Research Statement

Modern neuroscience has made great progress in understanding the properties of single neurons but it remains unclear how to use knowledge about single neurons to answer the high level question of how the brain generates behavior. We must first understand how the anatomical, physiological and molecular properties of the cells and their interconnections define the computations performed by each brain network and how different networks work together to generate behavior. This is a hard problem which cannot be studied by purely intuitive means, necessitating the use of mathematical models. In my research, I draw upon my training in neuroscience as well as physics and applied mathematics to study how computational functions emerge from the activity of networks, and how this activity is rooted in the underlying biophysics of single cells and synapses.

Oscillatory basis of working memory

As part of my dissertation, I studied how dynamical elements, which evolve in time according to simple rules give rise to complex collective behavior when connected together. This motivated me to study the emergence of rhythmic activity in neural assemblies using mathematical models. Wishing to move beyond an abstract understanding of neural dynamics, I accepted a Sloan fellowship in theoretical neuroscience at Brandeis.

My first postdoctoral project was to study the link between a biophysically generated oscillation (the 8-12 Hz theta rhythm) and a cognitive function, namely, working memory. Recordings from electrode grids on the cortical surface of epileptic patients made while they perform cognitive tasks provide a unique opportunity to observe brain activity with high spatial and temporal resolution. Using intracranial recordings from subjects during a short-term memory task (collected at Children's Hospital and Brigham and Women's Hospital), I showed that theta oscillations were *gated* by the demands of the working memory task: theta oscillations dramatically increased in amplitude, as subjects engaged working memory to remember a list of consonants [1]. Next, I investigated the spatial organization of theta oscillations during working memory. While task-related theta oscillations were observed across a variety of cortical regions, they appear to be generated locally rather than being driven by a common source. However, these multiple theta oscillators were able to synchronize briefly (presumably due to task demands) even at large cortical distances, suggesting that theta oscillations may be important in organizing the different brain regions that participate in human short-term memory. This is the first example of the cognitive gating of a brain oscillation pattern and models of multi-item working memory must account for oscillations.

The role of NMDA receptors in shaping network activity

My work on human EEG had given me an appreciation of the constraints that physiological mechanisms impose on abstract models of computation. I next wished to study a problem where I could directly explore the link between single cell biophysics and neuronal and network activity; the voltage-dependent post-synaptic potentials generated by NMDAR proved perfect for these purposes. The NMDA-type receptors have been mostly investigated for their critical role in the induction of long term potentiation, which is thought to be the mechanism for storing long term memories. However, pharmacological studies which block the NMDA receptors impair a variety of brain processes, suggesting that NMDA receptors also play a role in shaping the dynamic activity of neural networks. I proposed a model that showed how the biophysics of the NMDA channel can contribute to the dynamics of single neurons driven by synaptic input. The key element is the current-voltage relationship of NMDA channels which stabilizes two subthreshold states of the membrane potential. Thus, the neuron alternates between an "up-state" and "down state" in response to random input delivered via NMDAR, firing action potentials only in the depolarized, "up-state" [2]. Such fluctuations are remarkably similar to those observed *in vivo* from neurons in many brain regions. This model provided a parsimonious explanation for the observed two-state fluctuations and suggested a plausible biophysical mechanism for computing conjunctions or multiplying with neurons.

Neural integrators and parametric working memory

I next turned to a problem where I could use my insights into biophysics of NMDA channels to understand a computational function at the level of a network, namely sustaining persistent activity in a network for maintaining short-term memory. Working memory sits at the interface between perception and action, converting an evanescent piece of sensory information into a trace that persists over a time scale of seconds. In certain working memory circuits, neurons can maintain a range of firing rates that represent a graded stimulus parameter such as intensity or frequency. Integrator circuits, which transform brief inputs into sustained firing that represents the integral (in the sense of calculus) of previous inputs, are an example of graded persistent activity and form important elements for several computational functions of the brain.

Earlier models for integrator networks required that the recurrent positive feedback to be *exquisitely tuned*, a situation that is not tenable biologically. With my collaborators, I proposed a new class of integrator networks that *do not require fine tuning* [3]. At the heart of the model is the phenomenon of cellular **bistability**, which is observed in single neurons and neural populations. In this case, the bistability arises from the unique properties of the NMDA channel as discussed above. This novel design not only eliminated the requirement for fine tuning of recurrent connections, but exploited neuron-to-neuron variability to achieve integrator function. This new design principle can be applied to produce robustness in parametric working memory circuits as

well as in biochemical and genetic networks that have similar multi-stable properties.

Detailed modeling of synaptic transmission

While rapid progress has been made in understanding the mechanisms of fast transmission mediated by the AMPA type of glutamatergic channel at central synapses, several aspects of this process remain unclear. I have developed a highly constrained model of AMPA receptor mediated transmission, which incorporates recent data about the activation properties and subunit structure of AMPA receptors and physical structure and composition of hippocampal CA1 synapses. The model explains the properties of evoked and spontaneous responses in a single unifying framework that resolves many apparent contradictions in the field [6]. The model can be extended to resolve additional puzzles in synaptic transmission and potentiation.

Future research directions

My research goals center around two fundamental questions:

1. How do neural networks use biophysics and synaptic feedback loops to perform computations?

2. How do abnormalities in neurons and synapses lead to behavioral disorders?

To this end, I wish to set up a theoretical neuroscience lab to integrate behavioral, electrophysiological and pharmacological observations into mathematical models for high-level computation. I plan to address the first question by models of persistent activity in neural integrators and their possible role in decision making and judgement of temporal intervals. My approach to the second question is to explore how deficits in NMDA-mediated transmission in neural networks disrupts computation and leads to schizophrenia-like behavior. I strongly believe that progress in systems neuroscience requires a dialog between theorists and experimentalists from diverse disciplines which I hope to participate in by forging close collaborations.

Neural integrators for cognitive computations

My immediate research agenda will follow several broad themes that build upon my previous work. First, I shall continue my theoretical development of the biophysical principles that underlie neural integrators. While recurrent positive feedback is sufficient for their operation, integrators, if present in the cortex, would clearly be subject to inhibition. Further, spontaneous activity and probabilistic synaptic transmission, ubiquitous in the cortex, may be critical in setting their performance. These issues are best explored in concrete examples of computational tasks that rely on integrators. For example, elegant experiments by Michael Shadlen and colleagues have demonstrated that neurons in the association cortex integrate ambiguous sensory information to make a decision. My working hypothesis is that two integrator networks, one each for positive and negative evidence, connected by mutual inhibition can account for the basic behavior. Since trial to trial variation due to noise will result in differences to threshold, the model will be used to examine the relationship between spontaneous activity (and other forms of noise) and response-time distributions in perceptual discrimination tasks.

Neural integrators also appear to play a central role in models for tracking time intervals in the seconds to minute range. Animals have the ability to sense the “flow” of time, even though there is no explicit time sensing organ in the brain. The neural mechanisms of this cognitive timer are not clear. A key behavioral finding (called *scalar timing*) replicated across species is that the variance of the timed interval is proportional to the mean length of the interval. I plan to test the hypothesis that noisy integrator networks that accumulate pulses from a noisy pacemaker can account for this scalar timing property. These models will further our understanding of the biophysical influences on integrator systems that operate in various computational tasks that underlie behavior.

NMDA and context processing in schizophrenia

Second, I plan to develop a better understanding of the role of voltage-dependent postsynaptic potentials produced by NMDA receptors. Drugs that block NMDA receptors act in an immediate manner to produce a broad range of schizophrenic symptoms, which suggests that NMDAR strongly influence network activity. The dynamic nature of these effects can only be understood through the mathematical analysis of biophysically detailed models. I have a current award (NARSAD Young Investigator) to study the role of NMDAR in generating subthreshold membrane potential fluctuations in neurons of the nucleus accumbens (NAcc). The NAcc, a structure in the ventral striatum, combines inputs from the limbic systems and the cortex to select goal-directed behavior that is contextually appropriate and is under modulatory control by dopamine. My previous work on two-state fluctuations shows that stochastic NMDA inputs act as a gate, regulating the efficacy of AMPA inputs in firing the neuron. Thus, my model provides a mechanism that explains how hippocampal NMDA input to the NAcc can gate the efficacy of prefrontal cortex inputs to the accumbens. The key role of NMDAR in contextual gating in this model will give insight into how NMDAR hypofunction that is implicated in schizophrenia might lead to cognitive deficits. My model will allow me to investigate whether input gating by two-state fluctuations could provide a mechanistic explanation for a high level cognitive deficit (inability to integrate information with context in schizophrenics) from a bottom-up molecular level. Finally, I plan to extend the model to integrate and test specific roles for dopaminergic and glutamatergic transmission on information processing in schizophrenia.

Detailed modeling of synaptic transmission

A fundamental question in synaptic transmission is whether spontaneous synaptic events are composed of a single or multiple vesicles. Experiments that study the effect of low-affinity antagonists suggest that multivesicular transmission can occur in CA1 hippocampal synapses in culture. However, these experiments remain to be done in slices. I plan to extend the model to simulate the interaction between vesicle release and low-affinity antagonists in shaping the synaptic response. The model predictions can then be tested against experimental data. Synapses on CA1 pyramidal cells show a remarkable distance-dependent scaling, i.e. distal synapses are stronger compared to proximal ones. The origins of such scaling are not clear. One possibility is that synaptic scaling contributes to this distance-dependent effect. My model makes very specific predictions about the variability of spontaneous events in the proximal and distal population and the effects of drugs and low-affinity antagonists. The predicted values of miniature EPSC amplitude, kinetics and variability can be tested against experimental data. Another direction that I plan to extend the model is to include NMDA-receptor mediated transmission. Recent recordings from putative single spines show that while AMPA and NMDA mediated responses are tightly correlated, they nevertheless exhibit striking variability, whose origin is not clear. Another fruitful avenue of research will be to

combine the model of synaptic transmission to molecular signaling cascades in synaptic plasticity to study how synaptic modification affects quantal transmission.

New methods of data analysis and applications

The high volume of EEG data and the precise temporal constraints of the task required the development of a variety of statistical methods for the spectral analysis of time series. I have developed a powerful set of multivariate spectral analysis tools that can used to analyze and interpret the temporal correlation structure of neuronal activity within and between local and distant cortical areas. I have been successfully able to apply these techniques to human intracranial EEG [4] as well as spike train data from monkey prefrontal cortex [5]. I plan to actively seek collaborations with researchers who record activity in neural populations using large electrode arrays in order to elucidate the organization of temporal structure and correlations in neuronal activity during various cognitive tasks and determine the underlying functional architecture.

References

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