rat hippocampal ensemble spiking activity, we apply a hierarchical Dirichlet process-hidden Markov model (HDP-HMM) using two Bayesian inference methods, one based on Markov chain Monte Carlo (MCMC) and the other based on variational Bayes (VB). We demonstrate the effectiveness of our Bayesian approaches on recordings from a freely-behaving rat navigating in an open field environment. We find that MCMC-based inference with Hamiltonian Monte Carlo (HMC) hyperparameter sampling is flexible and efficient, and outperforms VB and MCMC approaches with hyperparameters set by empirical Bayes.

Woodrow Shew, University of Arkansas
Wesley Clawson, University of Arkansas
Jeff Pobst, Washington University
Yahya Karimipanah, Washington University
Ralf Wessel, Washington University

Adaptation Tunes Cortical Dynamics to a Critical Regime during Vision

Cortical circuits adapt when presented with changing sensory input. Such adaptation is a homeostatic process known to prevent excessive firing rates and correlations. Adaptation also optimizes aspects of sensory function by tuning gain, stimulus selectivity, and sensory information transmission. What regime of cortical network dynamics supports the moderate firing rates, the intermediate correlations, and the anticipated functional advantages brought about by adaptation? What is the network-level *modus operandi* that emerges during adaptation?

A possible answer to these questions is offered by recent computational models in which activity-dependent adaptation dynamically tunes the network to a "critical" regime at the boundary between two extreme types of network dynamics: one with low firing rates and weak correlations, the other with high firing rates and strong correlations. The critical regime strikes a balance between these extremes, with moderate firing rates and correlations. Moreover, the critical regime can provide functional advantages including optimal dynamic range and information transmission. Thus, optimized function together with moderate firing rates and correlations are associated with both adaptation and the critical regime. This commonality condenses the two questions raised above to one: Does adaptation to dynamic sensory input tune cortex network dynamics towards the critical regime?

Here, we addressed this question in turtle visual cortex during naturalistic stimulation of the retina and in a companion computational model. We obtained long-duration 96-electrode recordings of population activity from visual cortex, allowing us to measure multi-scale spatiotemporal patterns of visually-evoked activity and quantify their statistics. We examined statistics of "neuronal avalanches", which are bouts of elevated population activity with correlations in space and time. We carried out a parallel study in a model network, implementing adaptation in the form of synaptic depression.

In both the experiments and the model, we found multifaceted evidence for the critical regime after a transient period of adaptation. In contrast, during the transient period, avalanches were predominantly large scale, inconsistent with the critical regime. Our findings suggest that adaptation plays a crucial role in tuning cortical circuits towards the critical regime during vision.

Giorgio A. Ascoli, George Mason University
Dan N. Cox, Georgia State University

Cytoskeletal Mechanisms of Dendrite Arbor Shape Development

A quantitative systems-level understanding of how multiple local interactions of cytoskeleton components during differentiation define mature dendrite arbor shape is still missing. How are these processes regulated in a class-specific manner to give rise to the characteristic arbor shapes of different neuron classes? Our "closed loop" computational approach seamlessly links the wet lab with quantitative analysis and modeling software. Starting with 4D series of in vivo multi-parameter confocal imaging data, we are advancing state-of-the-art software to accurately reconstruct the neurons, compute morphological features, generate computational anatomical models, and compare simulated data with actual data to aid the planning of the next round of wet experiments. This strategy requires integration of different disciplines, including genetics and developmental neurobiology, in vivo multi-parameter confocal imaging of fluorescent proteins, computer vision, computational morphological modeling, and neuroinformatics. Specifically, we are testing four fundamental hypotheses on the role of cytoskeletal organization and dynamics during development in determining emergent class-specific dendrite arbor shape in a Drosophila larval sensory neuron model using genetic manipulations and computational tools (PMIDs: 21811639, 23902691). First, we simultaneously acquire temporal sequences of whole dendrite arbor structures and multiple co-registered sub-cellular components by high-resolution time-lapse multi-channel confocal microscopy. We then digitally reconstruct both the neurites and the cytoskeletal distributions with semi-automated tracing algorithms, thus enabling high-throughput identification of spatial-temporal associations between multiple sub-cellular components imaged within the dendrite arbor and quantitative morphometric features (DiademChallenge.org). Lastly, we use the extracted statistics to stochastically simulate the growth of anatomically realistic virtual neuronal analogues and underlying developmental dynamics (PMID: 18483611, 18451794). Comparing simulated and real arbors as well as their subcellular components helps assess the plausibility of the model (that is, of the hypothesized biological interactions) or reveal additional necessary mechanisms. We plan to share both experimental data sets (NeuroMorpho.org) and corresponding models freely and publicly for broadest community impact.

Namrata Mohapatra, Goethe-University
Songqing Lu, University of Texas at San Antonio
Fidel Santamaria, University of Texas at San Antonio
Peter Jedlicka, Goethe-University

Modeling the Effects of Neuronal Morphology on Dendritic Chloride Diffusion and GABAergic Inhibition

Gamma-aminobutyric acid receptors (GABAARs) are ligand-gated chloride (Cl-) channels which mediate the majority of inhibitory neurotransmission in the CNS. Spatiotemporal changes of intracellular Cl- concentration alter the concentration gradient for Cl- across the neuronal membrane and thus affect the current flow through GABAARs and the efficacy of GABAergic inhibition. However, the impact of complex neuronal morphology on Cl- diffusion and the redistribution of intracellular Cl- is not well understood. Recently, computational models for Cl- diffusion and GABAAR-mediated inhibition in realistic neuronal morphologies became available [1-3]. Here we have used computational models of morphologically complex dendrites to test the effects of spines on Cl- diffusion. In all dendritic morphologies tested, spines slowed down longitudinal Cl- diffusion along dendrites and decreased the amount and spatial spread of synaptically evoked Cl- changes. Spine densities of 2-10 spines/m decreased the longitudinal diffusion coefficient of Cl- to 80-30% of its value in smooth dendrites, respectively. These results suggest that spines are able to limit short-term ionic plasticity [4] at dendritic GABAergic synapses. Computational predictions will be tested by assessing synaptic inhibition with chloride imaging, electrophysiology, and 2-photon neurotransmitter photolysis.

Supported by the NSF/BMBF (US-German Collaboration in Computational Neuroscience, No. 01GQ1203A).

References

[1] Jedlicka P, Deller T, Gutkin BS, Backus KH: Activity-dependent intracellular chloride accumulation and diffusion controls GABAA receptor-mediated synaptic transmission. Hippocampus 2011, 21:885-898.
[2] Doyon N, Prescott SA, Castonguay A, Godin AG, KrÜger H, Koninck YD: Efficacy of synaptic inhibition depends on multiple, dynamically interacting mechanisms implicated in chloride homeostasis. PLoS Comput Biol 2011, 7(9):e1002149.
[3] Lewin N, Aksay E, Clancy CE: Computational modeling reveals dendritic origins of GABAA-mediated excitation in CA1 pyramidal neurons. PLoS One 2012, 7(10):e47250.
[4] Raimondo JV, Markram H, Akerman CJ: Short-term ionic plasticity at GABAergic synapses. Front Syn Neurosci 2012, 4:5.

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Asif Rahman, The City College of The City University of New York
Marom Bikson, The City College of The City University of New York
Lucas C. Parra, The City College of The City University of New York

Synaptic Input Required for Firing is Modulated by Extracellular Electric Fields

Transcranial direct current stimulation (tDCS) is gaining importance both in clinical as well as basic neuroscience research. tDCS generates weak electric fields in the brain of ~1 V/m per mA of current applied. This causes an incremental passive membrane polarization in pyramidal cells of up to 0.1mV. This incremental polarization has been shown to acutely affect spike timing, modulate firing rate, and synaptic efficacy. Moreover, plastic changes elicited by electric fields have been assessed in terms of synaptic efficacy. However, neuronal firing for a constant synaptic input has not been documented in-vitro under concurrent stimulation yet.

We hypothesized that due to membrane polarization the synaptic input required for firing will be affected, therefore modulating the neuronal input-output (I/O) function. We first characterized the effect of 35 V/m fields on synaptic inputs (field excitatory post synaptic potentials, fEPSP) and neuronal output (population spike) in the CA1 region of rat hippocampal slices separately. Measurements were taken in three conditions: control, positive and negative fields. DC stimulation that depolarizes the soma and hyperpolarizes apical dendrites, increase the fEPSP by (8.23 $\pm$ 4.44) % and the opposite polarity reduces it by (-14.05 $\pm$ 4.31) %. Population spike is modulated in the same direction, with a (31.08 $\pm$ 10.80) % increase and a (-11.25 $\pm$ 6.36) decrease. A two-compartment model showed that the synaptic input modulation comes from increased driving force at the apical dendrites.

The computational model predicted a symmetric shift of the neuronal I/O threshold. Fields that depolarize the soma induce a leftward shift, increasing the amount of firing for a given input and vice versa. Next, we measured the I/O function under DC fields by simultaneously recording fEPSPs (synaptic input) and population spikes (neuronal output) in CA1. The experimental data shows an effect in the same direction of the prediction. This increased spiking activity of a neuronal population observed here can have important implications for the effect of fields during acute stimulation as well as plastic mechanisms.

Mary Kennedy, Caltech
Thomas Bartol, The Salk Institute for Biological Studies
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Justin Kinney, MIT
Chandrajit Bajaj, University of Texas Austin
Kristen Harris, University of Texas Austin
Terrence Sejnowski, The Salk Institute for Biological Studies

Molecular Simulation of Calcium Transients in a Spine

Molecular simulations can serve many purposes. Here we have used the program MCell to simulate the handling of Ca^{2+} during activation of a spine synapse. Our goal was to determine whether the characteristics of the individual proteins believed to control Ca^{2+} transients in a spine can account for measurements of Ca^{2+} transients in living spines. By "characteristics", we mean binding and enzymatic rate constants measured *in vitro* after purification of the proteins, numbers of proteins in the spine (measured or not), and locations of the proteins (determined by cell biological techniques). This kind of simulation is akin to "reconstitution experiments" in which biochemists assemble a mixture of purified proteins to test whether the mixture can carry out complex functions that occur in a cell. A real reconstitution of a synaptic spine is impractical because of the complex arrangement of proteins in space and along the surfaces of membranes. MCell allows placement of set numbers and densities of proteins within a computer representation of a reconstructed dendrite. It simulates diffusion and stochastic interaction of molecules with resulting state changes. We have incorporated NMDA receptors, AMPA receptors, voltage-dependent calcium channels (VDCCs), Na^{+}/Ca^{2+} exchangers (NCXs), plasma-membrane Ca^{2+} pumps (PMCAs), smooth ER Ca^{2+} pumps, and cytosolic Ca^{2+} "buffers", including calbindin into a reconstruction of a dendrite in stratum radiatum of the hippocampus. Boundaries on their characteristics were determined from *in vitro* data. Release of glutamate was simulated by previously established methods. We made small adjustments to eight parameters to reproduce the size and timing of Ca^{2+} transients measured experimentally. We further constrained the model to reproduce measured Ca^{2+} buffering capacity, and the correct proportions of Ca^{2+} decay attributed to pumps and to diffusion. The model reproduces the first order characteristics of spine Ca^{2+} transients. It can now be used to test the effects of additional proteins and to simulate the behavior of enzymes regulated by Ca^{2+} in the spine.

Harel Z. Shouval, University of Texas Medical School, Houston
Sajiya J. Jalil, University of Texas Medical School, Houston
Todd Charlton Sacktor, SUNY Downstate Medical Center

Atypical PKCs in the Maintenance of Memory: Molecular Model, Experimental Verification

Memories that last a lifetime are stored by changes to synaptic efficacies, which are determined by the state and number of specific synaptic proteins. Synaptic proteins have limited dwell-times in synapses due to molecular turnover and diffusion, leading to a fundamental question: how can this transient molecular machinery store memories that last a lifetime? Synaptic changes, which lead to memory, are synapse-specific and therefore mechanisms that lead to long lasting synaptic efficacies must also reside locally in synapses. Extensive experimental evidence points to atypical protein kinase-C (PKC) isoforms as key components involved in memory maintenance. Further, it is evident that establishing long-term memory requires new protein synthesis. However it is not clear on both the theoretical and experimental levels how these observations lead to the preservation of synaptic changes. We propose a theoretical molecular model that can account for key experimental observations of late-phase long-term potentiation (L-LTP), its protein synthesis dependence, and its dependence on atypical PKC's. Recently several high profile papers, using PKMζ knockout animals, cast doubt on the role of PKMζ in memory maintenance. We propose that the two atypical PKC subtypes, PKMζ and PKCι/λ, can form redundant parallel pathways, making the system more robust. Specifically, in the knockouts compensation at the level of synthesis is able to generate memories when one of these pathways is eliminated. We also show experimental evidence using a selective anti-sense for PKMζ that PKMζ is indeed necessary for the formation of long-term memory in wild type animals, but not in mutants that do not have the PKMζ gene. Further we show that in knockouts PKCι/λ is up regulated; compensating for the lack of PKMζ as proposed in the theoretical model. Our combined experimental and theoretical results account for the apparent discrepancy between the different experiments and explain the mechanisms by which atypical PKC's solve the maintenance problem.

Maria Bykhovskaia, Universidad Central del Caribe
Chung-Yuen Hui, Cornell University
Anand Jagota, Lehigh University
Troy Littleton, MIT

Computational Modeling of the Molecular Machinery Involved in Membrane Fusion

At the cellular level, learning and memory are governed by changes in the efficacy of synaptic transmission and, in particular, by the dynamic regulation of neuronal transmitter release. Neurotransmitters are packaged into synaptic vesicles that dock at the synaptic membrane, undergo a series of preparatory steps and fuse with the synaptic membrane, releasing transmitters into the synaptic cleft. This process is very dynamic, plastic, and highly regulated. The process of docking and fusion is controlled by forces exerted on the vesicle and membrane by a dynamic complex of proteins, and our work focuses on computational molecular modeling to understand its details.

We employed molecular dynamics (MD) computations to understand how neuronal calcium sensor synaptotagmin 1 (Syt1) interacts with the SNARE complex and responds to Ca2+ binding. First, we employed prolonged (several s) MD simulations to investigate Syt1 conformational states. We found that two Syt1 domains tightly interact with a preferable orientation of Ca2+ binding loops facing opposing surfaces. Strikingly, we found that binding four Ca2+ ions to Syt1 C2A and C2B domains destabilize interdomain interactions and drastically enhances Syt1 conformational flexibility.

We combined molecular biology with MD simulations to reveal the residues critical for the Syt1 conformational flexibility and interactions with the SNARE complex. We developed a coarse-grained model that includes a continuum model of the membranes and an alpha-carbon based model for the SNARE complex. We used this model to study the question of force balance between electrostatic repulsion between the membranes and attraction between components of the SNARE complex. Our results show that only a few SNARE bundles, 2-5 in number, are sufficient to overcome electrostatic repulsion bringing the vesicle and plasma membrane surfaces into a docked pre-fusion state with separation of about 2 nm.

Main Meeting Speakers (Saturday)

Yuwei Cui, University of Maryland, College Park
Liu D. Liu, McGill University,
James M. McFarland, University of Maryland, College Park
Christopher C. Pack, McGill University
Daniel A. Butts, University of Maryland, College Park

Cortical Variability, Perception-based Decisions, and Network Activity

Sensory neuron responses in awake cortex can be quite variable across repeated presentations of the same stimulus. In many cortical areas, only a small fraction of neuronal activity is repeatable from trial-to-trial, raising the question of what these neurons are representing in their response, if not the stimulus? Here, we demonstrate a direct link between trial-to-trial variability of cortical neuron responses and network activity that is reflected in local field potentials (LFPs), and show that the network activity is correlated with perceptual decisions. We simultaneously recorded spikes and LFPs with a multi-electrode array from the middle temporal area (MT) of alert macaque monkeys during passive fixation, and also during the performance of a motion discrimination task. A maximum-likelihood based modeling framework that incorporates both the visual stimulus and recorded LFPs was developed to predict MT neuron responses in both conditions. In the passive condition, incorporating LFPs into the model dramatically improved its ability to predict MT neuron responses, and specifically explained the non-stimulus-locked elements of the response. During the motion discrimination task, we found a subset of the network activity could accurately predict correlation between single neuron responses and the subject's decision (i.e., "choice probability"). In addition to demonstrating the network origin of single-neuron modulation during decision making and identifying its signatures in recordings, these results more broadly suggest the importance of including non-stimulus-driven elements in descriptions understanding sensory neuron processing.

Christopher K. Hauser, Wake Forest School of Medicine
Dantong Zu, Wake Forest School of Medicine
M Gabriela Costello, Wake Forest School of Medicine
Terrence R. Stanford, Wake Forest School of Medicine
Emilio Salinas, Wake Forest School of Medicine

Cognitive Modulation of Oculomotor Activity in the Frontal Cortex of Monkeys Performing a Simple Reaction-time Task with Reward Bias

Reward availability is key for guiding goal-directed actions, and can strongly influence choice, reaction time (RT), and movement metrics. We investigated the neural correlates of these effects by asking how the internal expectation of reward modulates perceptual processing and motor planning in the frontal eye field (FEF). Monkeys were trained in a RT variant of the one-direction-rewarded (1DR) task. In each trial, they maintained fixation at a central spot and made a saccade when an eccentric stimulus appeared at one of 4 possible locations, but crucially, only one location was associated with the primary reinforcer, water. The rewarded location varied across blocks of 30-60 trials. Strong behavioral effects were observed; most notably, saccades to rewarded locations were consistently fast (152 ± 28 ms, mean RT ± 1 SD), whereas those to unrewarded locations were slow and much more variable (245 ± 85 ms). We exploited the large spread in RT and spatially distinct reward conditions in the 1DR task to study how individual FEF neurons contribute to saccade production. We found that FEF activity was robustly modulated by reward contingency and covaried with RT in two complementary ways: for some neurons the peak activity increased as a function of RT, whereas for others it decreased. This was true for all three of the traditional neuronal classes found in FEF, visual, visuomotor, and motor. These findings are significant for two reasons. First, it is thought that saccades are triggered when the firing rate of motor-related FEF neurons reaches a fixed threshold, but according to our results, this is true only for the overall average activity. In contrast, for a given individual cell, the presaccadic firing rate attained may indeed vary quite substantially with RT, either positively or negatively. And second, modeling results suggest that the relative activity of the two complementary neuronal populations, which have similar receptive fields but are selective for either fast or slow saccadic responses, is precisely what determines whether the ensuing RT is short or long. These results provide a more nuanced account of the mechanisms whereby neuronal activity in FEF determines saccadic RT.

Patrick T. Sadtler, University of Pittsburgh
Kristin M. Quick, University of Pittsburgh
Matthew D. Golub, Carnegie Mellon University
Steven M. Chase, Carnegie Mellon University
Stephen I. Ryu, Stanford University
Elizabeth C. Tyler-Kabara, University of Pittsburgh
Byron M. Yu, Carnegie Mellon University
Aaron P. Batista, University of Pittsburgh

Neural Constraints on Learning

Learning, whether motor, sensory, or cognitive, requires networks of neurons to generate new activity patterns. As some behaviors are easier to learn than others, we asked if some neural activity patterns are easier to generate than others. Here, we investigate whether an existing network constrains the patterns that a subset of its neurons is capable of exhibiting, and if so, what principles define this constraint. We studied this question using a brain-computer interface (BCI) paradigm, which allows us to directly specify which neural activity patterns we would like the subject to show. We identified a simple network principle that can predict which types of new activity patterns the subjects are able to learn to generate on the timescale of hours. This work provides a novel network-level explanation for why learning some tasks may be easier than others.

Robert Kozma, University of Memphis
Frank Ohl, Leibnitz Institute for Neuroscience, Germany

Phase Transitions in the Auditory Cortex of Gerbils During Reinforcement Learning Indicating Strategy Change

The ability of strategy change, i.e., the change in action selection and action planning while an overarching goal is maintained, is a fundamental, but still hardly understood capability of cognitive systems. Sudden cognitive transitions have been well documented in behavioral and neurophysiological experimental data, but a consistent theory of the underlying spatiotemporal neurodynamics is still missing. Current physiological and theoretical frameworks of learning focus on incremental learning mechanisms (as exemplified by the reinforcement learning framework), while the discontinuous nature of behavioral development observed in strategy change is not well understood.

In this collaborative US-German project (CLION-LIN), we exploit the experimental and theoretical accessibility of a particular rodent learning model, to analyze the neuronal mechanisms of behavioral strategy change. Our aim is to understand better the nature and functional role of state transitions in brain networks as the basis of cognitive strategy change. Partner LIN performs behavioral experiments and neurodynamics measurements using multi-electrode arrays in the auditory cortex (4x5 array) and ventral striatum of Mongolian gerbils trained using classical conditioning paradigm. Partner CLION provides graph theoretical models featuring phase transition behavior, to interpret the experimental findings.

Our analysis at present focuses on data obtained over the auditory cortex (AC) with “Go” or “No-Go” conditions during a training sequence of 4 to 6 days for any given subject. Gerbils typically perform poorly in days 1 and 2; however, they exhibit sudden improvement in their performance from day 2 or 3 (depending on the individual subject). The good performance is maintained for the rest of the trials. Our analysis confirms that AC array measurements produce classifiable amplitude modulation (AM) patterns in the gamma band, in agreement with expectations. Moreover, using a generalized Granger causality metric (NC), we document the formation of enhanced connectivity between certain electrode locations in the auditory cortex as learning progresses, reaching a plateau after day 2 or 3. Such behavior supports the hypothesis about the formation of Hebbian cell assemblies (HCA) during reinforcement learning, leading to a phase transition when a critical connectivity density pattern is reached. Work is underway to interpret these findings using neuropercolation model of the cortical tissue at the edge of criticality.

Arup Sarma, The University of Chicago
Xiao-Jing Wang, New York University
David J. Freedman, The University of Chicago

Mixed Selectivity and Multiplexing of Visual and Cognitive Encoding during Category Learning

The lateral intraparietal (LIP) area can encode the category membership of visual stimuli following long-term categorization training. However, little is known about how neuronal representations in LIP develop and change throughout the learning process. To address this, we recorded from neuronal populations in LIP before, during, and after categorization training. Two monkeys were initially trained to perform a delayed match to sample (DMS) task using 360° of motion directions as sample and test stimuli. Monkeys released a lever to indicate whether a test stimulus was the same direction as a previously presented sample, using 8 sample directions. Monkeys were then trained on a delayed match to category (DMC) task (using the same stimuli as DMS) in which they indicated whether sample and test stimuli were in the same category, defined by an arbitrary category boundary.

We recorded LIP neurons during the DMS task (N=168), partially trained DMC task (N=171), and fully trained DMC task (N=124). A majority of neurons were direction selective (one-way ANOVA, $P<0.01$) during sample presentation in the DMS task and both DMC training stages. Prior studies in LIP during the DMC task found strong, and often sustained, category selectivity during the memory delay. Surprisingly, very few LIP neurons in our study showed persistent activity or selectivity during the DMS task, prior to categorization training. After categorization training, we found a much greater incidence of persistent delay activity and stronger direction selectivity during the delay (chi-square test, $P<0.01$). In both DMC training stages, we observed mixed selectivity for direction and category during the sample period, while delay-period category selectivity only appeared in the final DMC training stage.

This suggests that category learning has a marked impact on both the selectivity and temporal dynamics of neuronal activity in LIP. In particular, categorization training was accompanied by an increase in mixed selectivity and an increase in persistent delay-period activity. This gives insight into how encoding of cognitive factors emerges during learning, and suggests that training on more abstract or demanding tasks (e.g. categorization) can enhance persistent network activity and selectivity for tasks which require short term working memory.

Stephanie Jones, Brown University
Christopher Moore, Brown University

A Novel Neocortical Beta Origin Hypothesis: Converging Evidence from Humans, Computational Modeling, Monkey, and Mouse

Beta frequency (15-29 Hz) neocortical rhythms are among the most prominent activity measured non-invasively in humans with electro- and magnetoencephalography (EEG/MEG), particularly in sensorimotor cortices. Evidence suggests spontaneous beta inhibits perception (Jones et al. 2010) and motor action. Further, beta decreases with attention and movement suggesting the flexible modulation of beta is necessary for optimal function. In Parkinson's Disease (PD) this modulation is disrupt and over-expression correlates with motor deficit. Understanding the cellular level generators of beta is crucial to dissecting its functional importance and targeting treatments when it is disrupt in disease.

Combining computational neural modeling, human brain imaging (MEG), and electrophysiological and optogenetic techniques in mice we have previously proposed a novel hypothesis on the mechanistic origin of beta. This hypothesis predicts that beta emerges from the dendritic integration in cortical pyramidal neurons of two nearly-simultaneous stochastic 10Hz rhythms from lemniscal and non-lemniscal thalamus to distinct cortical layers. This rhythmic drive creates ongoing rhythms that have the same characteristic features of the spontaneous rhythm in human somatosensory cortex, which contains a complex of alpha (7-14H Hz) and beta components (Jones et al. 2009). The stochastic nature of the input produces beta "events" that last typically only 1-2 cycles in agreement with the recorded human data. Here, we extend our investigation to characterize the individual beta "events". Reproduction of these events in our model suggests that the key feature defining a beta "event" is a strong excitatory synaptic input to the distal dendrites of pyramidal neurons that lasts a beta period (~50ms). Further, we present initial evidence from laminar recordings in both mice and monkeys that validate this prediction. We also present recent intracranial recordings in human thalamus from patients undergoing deep brain stimulation for PD and Essential Tremor that are supporting and informing our model development. In total, our results are providing a deeper mechanistic link between beta rhythms and sensorimotor processing.

Fanny Cazettes, Albert Einstein College of Medicine
Brian J. Fischer, Seattle University
Jose Pena, Albert Einstein College of Medicine

Emergence of a Reliability Code in the Owl's Midbrain

Perception can be seen as statistical inference. This implies that the brain generates an internal model of stimulus statistics. Yet, demonstrations that the brain represents natural statistics are scarce and the mechanisms for how this is achieved are unknown. A model of probabilistic computation in the owl's midbrain has proposed that the reliability of auditory cue is encoded in the selectivity of neural responses. Here, we focus on the interaural time difference (ITD), a primary cue used to localize sound in horizontal space. We estimated the statistical uncertainty of this cue as a function of direction from the filtering effect of the head on the sound arriving at the two ears. We show that these statistics are captured by the tuning properties of auditory neurons. The widths of the ITD tuning across the neural population match the statistical dependence of ITD on sound-source direction in azimuth. This effect results from the auditory system adapting its basic organizational principle, tonotopy, to represent reliability along with space. Additionally, by manipulating the reliability of the cue, we demonstrate that the tuning curve widths increase as the reliability of ITD decreases. Using a model, we demonstrate that spatial-tuning width can represent reliability dynamically by virtue of direction-dependent frequency convergence and the cross-correlation mechanism that generates the selectivity. Finally, we show that as stimulus uncertainty changes, the owl's behavior can only be decoded from the population if it is reliability encoded in the widths. Thus we provide a complete case for a sensory system representing cue reliability, where it occurs, and how it emerges.

Julie Elie, University of California, Berkeley
Hedi Soula, INRIA, France
Frederic Theunissen, University of California, Berkeley

Encoding Models Reveal How and When the Meaning of Communication Calls is Extracted by the Avian Auditory Cortex

Understanding how the brain extracts meaning from vocalizations is a central question in auditory research. Communication sounds distinguish themselves not only by their acoustical properties but also by their information content. Here, we are developing the birdsong model to investigate how the auditory system extracts invariant features to categorize communication sounds according to their social meanings. Songbirds have been used extensively to study song learning but the communicative function of their calls and their neural representation has yet to be examined. In our research, we first generated a library containing the entire zebra finch vocal repertoire and organized communication calls into 9 different categories. We then investigated the neural representations of these semantic categories in primary and secondary avian auditory areas. To decrypt the neural computations underlying the semantic classification of these calls, we compared the results of three encoding models of the neural response that took into account the acoustical properties of the sound and their semantic grouping either separately or together. By examining the predictions of the different models for the 290 cells that encode a significant amount of information about semantic, we show that neural responses in a majority of these neurons are best explained by non-linear transformations of spectro-temporal sound patterns and that these non-linearities emphasize the semantic grouping of calls. In addition, we used time-varying models in order to examine the evolution of the semantic coding through the course of a call presentation. On average, neurons tend to be linearly tuned to acoustic spectro-temporal features during the first 70ms following the call onset. This initial auditory tuning is followed by a period of 80ms centred around 110ms where semantic information significantly enhances the prediction of the neural response. Combining these neurophysiological results with the anatomical properties of cells gives new insight into the neural representation of meaningful stimuli in the avian auditory neural network.

Roland Fleming, University of Giessen, Germany
Steven W. Zucker, Yale University

Key Features from Texture, Shading, and Color Flows Enable Surface Inferences

What information is available for inferring the shape of an apple? Brightness variations provide a shape-from-shading cue, and surface markings provide a shape-from-texture cue. But at the same time pigmentation in the skin of the apple also leads to brightness changes, which frequently confound those due to shading. We present evidence that crucial information is extracted from the variation manner that local image orientation signals vary across projected surfaces ('orientation flows'), and that these flows provide the foundation for surface inferences. Striking regularities in the flows emerge when computer renderings of shaded and textured objects are represented in a (position, orientation) space. These orientation flows change when illumination and texture patterns change, leading to a number of psychophysical predictions. A model of shape inference from shading flows reveals how surface and light source properties emerge from the flows, and the geometry of the model could be learned by the visual system. Finally, returning to the apple example, we show how flows of color can separate material from reflectance changes. Physiologically, these flows can be represented by oriented color double-opponent cells.

Most importantly, these flows remain invariant for certain key features of shape, which we conjecture anchors the shape inference process.

Sabato Santaniello, Johns Hopkins University
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Erwin B. Montgomery, Greenville Neuromodulation Center
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Sridevi V. Sarma, Johns Hopkins University

Neural Restoration via Loop-based Reinforcement: A Mechanism of Therapeutic High Frequency Stimulation in Parkinson's Disease

Deep brain stimulation (DBS) is a clinically recognized treatment for movement disorders in Parkinson's disease but its mechanisms remain elusive. Two questions have hampered our understanding of the mechanisms of DBS so far: (1) Why is DBS therapeutic only when the frequency of stimulation belongs to a specific high range (130-180 Hz)? (2) What is the fundamental mechanism that keeps high frequency DBS therapeutic even if the stimulation target is moved across distinct (and physiologically different) structures in the brain?
To answer these questions, we developed a detailed computational model of the direct pathway in the motor loop, including the motor cortex, ventro-lateral thalamus, striatum, and internal globus pallidus, and we validated the neuronal activity of each structure with single unit recordings from non-human primates and rats, both in normal and parkinsonian conditions. Then, we used the model to study the effects of several DBS settings (i.e., DBS frequency ranged from 20Hz to 180Hz, both regular and irregular DBS pattern) via numerical simulations.

Regarding to 1), we show that, differently from current hypotheses, the therapeutic effects of DBS do not entirely stem from local changes of the neuronal activity in the stimulation target but they also depend in part on the fact that the motor loop is a closed reentrant system. Due to the closed-loop nature, perturbations induced by consecutive DBS pulses may travel along the system both forward and backward through multiple pathways, they can rendezvous, and positively overlap if the pulses are constantly spaced (DBS is regular) and close enough one to one another (DBS is high frequency). This suggests that DBS globally impacts the entire loop, the therapeutic merit of clinically-used DBS settings depends on the anatomical properties of the treated system, and DBS in different individuals may require slightly different settings, which is consistent with clinical practice.

Regarding to 2), we show that the rendezvous occurs in the striatum and may determine a dominant discharge pattern that percolates through the basal ganglia, projects towards the thalamus, and restores the normal function of the thalamo-cortical sub-system, which is primarily involved in the selective dis-inhibition of motor commands.

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Computation-Enabled Ventilatory Control System (CENAVEX)

Diaphragmatic pacing by electrical phrenic nerve stimulation and more recently intramuscular stimulation of multiple respiratory muscles has been demonstrated as a viable approach for ventilatory support following spinal cord injury (SCI). The open-loop stimulation strategy currently utilized for pacing has major limitations including the need for manual stimulation parameter tuning, and inability to alter stimulation parameters to account for muscle fatigue or changing metabolic demand. Our US-French (Florida International University and Institut Polytechnique de Bordeaux) collaborative team is designing and developing a novel computation-enabled adaptive ventilatory control system (CENAVEX) to address these drawbacks. To accomplish our objectives, we are developing a lung-respiratory muscles computational model for testing the abilities of the CENAVEX system, implementing the control scheme in software for real-time computer-based control of ventilation, and implementing the scheme in analog and mixed neuromorphic VLSI hardware with spiking networks, synaptic learning and bio-interface hardware for a standalone system. Assessments in a rodent model with and without chronic cervical incomplete SCI will be utilized. Experiments for diaphragmatic stimulation have been initiated, including development of an endoscopic stimulation electrode implantation procedure. These open-loop experiments with diaphragmatic neuromuscular stimulation have successfully shown ventilatory supplementation in the non-SCI anesthetized rat. Our first ventilatory computational model, which includes Hill-type muscle models interacting with the dynamic compliance of the lungs and surrounding structures, has shown that, even with high levels of fatigue, respiratory muscles are able to handle the typical demands of tidal breathing. Software implementations of an adaptive controller which uses a Pattern-Generator/Pattern-Shaper (PG/PS) closed-loop paradigm have been initiated. The controller can adapt the cyclic frequency and shape of the stimulation profile to multiple muscles in real-time. A spiking neural network (SNN) version of the PG/PS design with the same learning algorithm but Leaky-Integrate-and-Fire neurons and alpha-based synapses has begun. The SNN version will be used for the hardware implementation of the system on FPGAs. For experimental deployment, a hardware control system (MULTIMED) to host the FPGAs has been configured to communicate with a newly developed stimulator that can deliver stimulation pulses as specified by the real-time adaptive control system.

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Jeremy R. Manning, Princeton Neuroscience Institute
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Naseem Al-Aidroos, University of Guelph
Alexa Tompary, New York University
Nicholas Turk-Browne, Princeton Neuroscience Institute
David M. Blei, Columbia University

Hierarchical Topographic Factor Analysis: A Computationally Efficient Method for Computing Full-brain Functional Connectivity

The standard approach to studying functional connectivity in fMRI data involves choosing a "seed region" and then measuring how this seed region's time series correlates with other brain regions' time series (e.g. during a particular experimental condition). An alternative to this "seed region" approach is to compute the full connectivity matrix, looking at every possible pairwise correlation between voxel time series. The benefit of this approach is that it lets us discover interesting patterns that do not involve the seed region; the main drawback is that -- for images with tens of thousands of voxels -- the resulting connectivity matrices contain tens of millions of entries (occupying gigabytes of memory), and can be unwieldy to manipulate. Here, we describe a newly developed algorithm, Hierarchical Topographic Factor Analysis (hTFA) that allows researchers to more efficiently estimate the full brain connectivity matrix without relying on seed regions or ROIs, thereby yielding a more complete picture of the functional connectivity patterns across the entire brain. To accomplish this goal, hTFA re-represents each brain image as a weighted sum of k localized spatial sources, where k << the number of voxels; after enacting this dimensionality reduction process, we can work with a k-sources by k-sources connectivity matrix instead of the (vastly larger) number-of-voxels by number-of-voxels connectivity matrix. A further benefit of hTFA is that it treats multi-subject datasets hierarchically – each individual subject's source parameters (i.e., the locations and widths of the sources) are modeled as a noisy version of a group-level template, making it possible to draw statistical strength from the group when inferring a particular subject's source parameters. Importantly, the hTFA dimensionality reduction process can be enacted quickly, using readily-available computational resources, even when working with full-resolution, multi-subject datasets. In this presentation, I will describe the algorithm; then I will present some representative applications of hTFA to real-world fMRI datasets, including a spatial attention dataset collected by Al-Aidroos, Tompary, and Turk-Browne.

Jack L. Gallant, University of California, Berkeley
Alex T. Huth, University of California, Berkeley
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Cortical Representation of Phonetic, Syntactic and Semantic Information during Speech Perception and Language Comprehension

In the human brain conceptual and linguistic information are represented in multiple representations at a scale finer than can be measured in typical functional MRI experiments. Measurement of this fine-scale information could provide important new insights about conceptual and linguistic processing. To address this problem we used functional magnetic resonance imaging (fMRI) to record brain activity while subjects listened to natural narrative stories. We then used a novel voxel-wise modeling (VM) approach to recover detailed maps of spectral, articulatory, syntactic and semantic information across the cortical surface. Analysis of these maps reveals several interesting aspects of language representation in the human brain. (1) Voxels located more medial in primary and secondary auditory cortex are well fit by spectral and articulatory models, while those more lateral are well fit by syntactic and semantic models. (2) For most regions located outside primary and secondary auditory cortex, the syntatic and semantic models predict better than any low-level model. The one exeption is the motor cortex, where the articulatory model fits better than the other models in some subjects. (3) All subjects share a common semantic space that is mapped systematically across several dozen distinct functional areas located in the temporal, parietal and frontal lobes. (4) Comparison of semantic maps obtained with audio stories to those obtained with silent movies shows that semantic representation in some brain regions is stimulus-specific, while others represent semantic information that is modality-independent. These results provide a much richer view of language processing in the human brain than was available previously. These results might be used to constrain and improve computer systems for language understanding, or to develop brain-machine interface devices for decoding covert, internal human speech.

Poster Session 1 (Friday)

#1

Abhrajeet Roy, University of Minnesota
Sucharit Kytal, University of Minnesota
Vadim Petruk, University of Minnesota
Sheng He, University of Minnesota
Steve Engel, University of Minnesota
Bin He, University of Minnesota

Multimodal fMRI and EEG Neuroimaging Investigation of Binocular Rivalry

We have developed a novel method for simultaneous EEG-fMRI analysis to study binocular rivalry, using frequency-tagged steady-state visually evoked potential (SSVEP) driven by each monocular image. Our novel techniques successfully removed artifact and optimized signals for the SSVEP data collected simultaneously during fMRI. Rivalry-related SSVEP were co-localized with visual cortex activity seen in the fMRI activation maps. We have performed source localization analysis on both the averaged event related potential (ERP) and SSVEP data. SSVEPs were consistently localized to regions in primary visual cortex, even though SSVEP signals originally had a very low SNR when collected inside the scanner, showing that our preprocessing methods for maximizing SSVEP SNR have significant advantages over previous methods. Furthermore, SSVEP sources were generally co-localized with fMRI activation in the visual cortex across subjects. In contrast, Button-press related ERP were localized to frontal, parietal and temporal regions, supporting the idea that wide scale neural networks are involved in the processing of dichoptic stimuli during continuous binocular rivalry.

We have discovered a novel neural marker for the initiation of binocular rivalry using frequency-tagged SSVEPs. When rivaling dichoptic stimuli are frequency tagged at [f2] and [f1], the SSVEP amplitudes reflect perceptual alternations. There are also "intermodulation frequencies" likely reflect interocular interactions. Using a stimulus that induced a continuous spectrum of percepts from fusion to rivalry, data show evidence that the [f2-f1] signal is a correlate of the initiation of rivalry, peaking when rivalry is being initiated. Furthermore, during rivalry, the [f2-f1] component is related to the changes in perceptual state, increasing whenever the perceptual dominance transitions from one eye to the other. Thus the [f2-f1] component is likely a signal for interocular competition.

#2

Thiago Mosqueiro, University of California San Diego
Martin Strube-Bloss, University of Wuerzburg
Maxim Bazhenov, University of California, Riverside
Brian Smith, Arizona State University
Ramon Huerta, University of California, San Diego

Time Integration in Mushroom Bodies and Olfaction Learning

The olfactory modality in the insect brain is capable of discriminating subtle changes in odor mixtures and extract information from complex spatio-temporal patterns. These systems can reliably identify the presence of odors and estimate its concentrations (1). Odorants chemically trigger olfactory receptor cells in the antennae, which relay these signals to the Antennal Lobe (AL). A certain odorant recruit activity of a specific subset of Projection Neurons (PNs) in the AL (2). The PNs then excite the Kenyon cells (KCs) present Mushroom Bodies (MBs), the very same anatomical region where the Extrensic Neurons (ENs) compute odor identity (3). The main hypothesis is that the KCs are a big screen, operating under sparse coding, over which the ENs can easily discriminate the odors. Recent contributions have shown that these systems implement classical Machine Learning strategies (4,5), such as lateral inhibition in EN layer (6). However, most of the current modeling lack the integration of time during the learning process, and mechanistic explanations of how learning is implemented in such scenario is still a conundrum. We show in this study our preliminary results on constructing a model of the MBs using dynamical neuron models. We use electrophysiological recordings from PNs in the AL, while stimulated by two different odorants (3), as input to this network model. We then fit the network parameters by comparing recordings of ENs (in the MB) with the activity of our model ENs. We have developed a Monte Carlo Markov Chain (MCMC) algorithm that converges efficiently to a few parameter values. Especially because we currently do not have data from KCs, we report over-fitting. Our investigations show that, to fit the EN activity reasonably well, sparse coding in KCs is necessary.

[1] Bazhenov, Huerta, Smith, J Neurosci 2013 33:5686
[2] Joerges, Kuttner, Menzel, Nature 1997 387:285
[3] Strube-Bloss, Herrera-Valdez, Smith, Plos One 2012 7:e50322
[4] Nowotny, Huerta, CISS

#3

Michelle M. McCarthy, Boston University
Nancy Kopell, Boston University
Xue Han, Boston University

Deep Brain Stimulation to the Parkinsonian Subthalamic Nucleus Can Restore Function in Striatal Networks: A Model

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) can be highly effective in improving motor function in patients with Parkinson's disease. Its therapeutic mechanism of action is currently unknown. DBS is most effective at reducing Parkinsonian motor pathology if the frequency of stimulation is relatively high (~130 Hz). However, DBS at beta frequency is either ineffective or may worsen Parkinsonian motor symptoms. These findings suggest that interruption of the exaggerated beta frequency rhythms found in the Parkinsonian basal ganglia may be involved in the therapeutic action of DBS. Previous computational models suggest that robust beta oscillations can emerge in networks of striatal medium spiny neurons (MSNs) in the presence of high cholinergic tone, a condition relevant to Parkinson's disease. An interaction between the MSN synaptic GABAa current and the intrinsic membrane M-current promotes the formation of beta oscillations in the model striatum. In the current work, we study how DBS may be interfering with the production of exaggerated beta rhythms in striatal networks. We find that a subset of neurons in the external segment of the globus pallidus (GPe), which projects to the striatal MSNs, can normalize the MSN network dynamics when driven to spike at high frequency (~ 130 Hz): returning the power of the striatal beta oscillations to normal, non-Parkinsonian levels. Conversely, input from the GPe neurons to the striatum at beta frequency increases the beta power in MSN networks. We show that beta frequency inhibitory input to the MSN network creates resonance within the MSN network, increasing beta frequency spiking of the population of MSNs. In contrast, high frequency (130 Hz) inhibitory input to the MSN network leads to increased inhibition of the network, opposing the increased excitation of the indirect pathway MSNs in the Parkinsonian state. These findings suggest that a therapeutic mechanism of DBS to the STN may engage network mechanisms in the indirect pathway of the basal ganglia and lead to restoration of striatal network dynamics.

#4
Xue Han, Boston University

Origin and Propagation of Parkinsonian Beta Oscillations in the Basal Ganglia-thalamo-cortical Loop

Enhanced beta-band oscillations (15-30 Hz) are observed in the basal ganglia-thalamo-cortical loop of Parkinson's disease (PD) patients and are correlated with bradykinesia. Deep brain stimulation alleviates Parkinsonian motor symptoms and reduces the level of beta oscillations in PD patients. However, the mechanism by which beta oscillations emerge in the Parkinsonian state is unknown. Previous computational modeling has shown that interactions between the M-current and GABAA currents in striatal medium spiny neurons (MSNs) increase beta oscillations. Dopamine tonically inhibits acetylcholine release and increased cholinergic tone in the striatum is characteristic of PD; this can lead to Parkinsonian beta oscillations even in the absence of long-term striatal plasticity. We have previously shown that infusion of the acetylcholine agonist carbachol into the striatum can induce strong, persistent beta-band oscillations in the local field potential (LFP) of the striatum. Here, we used optogenetic stimulation of cholinergic interneurons (ChIs) and pharmacologic application of an acetylcholine agonist to examine how cholinergic activity in the striatum induces beta-band oscillations, and how these oscillations propagate from the striatum to the subthalamic nucleus (STN) and to deep layers of motor cortex (M1).

#5

Bijan Pesaran, New York University
Nathaniel Daw, New York University

Coherent Neuronal Ensembles are Rapidly Recruited when Selecting a Movement Plan

Selecting and planning movements recruits neurons in many different areas of the brain but how ensembles of neurons select movement goals is unknown. Coherent neural activity may provide a mechanism by which ensembles of neurons communicate with each other to select goals. If so, neurons that form distributed, long-range and locally-coherent ensembles may signal newly-planned movements before other ensembles. We recorded neuronal activity in the lateral and medial banks of the intraparietal sulcus (IPS) of the posterior parietal cortex (PPC), while monkeys made choices about where to look and reach and decoded the activity to predict the choices. We find that ensembles of neurons with distributed coherent activity extending within and across the IPS predict movement choices substantially earlier than other neuronal ensembles. We propose that selecting where to move depends on a distributed network of coherently-active PPC neurons that extends within and across the IPS.

#6

Florence Campana, Georgetown University Medical Center
Jacob Martin, Georgetown University Medical Center & CNRS, France
Levan Bokeria, Georgetown University Medical Center
Ben Trans, Georgetown University Medical Center
Xiong Jiang, Georgetown University Medical Center
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Ultra-rapid Object Localization: Shortcuts in the Brain's Visual Hierarchy?

Prior studies have indicated that the human visual system can perform rapid object detection based on a single pass through the visual hierarchy, in about 200ms. However, this "Standard Model" was recently challenged by demonstrations that reliable saccades to images containing faces were initiated as early as 120-130ms after image onset (Crouzet et al. 2010, 2012). The short latency of these saccades suggest that instead of the classic hierarchical model, in which objects can only be coded at the very top of the system, "objects" can be detected by neurons located in early areas.

While the project is still in its first year, preliminary data from eye tracking, EEG, fMRI and computational modeling provide converging support for our core hypothesis. Using eye tracking, we find that participants trying to saccade as fast as possible to a real face in the presence of a "configural" face (whose parts were moved) actually saccade as often to the configural as to the real face, compatible with ultra-rapid face detection being based on simple features selective for face parts, rather than on more high-level, holistic representations (as, e.g., found in the fusiform face area). Besides, through computational modeling using the HMAX model of object recognition in cortex (Riesenhuber & Poggio, 1999), we can show that neuronal selectivities in early visual areas can suffice to build simple face detectors. Moreover, preliminary results show that EEG activity starting around 50 ms after the appearance of a face target predicts its location (left or right). Finally, preliminary fMRI data are compatible with the existence of face-selective representations in early visual areas.

In sum, ongoing work using various techniques suggest that, in contrast to the prevailing "Standard Model", object detection for particular object classes might be based on selective representations in early visual areas, much earlier in the cortical hierarchy than usually assumed. This early selectivity presumably underlies our outstanding ability to rapidly detect and saccade to faces. Future work will explore whether early visual object-selective representations can be trained for novel detection tasks as well, to permit ultra-rapid localization of arbitrary objects.

#7

Urs Koester, University of California, Berkeley
Charles Gray, Montana State University

Laminar Structure of Gamma Activity in Cat Visual Cortex

Stimulus-dependent oscillations of neuronal activity are a robust feature of the mammalian visual cortex. However the laminar organization of this activity is poorly understood. One of the goals of the CRCNS project is to further elucidate the laminar profile of oscillatory activity. We recorded neuronal responses to full-field, drifting sine wave gratings, varying in direction, spatial frequency and temporal frequency, from all cortical layers simultaneously using silicon polytrodes in cat primary visual cortex. Data was obtained from 4 animals and the laminar position of the polytrode at each recording site was confirmed histologically. Stimulus-selective oscillatory activity in the gamma band of the LFP was found to be strongest in cortical layers II/III and upper layer IV. Unit activity is synchronized across all layers, with layer IV activity leading deep and superficial layers, and with layer II/III showing the strongest phase lags. LFP activity is locked to the local unit activity, suggesting that gamma oscillations play a role in synchronizing activity across the cortical column.

#8

A. Kuznetsov, IUPUI
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M. Mamelli, Institut du Fer a Moulin, INSERM, France
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A Model for VTA Circuitry: Toolbox for the Study of Addictions

Dopamine neurotransmission has been found to play a role in the physiology of motivational states and its dysfunction underlies psychiatric disorders including addiction. Midbrain dopaminergic (DA) neurons display two distinct patterns of spiking: low frequency tonic spiking and short burst-like episodes of high-frequency spiking, which occur following an unpredicted stimulus perceived as rewarding in vivo. Synaptic inputs are suggested to be responsible for the bursts, but the mechanisms are not clear. In order to explore this, we model the circuitry of the ventral tegmental area (VTA) and analyzed the influence of synaptic inputs on the model. We find that the burstiness (the number of spikes in bursts) is drastically reduced when NMDA, but not AMPA receptors are blocked. AMPA receptor contributes to bursting maximally (around 20%) when its conductance is approximately 1/30 of the NMDAR, which is very close to their ratio measured in experiments. The data on the DA levels during the blockade of the DA transporter (by cocaine) applied to calibrate the model revealed interesting properties of the DA release/reuptake system. The model predicts that sharp activation of the DA transporter is necessary to prevent steep increases in the extrasynaptic DA levels during bursts. Further, the D2 autoreceptors are near their saturation in control conditions so that an increase in the extrasynaptic DA never causes a blockade of firing. When DA and GABAergic neurons are combined to simulate the local circuitry of the VTA, we find that high-frequency firing can be facilitated by the interaction between these two types of neurons. In particular, when GABA inputs are synchronized, the GABAa receptor currents contribute to high-frequency firing of the DA neuron by augmenting the fast AHP. When the GABA inputs are desynchronized, they only inhibit the DA neuron, and a burst emerges at the offset of these inputs, according to the disinhibition mechanism. Thus, the study suggests a combination of NMDA, AMPA and GABA receptor activation that contributes most significantly to the bursting pattern of the VTA DA neurons. These mechanisms are explored in the context of the action of addictive drugs (e.g. alcohol) and salient environmental stimuli.

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#9

Bruno Olshausen, University of California, Berkeley
Urs Koester, University of California, Berkeley
Charles Gray, Montana State University
Chris Rozell, Georgia Institute of Technology

Do V1 Neurons Have Receptive Fields?

The idea that the response properties of visual neurons may be characterized in terms of "receptive fields" is widely accepted in vision science, and it has inspired the computational architecture of computer vision systems (so-called "deep nets"). Yet a closer examination of how neurons actually respond to time-varying natural scenes, the complex neural architecture of visual cortex, and the biophysical properties of dendritic trees, leads us to question this idea. This CRCNS project presents neurophysiological evidence that V1 response properties are not well described in terms of receptive fields, as it is extremely difficult to predict many aspects of a neurons response to time-varying natural images (or even gratings) in terms of a direct function of the stimulus. Indeed, the computations required by perception demand far more than a feedforward processing chain, but rather rely upon inferential processes to disentangle scene properties. Disentangling requires propagating information both within and between levels of representation in a bi-directional manner. The inferential framework shifts us away from thinking of "receptive fields" and "tuning" of individual neurons, and instead toward how populations of neurons interact via horizontal and top-down feedback connections to perform collective computations.

#10

Dina Popovkina, University of Washington
Eric Nicholas, University of Washington
Majid Moshtagh, University of Washington
Anitha Pasupathy, University of Washington
Wyeth Bair, University of Washington

Advancing Models of Shape Selectivity in V4

Our goal is to develop models of shape processing in the ventral visual pathway that accurately predict responses of V4 neurons to a wide variety of visual stimuli. Past work has shown that V4 neurons are tuned to contour features at specific positions along the boundary of simple shapes (Pasupathy and Connor, 2001, J Neurophys 86:2505-19), and this selectivity for contour curvature has been fit successfully with a hierarchical model (Cadieu et al., 2007, J Neurophys 98:1733-50). However, we are collecting novel data sets that present a challenge to existing V4 models using stimuli that include (1) variations in luminance and color contrast, (2) the addition of occluding shapes and textures, (3) the addition of a background texture, and (4) outlines vs. filled shapes. We seek to determine the nature of modifications to existing V4 models that are required to account for responses to these more complex stimuli, thereby gaining deeper insight into mid-level visual representation. We will present our latest electrophysiological and modeling results and will describe our web-based modeling framework that is designed to facilitate open collaboration in elucidating the neural basis of visual perception.

#11

Honi Sanders, Brandeis University
Daoyun Ji, Baylor College of Medicine
John Lisman, Brandeis University

Does Rate Remapping Interfere with Phase Coding in Hippocampal Place Cells?

Place cells in the hippocampus preferentially fire when an animal is in a particular location in a given environment, so the population collectively represents the spatial location of the animal. However, the precise *timing* of spikes with respect to the ongoing theta cycle (phase coding) carries important information (place can be more accurately predicted if theta phase is considered). Another aspect of neural coding in the hippocampus is the unusual way in which sensory information is encoded. Specifically, there is a conjunctive code in which a sensory item at a given place is encoded by the firing rates of the place cells that represent that place (rate remapping). A key question that arises from these facts is how the same cells organize their firing to provide two separate streams of information through two separate aspects of its firing behavior, spike rate and spike timing. In particular, a possible concern is that increased firing rate of a place cell that encodes a sensory item might degrade the precision of the phase code if extra spikes occur at phases of theta not representative of where the animal is in its place field.

In this project, we have analyzed *in vivo* extracellular recordings of place cell spiking activity and the local field potential in dorsal CA1 of rats. The rats were trained on alternation task on a figure 8-shaped maze. Each time the rat went down the central arm, it had to go the opposite direction of the choice it had taken on the previous lap. Many cells with place fields on the central arm rate remapped depending on which arm the rat is coming from, as previously reported (Ji and Wilson, J. Neuro., 2008). We found that changes in firing rate of place cells on the central arm during different trajectories did not cause degradation in the precision of the theta phase of spikes. This occurs because 1) an increase in the probability that there will be any spikes at all on a given theta cycle (thus phase need not be compromised and 2) an increase in the probability of brief multi-spike bursts (because the interval between spikes is so short, phase is not compromised). Thus rate remapping does not compromised phase coding.

#12

Pavel Sanda, University of California, Riverside
Tiffany Kee, University of California, Riverside
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Mark Stopfer, National Institute of Health
Maxim Bazhenov, University of California, Riverside

Odor Transformations through Multiple Layers of the Insect Olfactory System

Neural representations of odors undergo multiple transformations as they progress through the olfactory system. To examine the odor information content in different structures of the insect brain, we designed a model of the antennal lobe (AL)-mushroom body (MB)-lateral horn (LH) network based on experimental recordings in the locust (Schistocerca americana).

Using single projection neurons (PNs) of the AL for classification yielded low accuracy (20-50% error rate; 50% = chance). Interestingly, most individual PNs showed greater accuracy either for high or low odor concentrations, but not for both. By contrast, many individual lateral horn neurons (LHNs) (receiving input from 70% of PNs in our model) showed moderate discrimination accuracy (30-35% error rate) for the entire range of odor concentrations and odor-pairs constructed to share varying degrees of similarity. When the full population of each type of neuron was used for odor classification, classification accuracy increased dramatically for all odor pairs. Odor classification improved with increasing stimulus duration: Kenyon cell (KC) and LHN ensembles reached optimal discrimination (<5% error) within the first 300-500ms of odor responses.

We then tested how odor classification changed upon optimizing connection strengths between PNs and downstream neurons. We applied PCA to spike trains across the PN ensemble; each component was interpreted as an “ideal” downstream neuron receiving inputs from the entire PN population, with connection strengths determined by the coefficients of each given PCA component. Then we tested how sequentially adding additional components changed error rates. The first PCA component provided moderate discrimination accuracy (~20% error rate) even given very similar odors (~99% overlap). Error rates decreased very quickly (below 10%) when the second component was included and saturated with 15-20 components. Our study suggests that even very small populations of LHNs could provide very accurate odor representations if they sampled the large population of PNs, and synaptic weights are optimal. Further, for PNs, LHNs, and KCs, ensemble responses were always much more informative than single cell responses, despite the accumulation of noise along with odor information.

#13

K. M. Shaw, Case Western Reserve University
D. N. Lyttle, Case Western Reserve University
J. P. Gill, Case Western Reserve University
M. J. Cullins, Case Western Reserve University
J. M. McManus, Case Western Reserve University
H. Lu, Case Western Reserve University
P. J. Thomas, Case Western Reserve University

Central Pattern Generators (CPGs) Must Integrate Sensory Feedback in order to Respond Adaptively in Variable Environments

Dynamical architectures proposed for oscillatory pattern generation include stable limit cycles, sequences of stable fixed points (chain reflexes), and stable heteroclinic channels. Understanding how these different architectures enable sensitivity to sensory feedback remains a challenging problem.
We study this problem using a neuromechanical model of swallowing in the marine mollusk *Aplysia californica*. The model nervous system is represented by three neural pools connected by asymmetric inhibition, with dynamics containing a stable heteroclinic channel (SHC). In an SHC, a stable limit cycle passes near a sequence of saddle equilibrium points, creating localized regions of slowing that can serve as control points. The neural pools drive a simulated swallowing in a biomechanical model of the *Aplysia* feeding apparatus, which in turn sends proprioceptive feedback to the nervous system. By applying a range of fixed forces resisting the inward movement of food during swallowing, we can study how the model adapts to different mechanical loads.

Surprisingly, as the strength of proprioceptive input varies, the neural dynamics switch discontinuously between two distinct dynamical regimes. In the "heteroclinic regime" proprioceptive feedback selectively prolongs the retraction phase of the neural dynamics in response to increased mechanical load. In the "limit cycle regime" proprioceptive feedback only weakly affects the timing of the CPG, and the neural dynamics are insensitive to changing loads. The increased sensitivity to load in the heteroclinic regime allows for more efficient seaweed consumption. Moreover, the behavior of the model in the heteroclinic regime agrees with experimental observations of *Aplysia* feeding behaviors. Phase response curves computed in the different regimes help explain how the timing of sensory feedback shapes the response of the system to perturbations. The differential sensitivity across these regimes suggests neural and mechanical perturbation experiments to probe the dynamical architectures of the *Aplysia* feeding system. It is possible that dynamical architectures other than limit cycles may also be present in many other pattern generator circuits.

#14

W. Baumgartner, University of Colorado at Denver
D.M. Waldera-Lupa, Heinrich Heine University, Germany
D. Pape, Heinrich Heine University, Germany
I. Georgiev, University of Colorado at Denver
I. Grichtchenko, University of Colorado at Denver
L. Hunter, University of Colorado at Denver
K. Stuhler, Heinrich Heine University, Germany
K. Cohen, University of Colorado at Denver
B. Grimpe, Heinrich Heine University, Germany

Artificial Intelligence in Systems Medicine: Finding a Treatment for Paralysis

Spinal cord injury (SCI) affects approximately three million people worldwide. In spite of over a century of research into this area, no treatment is available. A potential solution to this problem lies in capturing the complexity of the underlying processes that lead to regeneration failure and generating a computer model. Therefore, my laboratory is modifying an existing systems biology tool, called Hanalyzer, to work within the SCI domain. We are using the tool to evaluate proteomics results of tissue from contused rat spinal cords collected at different time points after trauma in comparison to sham or unlesioned animals. The contusion injury model is used because it the most common injury leading to SCI in humans. The results are concentrated in a data network and compared with the knowledge network of the Hanalzyer. This knowledge network is build from a wide variety of biological data sources, including the output of text mining, which are extremely general in their goals and which can also be applied to arbitrarily general or specific problems. The Hanalyzer is an example of a novel computational approach to the problems of high throughput data analysis, as it combines reading, reasoning, and reporting (Re3) methods to facilitate knowledge-based analysis of experimental data. The goal of the Re3 system is to assist scientists in forming explanations of the phenomena in genome and proteome-scale data, and to generate significant hypotheses that can influence the design of future experiments.

#15

Axel Wismueller, Ludwig Maximilians University, Germany
Xixi Wang, University of Rochester
Adora M. DSouza, University of Rochester
Lutz Leistritz, Friedrich Schiller University, Germany

A Mutual Connectivity Analysis (MCA) Framework with Convergent Cross-mapping and Non-metric Clustering

We explore a computational framework for functional connectivity analysis in resting-state functional MRI (fMRI) data acquired from the human brain for recovering the underlying network structure and understanding causality between network components. Termed mutual connectivity analysis (MCA), this framework involves two steps, the first of which is to evaluate the pair-wise cross-prediction performance between fMRI pixel time series within the brain. In a second step, the underlying network structure is subsequently recovered from the affinity matrix using non-metric network clustering approaches, such as the so-called Louvain method. Finally, we use convergent cross-mapping (CCM) to study causality between different network components. We demonstrate our MCA framework in the problem of recovering the motor cortex network associated with hand movement from resting state fMRI data. Results are compared with a ground truth of active motor cortex regions as identified by a task-based fMRI sequence involving a finger-tapping stimulation experiment. Our results regarding causation between regions of the motor cortex revealed a significant directional variability and were not readily interpretable in a consistent manner across subjects. However, our results on whole-slice fMRI analysis demonstrate that MCA-based model-free recovery of regions associated with the primary motor cortex and supplementary motor area are in close agreement with localization of similar regions achieved with a task-based fMRI acquisition. Thus, we conclude that our MCA methodology can extract and visualize valuable information concerning the underlying network structure between different regions of the brain in resting state fMRI.

#16

Lutz Leistritz, Friedrich Schiller University, Germany
Axel Wismueller, University of Rochester Medical Center
Mahesh Nagarajan, University of Rochester Medical Center
Herbert Witte, Friedrich Schiller University, Germany
Britta Pester, Friedrich Schiller University, Germany
Christoph Schmidt, Friedrich Schiller University, Germany

Impact of Multivariate Granger Causality Analyses with Embedded Dimension Reduction on Network Modules

High dimensional functional MRI data in combination with a low temporal resolution imposes computational limits on Granger Causality analyses with respect to large-scale representations of functional interactions in the brain. Currently, the problem is tackled by using bivariate approaches or by suitable transformations of high dimensional into lower dimensional systems, e.g. PCA or ICA. Then, the connectivity structure of derived components is studied with the drawback that revealed interactions between them cannot be readily transferred into the original high-dimensional space.

To overcome this limitation we propose a fully multivariate approach with embedded dimension reduction to compute highly resolved brain functional connectivity networks. A long-term objective might be a full brain representation without any predefinition of ROIs. The idea of the novel approach is a direct integration of a suitable dimension reduction into a multivariate linear time series model. Instead of modeling high-dimensional signals, dimension-reduced signals are modeled by means of a common time series model, which provides residuals in the low-dimensional space. After their back transformation into the original space, prediction errors may be defined there and a Granger Causality Index can be computed in the high-dimensional space using Granger's principle of prediction.

The influence of the embedded dimension reduction was systematically investigated by means of artificial data with known ground truth. As a proof of concept, we showed that a modular structure of these large-scale connectivity networks can be recovered. Moreover, we computed binary connectivity networks from resting state fMRI data and analyzed them with respect to their network module structure. The identification and clustering of network vertices with similar coupling patterns within the network may be used for functional segmentation, which can directly be projected onto neuroimaging data.

It could be shown that an appropriate dimension reduction can be integrated into time series models for extending the Granger Causality Index to high-dimensional data. As expected, the degree of dimension reduction affects the resulting identified network topology. Yet, we found only little impact on the module structure, which is of particular interest when the detection of functional similar vertices (voxels) is the primary objective.

#17

Jeremy R. Manning, Princeton University
Kimberly L. Stachenfeld, Princeton University
Rajesh Ranganath, Princeton University
Kenneth A. Norman, Princeton University
David M. Blei, Columbia University

The Hierarchical Topographic Factor Analysis MATLAB Toolbox

We present a newly developed MATLAB Toolbox that allows neuroscientists to efficiently discover, explore, and interpret patterns of functional connectivity in large multi-subject fMRI datasets. The fundamental goal of the toolbox is to approximate the matrix of pairwise correlations between the voxel activations using instead the correlations between the activations of a (typically) much smaller number of network "hubs" located throughout the brain. Given a multisubject dataset, the toolbox automatically determines the optimal number of hubs, the hub locations and sizes (which are similar across participants to facilitate across-subject comparisons), and the per-image hub activations. The hub activations are, in turn, used to estimate functional connectivity and compare activity across subjects. The primary benefit of our toolbox is that it reduces the computational burden of functional connectivity analyses by several orders of magnitude. Because our approach estimates connectivity between structures located in Euclidean space (rather than voxel space), it naturally accounts for structural variations across subjects and even allows one to combine data taken at different sampling resolutions.

#18

Yaroslav O. Halchenko, Dartmouth College
Michael Hanke, University of Magdeburg

Converging Catalogues, Warehouses, and Deployment Logistics into a Federated "Data Distribution"

Contemporary neuroscience is heavily data-driven, but today's data management technologies and sharing practices fall at least a decade behind software ecosystem counterparts. Distributed version control systems, such as Git, facilitate collaborative software development, and turnkey distributions, like NeuroDebian (http://neuro.debian.net), free researchers from tedious and unreliable maintenance tasks. In contrast, today's data-sharing practices involve various disconnected warehouses and sharing platforms that use heterogeneous interfaces to offer access to data hosted as files or in databases. Data access often requires manual navigation of web-portals and a variety of authentication schemes. Data versioning is often ad-hoc or completely absent, making updates and review of changes difficult.
The proposed solution, "DataGit"[1], will provide access to data available from various sources (e.g. lab or consortium web-sites such as humanconnectome.org; data sharing portals such as openfmri.org and crcns.org) through a single interface. Based on git-annex (https://git-annex.branchable.com) -- a versatile software for data tracking and deployment logistics -- it will enable users to operate on data using familiar concepts, such as files and directories, while transparently managing data access and authorization with underlying hosting providers. Because of access unification, established federated data distribution will be easy to integrate within software distributions, such as NeuroDebian, finally making data a first-class citizen in software ecosystem(s).

Here, we will present motivation and planned development of the DataGit project. Furthermore, we will familiarize audience with some aspects of current norms in data hosting (such as versioning, integrity verification, etc), paying due respect to which would ease access to their data through distributed version control system(s) and data distributions, such as DataGit.

[1] “DataGit” name is subject to change

Supported by NSF 1429999.

#19

Sharon Crook, Arizona State University
Suzanne Dietrich, Arizona State University

NeuroML: Model Exchange in Computational Neuroscience

Neural Open Markup Language project, NeuroML, is an international, collaborative initiative to develop a language for describing and sharing complex, multiscale neuron and neuronal network models. The project focuses on the key objects that need to be exchanged among software applications used by computational neuroscientists. Examples of these objects include descriptions of neuronal morphology, the dynamics of ion channels and synaptic mechanisms, and the connectivity patterns of networks of model neurons. This modular approach brings additional benefits: not only can entire models be published and exchanged in this format, but each individual object or component, such as a specific calcium channel or excitatory synapse, can be shared and re-implemented in a different model. We will provide an overview of the latest developments in NeuroML including NeuroML version 2.0, the NeuroML Model Database, and the use of the NeuroML language for model exchange at Open Source Brain.

#20

Caroline Moore-Kochlacs, Boston University
Jorg Scholvin, Massachusetts Institute of Technology
Justin P. Kinney, Massachusetts Institute of Technology
Jacob G. Bernstein, Massachusetts Institute of Technology
Nancy Kopell, Boston University
Ed S. Boyden, Massachusetts Institute of Technology

Principles of High Fidelity, High Density Neural Recording

New probe technologies, neural amplifier systems, and data acquisition systems enable the extracellular electrical recording of ever greater numbers of neurons in the live mammalian brain, with the potential to increase our understanding of neuronal network dynamics. To design and optimize a scalable system for extracellular neural recording, we must characterize how to accurately extract single neurons from such recordings and how to maximize the number of neurons extracted. Spike sorting attempts to separate raw electrode traces into the activity patterns of individual neurons. A scalable system requires an automated spike sorting method ideally committing no errors in spike assignment: each extracted individual neuron would be associated with all the spikes fired by a single neuron, with no spikes not fired by that same neuron. Existing extracellular data record many neurons on just a few electrodes, resulting in unresolvable ambiguities in spike assignment. Electron beam lithography techniques allow construction of probes with higher channel counts and electrode density, capable of recording more copies of neural signals on more electrodes.

Our spike sorting method is constructed for data from such spatially dense high channel count probes. First Independent Component Analysis is applied to the continuous data to estimate the underlying signals. Then we apply a classifier to the resulting components, keeping only putative single neuron units that are well separated from noise and other units. For *in silico* testing, we simulated multielectrode probe data encompassing many of the realistic variations and noisiness of natural neural data. Applying our spike sorting method against this simulated data, for a wide range of classifier parameters, we find no spike assignment errors are committed. This result is robust to varying neural and probe parameters. For probes with electrode counts and densities similar to those in commercial probes, few neurons are extracted. However, the number of neurons extracted is increased with higher electrode densities on a fixed area, to upper bound. This method also extracts low amplitude neurons that would not be extracted with threshold-based methods. Finally, analyzing in vivo recordings, we find the number of neurons extracted is higher than expected from our conservative simulations.

Poster Session 2 (Saturday)

#21

D. McNamee, California Institute of Technology
J. Gläscher, University of Hamburg, Germany
P. Bossaerts, California Institute of Technology, University of Utah
J. P. O'Doherty, California Institute of Technology

Cognitive Strategies and Neural Correlates of Hierarchical Latent Inference

Optimal decision-making requires an accurate estimation of the state of unobservable variables in an environment based on observable, conditionally related, signals. We aimed to clarify two important issues regarding this estimation process in a computational fMRI study. First, what heuristics do humans use to manipulate their internal model of the environment when performing such hierarchical inference? Secondly, what neural systems underpin the updating of latent variables in the brain?
Subjects (n=22) performed a hierarchical state estimation task based on three-dimensional stimuli (color, motion, shape). This task requires the tracking of up to six possible latent states as well as the detection changepoints. At the end of each trial, subjects were asked to report their beliefs as to the true unobserved state of the environment on a continuous scale. We show that subjects use state-space simplification strategies resulting in a cognitive algorithm inconsistent with the Bayesian updating or reinforcement learning of an inversion of the generative environment model. More specifically, threshold parameters were introduced which (a) gated the updating of an internal model by requiring a preponderance of evidence over multiple trials demonstrating a significant error in the current beliefs, and (b) triggered the elimination of latent state hypotheses from the internal state-space when their posterior probabilities dropped too low.

This task was performed while subjects were scanned using fMRI. The negative entropy (NE, measuring information accumulation) of the prior/posterior distributions and the divergence between prior and posterior (BPE, “belief prediction error”) were estimated in a general linear model of BOLD signaling as parametric modulators time-locked to corresponding task events. This was done for both the observable and unobservable variable distributions in the hierarchy. In the observable case, NE(prior) and BPEs were reflected in the neural activity of distinct regions within the visual stream (e.g. area V4 for color) while the same signals for the unobservable variable were located in dorsolateral prefrontal cortex. Activity in ventromedial and dorsomedial prefrontal cortex correlated with NE(posterior) at the time of response consistent with previous studies implicating these regions in the use of abstract information in decisions.

#22

Sien Hu, Yale University
Jaime Ide, Stony Brook University
Sheng Zhang, Yale University,
C.-S. Ray Li, Yale University

Getting Ready to Stop: Neural Correlates of a Bayesian Belief and Its Motor Consequence

Previous studies have examined the neural correlates of proactive control using a variety of behavioral paradigms; however, the neural network relating the control process to its behavioral consequence remains unclear. Here, we applied a dynamic Bayesian model to a large fMRI data set of the stop signal task to address this issue. By estimating the probability of the stop signal – p(Stop) – trial by trial, we showed that higher p(Stop) is associated with prolonged go trial reaction time (RT), indicating proactive control of motor response. In modeling fMRI signals at trial and target onsets, we distinguished activities of proactive control, prediction error, and RT slowing. With exclusive masking, we showed that the anterior pre-supplementary motor area (pre-SMA) responds specifically to increased stop signal likelihood, and its activity is correlated with activations of the posterior pre-SMA and bilateral anterior insulae during prolonged response times. This directional link is also supported by Granger causality analysis. Furthermore, proactive control, prediction error, and time-on-task are each mapped to distinct areas in the medial prefrontal cortex. Together, these findings help dissect regional functions of the medial prefrontal cortex in cognitive control and provide systems level evidence associating proactive control to its motor consequence.

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#23

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Involvement of the Vibrissae in Sensing Fluid Flow

With the exception of some primates, the faces of nearly all mammals are covered in vibrissae (whiskers), typically arranged on the cheek in an orderly pattern of rows and columns. Researchers have focused on different aspects of whisker function, depending on the species under study. For example, research on harbor seals has described how these animals use their whiskers to track the wakes of fish. In contrast, research on rodents has focused on direct tactile sensation with the whiskers. In the present work, we compared the vibrissal morphology of seals and rats, and then investigated how vibrissae might aid rats in anemotaxic (wind-following) behaviors. The vibrissal array anatomy of the harbor seal and rat show several striking differences, including the overall orientation of the cheek, as well as the curvature and orientation of individual whiskers. Quantifying the response of isolated rat vibrissae to airflow showed that the vibrissae bend and vibrate in response to air currents. The primary direction of bending indicates the direction of airflow, bending magnitude correlates with airspeed, and vibration frequency occurs close to the natural resonant frequency of the vibrissa. We are presently constructing a numerical model of these deflections to quantify the mechanical signals at the whisker base. Complementing these mechanical studies, initial results from behavioral experiments suggest that vibrissae provide important cues to the rat during anemotaxic behaviors. Finally, we demonstrate a robotic model constructed by undergraduates at Elmhurst College that can locate the source of a jet of air by comparing signals between right and left sides of an artificial vibrissal array.

#24

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A Comprehensive Neuromechanical Model of Spinal Control of Locomotion: Experimental Model Verification and Testing Model Predictions

The organization of mammalian spinal locomotor circuitries is poorly understood because of their complexity and difficulties of in vivo neuronal recordings. The goal of this project has been to develop a
comprehensive neuromechanical computational model of cat spinal locomotion controlled by central pattern generators (CPGs) and motion-dependent afferent feedback, and use this model as a testbed to investigate spinal control of mammalian locomotion. In the developed model of neural circuitry each hindlimb CPG is based on the two-level model (Rybak et al., 2006) and includes a half-center rhythm generator (RG), producing alternating flexor and extensor activities, and a pattern formation (PF) network operating under control of RG and managing the synergetic activity of different hindlimb motoneuronal pools. The basic CPG model has been extended by incorporating additional neural circuits allowing the CPG to generate complex activity patterns of motoneurons controlling proximal two-joint muscles (Shevtsova et al., 2014). In addition, the neuronal model includes reflex circuits mediating reciprocal inhibition and disynaptic excitation of extensor motoneurons by load-sensitive afferents. The hindlimbs and trunk are modeled as a 10 degrees-of-freedom, 2D system of rigid segments actuated by 18 Hill-type muscle-tendon actuators with force-length-velocity dependent properties. The musculoskeletal model is tuned to reproduce the mechanics of locomotion and, as a result, the activity of motion-dependent muscle group Ia, Ib, and II and paw-pad cutaneous afferents (Prilutsky et al., 2014). In the combined neuromechanical model the CPG operation is adjusted by afferent feedback from the moving hindlimbs. The neuromechanical model demonstrates stable locomotion and exhibits realistic patterns of muscle activity and locomotor mechanics. The model has been used to determine the relative contribution of group Ia and Ib afferents from triceps surae to locomotor activity. Selective removal of triceps surae Ia feedback does not substantially change activity patterns of this and other muscles and the model maintains stable locomotion. This result has been verified experimentally in intact and spinal cats. When triceps surae Ib afferent feedback is removed in the model, the model is unable to produce stable locomotion. Results of other simulation experiments and model predictions will be discussed during the presentation.

#25

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Long Term Reactivation in Hippocampus: Experimental Evidence and Information Geometric Approach

Memory consolidation and reconsolidation involves a repetitive process of neuronal reactivation in several brain areas including the hippocampus and cortex. In hippocampus, reactivation occurs primarily during short periods of fast oscillations called sharp waves ripple complexes (SPWs). In this progress report we present analyses of the dynamics of SPWs before, during and after two different types of learning: Object novelty and spatial locations. We show that the SPWs density is highly variable. We also show that the synchrony magnitude of the SPWs amplitudes recorded simultaneously from multiple hippocampal sites varies significantly, suggesting different processing mode at different phases of the experiment.

The information-geometric (IG) analysis method has advanced in two directions. The first was to determine the influence of the external inputs and asymmetry of connections on the higher-order IG measures. The analytical solution using a small neural network showed that the influence of external inputs was highly non-linear. With a large neural network, we found that the influence of external inputs became negligibly small and that the IG measures were robust against modulation of asymmetry of connections. The second was to investigate stability of the IG measures under oscillatory brain states. Two oscillatory mechanisms, externally driven oscillations (e.g. theta inputs from the medial septum) and internally induced oscillations (e.g. SPWs), were considered. In both mechanisms, we found that the single-IG measure was linearly related to the magnitude of the external input and that the pairwise-IG measure was linearly related to the sum of connection strengths between two neurons. We also confirmed that the IG measures did not depend on the oscillation frequency.

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#26

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Potential of IVIM MRI as a Cerebral Microvascular Biomarker

IntraVoxel Incoherent Motion (IVIM) is a method developed to characterize microcirculation in tissue via the acquisition of a series of MR diffusion-weighted (DW) images. The aim of this work is to use IVIM to noninvasively quantify changes in the brain microvasculature induced by aging.

In a first step we performed numerical simulations in order to predict the evolution of the IVIM MRI signal in young and aged brains. The microvasculature was modeled as a network of capillaries with mean length L and mean blood velocity V. Using a classical diffusion weighted sequence, pulsed gradient spin echo (PGSE), and typical preclinical acquisition parameters (diffusion gradient duration δ = 3ms and diffusion gradient separation time Δ = 11ms), our initial results show that the MRI signal behavior depends on the acquisition parameters and the capillary network features. When the number of direction changes underwent by blood water molecules during the experimental encoding time, characterized by a parameter τ defined as $\tau = V\Delta/L$, is smaller than one (τ = 0.35) the MRI signal has a sinc-like shape. For $\tau > 2$ the MRI signal profile gradually approaches an exponential shape (pseudo-random walk process). For $\tau < 2$ an exponential model can potentially be used when suppressing the contribution from water molecules not changing direction using a flow compensated diffusion imaging pulse sequence.

In a second step we validated the numerical results obtained using a clinical MRI scanner. Such validation presents significant instrumentation challenges due to both the reduced SNR given the lower magnetic field and longer diffusion times necessary to achieve similar diffusion weightings using clinically available gradient strengths. A navigated 3D spiral multi-slab DW acquisition with iteratively field corrected reconstruction was used to maximize SNR efficiency and image quality achievable on a Siemens 3T Trio scanner. Both PGSE-DW and flow compensated DW pulse sequences were implemented. Through comparisons of the modeled data with data acquired on healthy volunteers, it is evident that in spite of reduced SNR, longer diffusion times are necessary in order to extract IVIM
parameters relevant to the characterization of the aging brain microvasculature.

#27
Uri Eden, Boston University

A Point Process Filter to Estimate Optimal Placement of DBS Electrodes in the Subthalamic Nucleus

Previously, we developed a point process modeling and estimation framework to characterize rhythmic spiking dynamics of neurons in the subthalamic nucleus (STN) of patients with Parkinson's disease. We have now analyzed spiking data from multiple locations in STN to characterize history dependent dynamics as a function of the distance to the clinically determined 'sweet spot' where deep brain stimulation (DBS) is thought to have its optimal therapeutic effect. Using the observed rhythmic spiking properties of these neurons, we also developed a simulation environment to generate new data with stochastic rhythmic firing properties at multiple STN locations. We then developed a Bayesian estimation framework and point process filter algorithm to compute the distance from the recording electrode to the 'sweet spot' based on a sequence of neural recordings as the electrode is advanced toward the target.

We applied these point process models to the problem of assessing variability in spiking dynamics among 182 STN neurons as a function of their location in the STN. From the model parameters, we found that pathological history dependent oscillations related to beta frequency activity are more prominent in the dorsolateral part of the STN, where the sweet spot has been hypothesized to be located. In addition, the coherence between EMG and spike trains, computed in the tremor band (3-6 Hz), is increased in this subregion.

Using a point process filter algorithm, we simulated the problem of navigating an electrode to the 'sweet spot' in simulated STN data that had history dependent spiking activity that matched the structure identified in recorded STN data. We computed the navigation accuracy as a function of the density of oscillatory neurons that could be observed during the implantation procedure and the recording duration at each depth. For sufficiently long recording durations (>60 sec at each observed oscillatory cell) and recording cell densities (>3 cells/mm), we were able to consistently navigate to within 0.5-1 mm of the optimal stimulation location within the 'sweet-spot.'

#28

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Modeling the Relationship between Extracranial and Intracranial K-complexes in Humans

The largest EEG phenomena in the healthy human brain are K-complexes (KCs), a defining characteristic of non-rapid eye movement (NREM) sleep stage NR2. KCs appear as ~500µV negative deflections broadly distributed over the frontocentral scalp with peak voltage over the midline posterior frontal cortex. KCs also appear in simultaneous magnetoencephalography (MEG), although not as widespread or prominent with respect to background activity. We have previously shown using intracranial recordings that KCs comprise cortical downstates with profound depression of cell-firing (Cash et al., Science, 2009). KCs can occur quasi-synchronously in widespread cortical areas (Mak-McCully et al., PLOS Computational Biology, in press). Inverse modeling has proposed a variety of KC sources, depending on prior assumptions. Here we combine novel measurements of intracranial KC generators with realistic modeling of their propagation to extracranial EEG and MEG, to test different hypotheses regarding the origin of KCs in humans. In order to calculate the EEG/MEG, it is necessary and sufficient to know the location, orientation, strength and synchrony of the generating equivalent current dipoles (ECDs). The location and orientation of potential ECDs were obtained from a topologically-correct reconstruction of each individual's cortical surface based on structural MRI. MRI was also used to estimate the cortical, inner skull, outer skull, and scalp surfaces for a boundary element forward solution. The distribution and synchrony of the generating patches were estimated from stereoencephalography (SEEG) during natural sleep in patients undergoing presurgical monitory for epilepsy. Laminar recordings (comprising 24 contacts, spaced every 150µ on center and spanning the cortical surface) were used to calculate, for the first time, the ECD strength of KCs in 4 subjects. A range of different generator configurations consistent with the intracranial data were used to calculate the resulting EEG/MEG fields, and these were quantitatively compared to those actually observed. Inferences regarding the size, synchrony and location of KC generators will be presented.

Supported by NIMH (MH099645).

#29

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Organization of Left-right Coordination of Neuronal Activity in the Mammalian Spinal Cord Locomotor CPG: Insights from Computational Modeling

Different locomotor gaits in mammals, such as walking, hopping or galloping, are produced by coordinated activity in neuronal circuits in the spinal cord. Coordination of neuronal activity between left and right sides of the cord is provided by commissural interneurons (CINs) whose axons cross the midline. Electrophysiological and genetic ablation studies have revealed the functional roles of different CIN types. Parallel CIN pathways mediated by inhibitory ($V0_D$) and excitatory ($V0_V$) subtypes of V0 CINs secure left–right alternation of neuronal activity at different locomotor speeds, and excitatory pathways mediated by V3 CINs may promote left-right synchrony. Ipsilaterally projecting excitatory V2a interneurons have also been shown to contribute to left-right alternation in a speed-dependent manner. The exact organization and connectivity patterns of different CIN types that allow them to control left-right alternation and synchrony at different locomotor speeds are, however, unknown. In this study, we have constructed and analyzed computational models of spinal circuits consisting of left and right rhythm generators interacting bilaterally via several parallel CIN pathways. Our study proposes network architectures and connectivity patterns of several genetically identified CINs that allow the models to closely reproduce the experimentally observed changes in speed-dependent left-right coordination in mutants lacking specific neuron classes. The models provide insights into the architecture of the spinal network and parallel inhibitory and excitatory CIN pathways and suggest explanations for how these pathways maintain alternating and synchronous gaits at different locomotor speeds. The models propose testable predictions about the neural organization and operation of mammalian locomotor circuits.

#30

Matthew Harrison, Brown University
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Robust Inference for Nonstationary Spike Trains

The coordinated spiking activity of simultaneously recorded neurons can reveal clues about the dynamics of neural information processing, about the mechanisms of brain disorders, and about the underlying anatomical microcircuitry. Statistical models and methods play an important role in these investigations. In cases where the scientific questions require disambiguating dependencies across multiple spatial and temporal scales, conditional inference can be used to create procedures that are strikingly robust to nonstationarity, model misspecification, and incidental parameters problems, which are common neurostatistical challenges. Examples include testing for cell assembly dynamics in human epilepsy data and learning putative anatomical networks from spike train data in behaving rodents.

#31

James Haxby, Dartmouth College & University of Trento

A Common High-dimensional Linear Model of Representational Spaces in Human Cortex

The functional architecture of human cortex can be modeled as high-dimensional representational spaces in which patterns of brain activity are recast as vectors with basis functions that have tuning profiles and patterns of connectivity that are common across brains. Transformation matrices that rotate individual anatomical spaces into the common model space are derived with searchlight-based, whole cortex hyperalignment. Patterns of brain activity in individual brains are modeled as multiplexed topographic basis functions. This model provides a common structure that captures fine-grained distinctions among cortical patterns of response that are not modeled well by current brain atlases.

#32

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Active Acoustic Sensing: Representing Space through Sound

Spatial navigation by echolocation depends on the dynamic interplay between auditory information processing and adaptive motor control. An important component of this adaptive system is the timing of sonar signals, which the bat adjusts, not only with respect to object distance, but also in the context of perceptual demands and planning. For example, the big brown bat, *Eptesicus fuscus*, produces stable groups of sonar signals, flanked by longer pulse intervals, when it is challenged by spatial tasks, such as figure-ground segregation and target trajectory uncertainty. We will present behavioral and neurophysiological findings, which indicate that the big brown bat's control over sonar call timing serves to sharpen its spatial representation of the environment. Behavioral studies were conducted in the laboratory and the field, as the bat tracked insect prey under a variety of conditions. Neural recordings from the midbrain superior colliculus of freely behaving animals show that auditory responses to echoes are modulated by the bat's production of sonar sound groups. Collectively, these data suggest that the bat temporally organizes its echolocation calls into groups, as an active strategy to build a detailed representation of the sonar scene.

#33
Brian J Fischer, Seattle University
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Optimal Prediction of Moving Sound Source Direction in the Owl

Capturing nature's statistical structure in behavioral responses is at the core of the ability to function adaptively in the environment. Sound localization is a critical skill for many species, involving both the localization of stationary sound sources as well as predicting the future location of a moving sound source. An outstanding open question in neural coding for sound localization includes how sensory cues are integrated over time to optimally guide behavior. We address this issue using the system that underlies sound localization in barn owls. The barn owl displays localizing behaviors consistent with the prediction of the location of a moving source. Furthermore, it has been shown that the owl's sound localization for brief sounds is consistent with a Bayesian model. Here we address how a neural system can perform Bayesian prediction given sensory information and prior assumptions.

We developed a Bayesian model of predictive localization of moving sound sources. The form of the model is determined by the dynamics of the moving target and the statistical relationship between the direction of the target and the auditory input. Next, we determined conditions on the neural representation of moving sources that allow the population vector to decode the Bayesian prediction. The work here shows that the population vector decoder will perform Bayesian prediction when the preferred direction of each neuron shifts in response to the target trajectory and the receptive fields sharpen over time. The model predicts that the magnitude of shift is proportional to target velocity, with faster speeds requiring greater shifts. The predicted shifts of preferred direction are shown to match the shifts observed in the owl's midbrain.

This work provides a theoretical description of optimal coding of sound localization for moving sources that may be tested in other systems. More generally, we show that neural populations can be specialized to represent the statistics of dynamic stimuli to allow for a vector read-out of Bayes-optimal predictions.

#34

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Time-domain Multiplexing of Multiple Items in an Auditory Coding Bottleneck

We often perceive more than one item at a time, but how we do so is poorly understood, particularly when the stimuli involved recruit overlapping populations of neurons. One way to encode multiple simultaneous items is via time domain multiplexing, or interleaving of multiple signals in time. That is, individual neurons might switch between representing each of multiple items across time.

We investigated time domain multiplexing using sound localization as a model system. The location (azimuth) of single sounds is encoded in the primate brain via firing rates that are proportional to and thus can encode sound azimuth (i.e. a "meter" as opposed to a map for sound location). This poses a capacity problem for multiple simultaneous locations.

We first verified that monkeys can successfully report the locations of multiple simultaneous sounds using an eye movement task. We then investigated the neural code supporting this behavior in the inferior colliculus (IC), an essential "bottleneck" of processing in the auditory pathway.

We found evidence that IC neurons multiplex representations of different sounds in their spike trains, both within and across trials. About 23% of tested cells showed evidence for multiplexing within trials (Hidden Markov Model analysis), and an additional 41% showed evidence of switching behavior across trials. In total, evidence for time domain multiplexing was seen in ~ 65% of the tested cells.

Two lines of evidence suggest that the population of IC neurons may switch in synchrony. 1. Pairs of neurons recorded simultaneously showed positive correlations in their switching behavior. 2. Local field potentials recorded simultaneously at different sites showed a consistent phase relationship with each other.

Together, these results support the multiplexing hypothesis and implicate neural oscillations as a signature related to the underlying mechanism.

#35

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Structured Patterns of Dendritic Inhibition Revealed by Array Tomography

Inhibition plays fundamental and diverse roles in shaping information flow through neuronal circuits. The majority of inhibitory inputs to CA1 pyramidal cells are made onto dendrites, where axons from distinct interneuron cell types target specific dendritic domains (basal, apical obliques, and apical tuft). This anatomical arrangement, along with stereotyped temporal firing patterns of interneuron cell types, has been hypothesized to provide structured spatiotemporal inhibition throughout pyramidal cell (PC) dendrites. However, little is known about the fine-scale organization of interneuron cell-type specific connectivity to individual PC dendrites.

Mapping synaptic connectivity on a large scale is technically difficult because the visualization of synaptic contacts requires sub-micrometer resolution, yet dendritic structures frequently span hundreds of micrometers in the lateral and axial dimensions. To overcome these issues, we used array tomography (AT) to reconstruct interneuron axons and their connectivity to dendrites of mouse CA1 PCs. AT affords ~5-fold increase in z-axis resolution compared to conventional one- or two-photon scanning microscopy, enables samples to be imaged using both light and transmission electron microscopy (TEM), and allows relatively rapid collection of large volumes.

Using mouse lines with Cre recombinase knocked into specific dendrite-targeting interneurons, we mapped inputs across the dendritic tree of CA1 PCs. Correlative light and electron microscopy experiments revealed that a large fraction (~85%) of putative synapses identified in AT reconstructions were *bone fide* synaptic contacts in TEM micrographs, while only ~15% were false positives. We found that the innervation of PC dendrites from genetically defined interneurons is sparse and not uniform between branch types (i.e., primary, secondary, or terminal branches) within a domain. Depending on the interneuron type, the density of inhibitory inputs on a CA1 PC branch was inversely correlated with the density of excitatory inputs, or dependent on the distance from the soma to the branch point. These data demonstrate that PC dendrite-targeting interneurons exhibit highly structured connectivity patterns. Identifying these patterns will ultimately inform experimental and computational efforts aimed at understanding both inhibitory control of dendritic computation and cell-type-based models of hippocampal function.

#36

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Fully-automated Multi-objective Optimization for Fitting a Realistic Neuron Model to Experimental Data

The role of dendrites in synaptic integration and neural plasticity has long been recognized. Patch-clamp and imaging experiments focusing on the dendrites of pyramidal neurons in mammalian neocortex and hippocampus have suggested that active dendrites may act as computational units that collectively sculpt the somatic response to synaptic inputs and shape the rules by which synaptic plasticity occurs.

Simulations using morphologically realistic compartmental models of pyramidal neurons have complemented these experimental efforts to understand complex dendritic processing; a difficulty with such models, however, is that tuning the accompanying high-dimensional parameter sets to relevant experimental data has typically been laborious and idiosyncratic.

We will describe a fully automated optimization methodology for fitting large-scale multi-compartment neuronal models. Using data from patch-clamp recordings of CA1 pyramidal cells in the presence of various ion channel blockers, we employ a multi-objective genetic algorithm to constrain a model cell built with a complete reconstructed morphology. Our implementation uses Python to control the NEURON simulator and features a clickable interface to explore the Pareto-optimal front of solutions. It is designed to be modular to allow flexibility and extensibility of both the model and the constraining experimental protocols. The software runs on both multi-core desktop computers and large clusters.

#37

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Hippocampal Spine Head Sizes are Highly Precise

Hippocampal synaptic activity is stochastic and because synaptic plasticity depends on its history, the amount of information that can be stored at a synapse is limited. The strong correlation between the size and efficacy of a synapse allowed us to estimate the precision of synaptic plasticity. In an electron microscopic reconstruction of hippocampal neuropil we found single axons making two or more synaptic contacts onto the same dendrites, which would have shared histories of presynaptic and postsynaptic activity. The postsynaptic spine heads, but not the spine necks, of these pairs were nearly identical in size. The precision is much greater than previous estimates and requires postsynaptic averaging over a time window many seconds to minutes in duration depending on the rate of input spikes and probability of release.

#38

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The Contribution of Active Dendritic Properties to Temporal Integration in a Network

In neural integrators, transient input signals are mathematically accumulated into sustained neuronal activity. Recent work suggests purely circuit-based mechanisms are insufficient to explain the robustness of this sustained neuronal activity to biological noise and perturbations. Here we examine the idea that dendritic nonlinearities can serve as a source of robustness and intracellular feedback in support of integration, an idea, which has previously only been explored in abstract models. To study how nonlinear processing at the microscopic level may contribute to robust temporal integration, we developed an integrating network model composed of neurons with multiple dendritic compartments and biophysically realistic conductances. We implemented a tuning procedure that involves first approximating the conductance-based model with a time-averaged, steady-state reduced model, and second, determining coupling parameters through optimization procedures. We find that with realistic parameters, the network can be tuned to integrate transient and continuous inputs with ~1 Hz gradations in output rate, consistent with the smooth, continuous encoding seen in experimental data. With bistable dendritic compartments, the network shows insensitivity to simulated lesions in which connectivity parameters are varied by ~10%, exhibiting robustness in combination with graded persistent activity. Associated with its robustness, the network is insensitive to weak stimuli; however the degree of sensitivity can be controlled by the addition of synaptic noise, permitting the system to be sensitive to small, low-frequency input signals. With this model, we are able to generate predictions of macroscopic dendritic calcium dynamics that depend on the microscopic distribution of channel types in various compartments. We are testing these predictions by imaging calcium activity in the dendritic branches of larval zebrafish integrator neurons loaded with calcium sensitive dyes. Preliminary data reveal spatially distinct activity zones, with some proximal-to-distal variation in dynamics consistent with the presence of nonlinear processing. Together, these theoretical and experimental approaches are enhancing our understanding of how active dendritic properties may contribute to robust temporal integration.

#39

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Beyond the Single Cycle: Alterations in Neuronal Properties and Input/Output Functions Lasting throughout the Theta Network State

Neuronal oscillations are postulated to be fundamental to how the brain encodes, processes, and transmits information, and to identify distinct network states. Despite striking behavioral and network-wide differences between network states, controversy remains about whether neurons process inputs in unique ways in different states. Work *in vitro* and *in silico* has suggested biologically realistic mechanisms for network states' origins and their impact on network behavior, but they have been difficult to validate in awake, behaving animals. In particular, extracellular recordings do not allow a detailed analysis of cell properties, nor observation of input and processing patterns. Therefore, we investigated how processing changes within a cell under different network states in behaving animals by recording intracellularly in awake, headfixed mice navigating a virtual maze, employing a modified Autopatcher, a system for semi-automated whole-cell recordings in vivo. As a model region we chose the hippocampal CA1 field, focusing on theta (6-12 Hz) and theta-modulated gamma (30-80 Hz) oscillations.

Throughout the theta state we observed subthreshold dynamics strikingly different from non-theta periods: without significant change in mean membrane voltage (V_m) (paired-sample t-test $p > 0.35$), the variability of the signal was strongly reduced (standard deviation from mean = 3.9 mV average in non-theta states, 2.7 mV during theta states, paired-sample t-test $p< 0.01$). Moreover, we found increased excitatory drive, measured via voltage-clamp recordings near GABA reversal potential. The unchanged V_m mean in the presence of increased excitation suggests a balanced increase in inhibition, and hence higher cell conductance.

In vitro and modeling studies suggest increased membrane conductance shifts the neuron's input-output function, altering its sensitivity to inputs of different strengths. Since the integration time is expected to decrease as conductance increases, the neuron should also better discriminate fine temporal patterns in the inputs and have more pronounced preference for tightly-synchronized inputs. We are currently testing the hypothesis that neurons are more conductive during theta states by directly measuring membrane properties, by driving neurons with threshold pulses, and through *in silico* models.

Together, these results demonstrate that network states characterized by distinct oscillatory frequencies fundamentally affect neuronal computation at timescales beyond the individual oscillatory cycle.

#40

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Effects of General Anesthetics on Somatosensory Cortical Neurons

In the US, 60,000 patients receive general anesthesia daily. The molecular mechanisms of action of anesthetic drugs are well studied, but the effects of such actions in cortical circuits during drug-induced loss of consciousness are poorly understood. In general, states of low awareness are regarded as consisting of sustained hyperpolarization interspersed with occasional short depolarizations of the neuron membrane potential, while the awake state is typically regarded as a persistent depolarization. However, studies in somatosensory cortex of awake mice show that the membrane potential of these cells oscillates between short depolarized and hyperpolarized states during quiet wakefulness, while persistent depolarized states only appear during active wakefulness. What are the effects of general anesthetics on the membrane potential of these cells? We are using in vivo robotics to perform automated patch-clamp in different layers of the somatosensory cortex in awake mice. Our robotic system (the multipatcher) allows us to record simultaneously from several neurons, while inducing loss of consciousness using anesthetic doses of three drugs: ketamine, an NMDA receptor antagonist; dexmedetomidine, an alpha-2 receptor agonist; and propofol, a GABA receptor agonist. In the awake state we observe that the membrane potential is characterized by 1-4 Hz slow oscillations during quiet wakefulness, interspersed by persistent depolarization during movement. Systemic infusion of ketamine, dexmedetomidine and propofol results in the abolishment of the persistent depolarization. However, each drug has a different effect on the slow oscillation: dexmedetomidine and ketamine make it more regular and highly coherent across neuron pairs (<500 microns). In contrast, propofol produces a pronounced hyperpolarization, followed by a more stochastic slow oscillation. Our results indicate that ketamine and dexmedetomidine have the effect of regularizing the slow membrane potential oscillations, perhaps by removing the excitation coming from brainstem arousal nuclei. Conversely, propofol inhibits and disorganizes the activity observed during quiet wakefulness, perhaps by enhancing GABA-mediated chloride currents in pyramidal cortical cells. Our studies will help to link the molecular mechanisms of anesthetic drugs to their effects in local cortical circuits during loss of consciousness, and to better understand the effects of anesthetics in human patients.

#41

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Assistive Respiratory Pacing of the Diaphragm in the Rat Model Based on Ventilatory and Electromyographic Recordings

Respiratory pacing can be used to provide a viable alternative to mechanical ventilation for individuals with high cervical spinal cord injury. Although the technique is sometimes successful, incorporating neuromorphic control strategies may provide improved ventilation and facilitate more widespread use. We are developing a system that aims to electrically stimulate respiratory muscles, while adapting to changes in electrode properties and physiological demands, to provide sufficient ventilation to the user. A rodent model for ventilatory measurement and assistive stimulation was developed to experimentally evaluate an adaptive controller for respiratory pacing. We present results of experiments designed to quantify the physiological response to respiratory challenges and we demonstrate the feasibility of electrically assisted ventilation in this model.

A pneumotachometer and a capnograph were incorporated in a breathing circuit with the animal subject to determine flow, lung volume, and peak end-tidal CO_2. Muscle activation parameters were obtained via intramuscular electromyogram (EMG) recordings from diaphragm and external intercostal muscles. Four experimental respiratory conditions were used to assess ventilatory and muscle response to increased ventilatory demands: 1) eupnic conditions with 0% CO_2, 2) an increase from 0% to 5% CO_2, 3) a decrease from 5% to 0% CO_2 and 4) step increments of 2.5% from 0 to 7.5% CO_2. O_2 was kept constant at 21%, with N_2 used as balance. Inspiratory period (T_i), determined from the flow data, remained constant among trials, but expiratory period (T_e) decreased at high ventilatory demands. Peak breath volume, peak inspiratory and expiratory flow, and EMG magnitude also increased with elevated respiratory demand. These parameters serve as the target ventilatory response for in vivo testing of the adaptive controller. A respiratory assist stimulation protocol was performed using custom designed stimulation hardware. Diaphragm activation time from EMG data was used to determine the stimulation pulse train duration. Stimulation bursts of 75 Hz were triggered at the onset of inspiration. Cycles with assistive stimulation showed increased breath volume of up to ~290% when compared with unassisted breaths. Future work will utilize these results to determine experimental conditions and paradigms for evaluation of a neuromorphic control system in this rodent model.

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Mechanisms of Interneuronal Control of Spontaneous Oscillations in a Full-scale Parallel Computer Model of the CA1 Network

The CA1 region of the hippocampus displays several well-characterized oscillations, such as theta oscillations, gamma oscillations, and sharp wave-ripples, characteristic of different behavioral states and associated with different functions in learning and memory. The behavior of the various interneuron types has been found to differ across types and also across states (Varga et al., 2012; Lapray et al., 2012; Klausberger and Somogyi, 2008). The relative importance of the network and cell properties, including connectivity, intrinsic cell properties, and relative number of each cell type, in driving and maintaining these differences is unknown. Here, we set out to quantify the roles of various properties in enabling and driving the variation across interneuron types and states, using a detailed, full-scale model of the rat CA1, run on a parallel supercomputer. Our network model exhibits spontaneous theta and gamma oscillations. The model includes eight interneuron types in addition to pyramidal cells. We include biologically realistic proportions of each interneuron type, as well as realistic connectivity between each neuron type (Bezaire and Soltesz, 2013). These numbers are now available in our recent, quantitative assessment of the CA1, which systematically examines the prevalence of each interneuron type and its divergence, as well as compares the estimated convergence onto pyramidal cells and interneurons with experimentally observed input synapses on each neuron class (Bezaire and Soltesz, 2013). In addition, we employ specialized models of each interneuron type, using experimental data to constrain their intrinsic properties and synaptic connections with other neuron types. We highlight the different environments experienced by each type of model interneuron to make experimentally testable predictions about the mechanisms by which interneurons achieve the variety of experimentally observed behaviors. We will also discuss how our new full-scale CA1 model is being expended to include the medial septum, taking advantage of the unique experimental data sets supplied by our CRCNS collaborative partner Dr Christophe Bernard's lab in France.

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The Distribution of Octopamine and Tyramine and Their Receptors in the Honey Bee Brain

Since Erspamer and Boretti first described the biogenic amine octopamine in the salivary gland of octopus as a molecule with "adrenaline-like" action, decades of extensive studies have demonstrated the important role of octopamine and its precursor tyramine play in invertebrate physiology and behavior. Octopamine is synthesized from tyrosine. First it is converted to tyramine by the enzyme tyrosine decarboxylase then to octopamine by beta-hydroxylase. Until recently, tyramine was considered to be only the precursor of octopamine. However, the recent discovery of the action of tyramine and its localization indicate that tyramine has its own functions with its own source independently of that of octopamine. Here we describe the source of the octopamine and tyramine in the antenna, antennal lobe and mushroom body of the honey bee using specific antibodies against each biogenic amine. We show that ventral unpaired median (VUM) neurons are both octopaminergic and tyraminergic. We found that varicose-like fibers from VUM neurons are mostly located in the rind/cortex area of antennal lobe glomeruli. In addition, we found that mushroom bodies receive intensive innervation from the paired large tyraminergic mushroom body neurons located in the ventro-rostral protocerebrum. Both amines trigger intracellular signaling pathways by binding with different affinities to G-protein coupled octopamine/tyramine receptors. Activation of OA1 receptors increases the intracellular Ca^{2+} concentration (Sinakevitch et al., 2011, 2013). Activation OA-2 beta increases cAMP, whereas activation of AmTYR1 receptors inhibits adenosine 3',5'-cyclic monophosphate (cAMP). Here we used newly developed antibodies against AmTyr1 receptors to characterize its distribution in the antenna, antennal lobe and mushroom body in combination of the neurobiotin tracing of neurons that are important components of these networks. We found that AmTyr1 is expressed in the presynaptic sites of the olfactory receptor neuron axons in the antennal lobe as well in the projection neuron endings in the calyx. We present these data in the contact of a growing understanding of modulation by octopamine and tyramine in these networks in the honey bee brain.