Carnegie Mellon University

Annual Progress Report: 2010 Formula Grant

Reporting Period

January 1, 2011 – June 30, 2011

Formula Grant Overview

The Carnegie Mellon University received $860,191 in formula funds for the grant award period January 1, 2011 through December 31, 2014. Accomplishments for the reporting period are described below.

Research Project 1: Project Title and Purpose

Research Program in Sensory Computation - Sensory systems allow humans and other species to collect information about the world. Our brains then integrate information from a variety of sensory modalities with stored information to generate our beliefs about what is happening around us. For many kinds of stimuli – e.g., written words, voices, faces, smells – humans are much better at interpreting stimuli than any machine ever created. Our goal is to understand the kinds of computations that underlie our remarkable abilities to interpret complex stimuli. Improving our understanding of such sensory computations will allow us to better understand brain disorders that involve abnormal perception (such as hallucinations observed in epilepsy or schizophrenia or the heightened sensitivity to certain stimuli seen in autism) and also possibly to engineer devices to improve perceptual abilities in individuals who have impaired vision, audition or other sensory systems.

Anticipated Duration of Project

1/1/2011 – 12/31/2014

Project Overview

Our long term goal is to understand how human sensory systems are able to collect, process and integrate information about the world. This process happens in the face of a highly variable and noisy sensory world, as well as in the face of growth, degradation and damage of peripheral sensory structures. Even the most sophisticated artificial sensory systems, such as airport scanners and face and speech recognition software fail or require human intervention when stimuli are embedded in noise or distorted. Human and animal sensory systems cope with or even exploit the variation seen in real world objects and conditions to improve their performance in a way that is unmatched by artificial systems.

The specific hypothesis that we plan to investigate is that the diversity in the individual neurons and in local neuronal circuits improves the brain's ability to effectively extract information from

sensory stimuli. This hypothesis highlights the differences between machines, in which variations in hardware degrade performance, and brains, where we have evidence that variation in neuronal properties reduces performance. We will address this hypothesis by experiments and analysis designed to achieve the following specific aims:

Aim 1: To understand how differences in the properties of cortical neurons contributes to accurate stimulus encoding in a variety of sensory systems.
Aim 2: To understand how trial-to-trial differences in neuronal responses influence performance in sensory systems.

In both these aims, in addition to collecting the data, we will develop approaches for using machine learning and information theoretic analyses to determine how the variability in neuronal responses contributes to or limits processing of sensory information.

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Expected Research Outcomes and Benefits

Understanding and treating the root causes of brain disorders requires an understanding of brain function and the relationship between brain function and perceptual and cognitive abilities. Many brain disorders include perceptual deficits as primary or secondary symptoms. Auditory hallucinations are a key symptom in schizophrenia, visual disturbances and auras are common in migraines, and olfactory and somatosensory abnormalities are commonly associated with seizures. Autism and dyslexia involve highly specific deficits in face and word recognition, respectively, along with abnormal sensitivities to certain kinds of stimuli. Many stroke and traumatic brain injury patients experience abnormalities in sensory perception. In some cases, these perceptual symptoms are among the most prominent and debilitating (such as the voices heard in schizophrenia), whereas in other cases they are not (such as in seizures). Nonetheless, in all cases perceptual symptoms can readily be studied both in patients and also in animal models of disease and thus can provide important insights into cellular and circuit level abnormalities that may be common across many brain areas. The proposed work will allow us to generate models of how diverse types of neurons and circuits are harnessed to improve perceptual abilities, especially in the context of discrimination and recognition of complex stimuli. We believe that understanding these models of perception will provide insights into the causes of and treatments for perceptual symptoms of many brain disorders.

Summary of Research Completed

Neuronal activity in many sensory systems is characterized by stochastic changes in the activity of many neurons. Different neurons, even neurons in the same area and of the same type, respond differently to sensory stimuli. The activity of different neurons may vary with respect to the level of activity, its timing or in terms of the stimulus features that best drive the neurons to fire. Moreover, the same neuron may respond differently from trial to trial, even when the same stimulus is applied. Work under this proposal in the current funding period has focused on understanding how the intrinsic properties of individual neurons influences sensory evoked responses.

Diversity and stimulus coding

One set of experiments has sought to characterize the intrinsic biophysical properties of cortical neurons and to understand which features of these neurons contributes most strongly to the efficient and robust encoding of fluctuating stimuli. To tackle these questions, we recorded the spiking (action potential) responses of many individual cortical neurons recorded in brain slices from young mice. The cells were stimulated by directly injecting fluctuating current into the cell somata via whole cell recording techniques. This stimulus was chosen because its spectral properties are effective at driving reliable spiking in mitral cells. Synaptic responses were blocked pharmacologically, so that differences in the cells' spiking responses were determined by differences in their intrinsic firing properties. The cells chosen for this experiment were primarily from layer 2/3 of mouse somatosensory cortex and also from the mitral cell layer of the mouse olfactory bulb. We observed that while neurons fired action potentials that were correlated across trials ($r \sim 0.25$) cell-to-cell correlations were lower, indicating that these neurons were not identical in their response properties. This suggests that populations of different neurons may be better able to represent the properties of stimuli by capturing many different features.

To explore these data more completely, we have developed measures of neuronal population diversity based on statistical models that accurately reproduce the responses of individual neurons. This approach allows us to determine which features of real neurons show the greatest diversity and to analyze how the diversity of neuronal populations influences population coding. We modeled each neuron's spiking response to input current using a generalized linear model (GLM) consisting of a constant bias term to account for baseline firing, a linear stimulus filter that determines the neuron's stimulus preference, and a spike history function that captures the neuron's refractory period and/or bursting properties. The summed contributions of these three terms are then passed through an exponential nonlinearity to generate an instantaneous spiking probability. Individual spike times are generated randomly based on this probability. These GLMs are a generalization of the Linear Nonlinear Poisson (LNP) models used widely to describe temporal receptive fields of sensory neurons recorded in vivo. Recently, GLMs have been useful in providing a framework for describing how neurons fire as a result of input factors like receptive field structure or activity among other neurons but to our knowledge this is the first time they have been systematically used to model the response to directly injected current.

The GLM corresponding to each MC was then validated by comparing the GLM and real neuron's spike train responses to a novel stimulus. The GLMs accurately capture the majority of stimulus-evoked responses, as evidenced by the high correlation (85 +\- 8 %) between the MC and GLM peri-stimulus time histograms. The GLMs were much better at modeling neuronal activity than a linear stimulus model (LNP) alone (56 +\- 11 %), indicating that post-spike refractory and bursting effects substantially contribute to spiking in these neurons. The parameters of the GLM loosely reflect physiological features of the modeled neurons. Thus comparing filters across GLM models fit to different neurons provides an illustration of the diversity among these neurons. Furthermore, the interaction of these filters dictates how each MC fires to stimuli and defines the complex stimulus features that each neuron best encodes.

Because the GLM parameters capture the intrinsic diversity across neurons, when presented the same fluctuating stimulus different model neurons emit unique spike trains and represent the stimulus differently. We utilized this simulation-based approach to ask which features of these individual neurons influences the information available in their spike trains. Quantifying stimulus representation using information theoretic methods, we found a strong linear relationship between neuronal firing rate and information transmission rate ($R^2 = .75$). We also observed that neurons whose spike times were reliable across stimulus repeats and whose spikes were strongly stimulus driven (as opposed to driven by bias or spike-history terms) were more informative per spike.

Diversity and Oscillations

Another major effort has been to determine how of intrinsic heterogeneity of neurons in sensory systems effects synchronization. In preliminary simulations, we showed that synchrony is maximal when neurons being synchronized have identical biophysical properties. Real cells obviously differ from each other in many respects, most notably in their intrinsic preferred firing rates, and also in their responses to inputs. The phase resetting curve (PRC) is a function that describes how the spike times of a repetitively firing neuron are influenced by the timing and amplitude of ongoing input. Specifically, the PRC treats the repetitively firing neuron as an oscillating system (think of a clock) and describes the effect (in terms of a change in the phase) of a brief input arriving at different phases of the neuron's oscillating activity. Positive changes in phase indicate that the input is causing the spike to come earlier whereas negative changes in phase are delays in spiking. The PRC is a very useful measure of a neuron's responsiveness when trying to determine how neurons synchronize. Previously, we have developed combined experimental and computational methods for estimating the PRC of real neurons and applied these to mitral cells. This analysis has allowed us to determine that PRCs of different mitral cells generally have a particular shape (which consists of both negative and positive regions as indicated). In the last year we have begun to analyze the differences in mitral cell PRCs. To simplify these differences, a first step was to identify a function that could be fit to many PRCs that would allow us to capture the differences in PRCs by the fit parameters. For this we have chosen a particular function that allows us to fit the PRC of a given neuron using three parameters (*A, B* and *C*). We find that mitral cell PRCs are generally well fit by this equation and thus that this parameterization allows us to describe the diversity in mitral cell behavior in a highly simplified, yet accurate form. In addition, this parameterization allows us to independently vary different features of PRCs in populations of simulated neurons to determine

how sensitive synchrony will be to small changes in particular PRC features, such as PRC magnitude and shape.