Computational Neuroscience of Elemental Cognition (Xiao-Jing Wang)

Abstract: In the first lecture, I will review developments in computational neuroscience as it pertains to cognitive processes such as working memory (the brain's ability to internally maintain and manipulate information in the absence of external stimulation)[5] and decision-making (the deliberate process of making a choice among several options under uncertainty)[7]. I will especially discuss biologically-realistic neural circuit modeling that is based on two pillars of neurobiology: anatomy and neurophysiology. Computational work in close interplay with experiments of behaving animals has shed insight onto the mystery of the prefrontal cortex, often called "the CEO of the brain". Mathematically, our work revealed a novel type of attractor networks that does not merely behave as switches between steady states but is characterized by a duality: slow transients underlying graded accumulation of information over time in the form of quasi-linear ramping neural activity, and winner-take-all competition giving rise to a categorical choice by virtue of convergence to an attractor state.

The second lecture will focus on a unifying recurrent neural circuit model of working memory and decision-making, which led to the concept of "cognitive-type" neural circuits[6,9], in contrast to those dedicated to early sensory processing or movement generation. Several model predictions and their experimental tests will be discussed, and current debates in the field including the controversy over the dynamical nature of working memory representations will be addressed. Importantly, by incorporating reward-dependent synaptic plasticity, the model is shown to have explanatory power for a variety of learning value-based adaptive choice tasks, such as stochastic foraging, competitive games and probabilistic inference. I will also discuss contributions of subcortical structures to cognition in a spiking network model of a cortico-basal ganglia-thalamocortical loop for decision-making and inhibitory control of habitual responses[12]. Because this brain system is critically implicated in mental illness, neural circuit modeling that bridges levels (from receptors and cells to circuits and behavior) serves as a potentially powerful platform for investigations of how this system goes awry in psychiatric disorders like Schizophrenia or addiction. I will provide examples that illustrate this nascent field called "*Computational Psychiatry*"[10].

The third lecture will be devoted to computational modeling that goes beyond local circuits towards muti-regional large-scale brain system modeling. This is becoming possible only now, thanks to the availability of novel technological advances in anatomy (connectomics) and neurophysiology (optogenetics and neuropixel recording). I will present a dynamical model of large-scale macaque cortex based on recently published weighted- and directed- inter-areal connectivity matrix. A hierarchy of timescales naturally emerges in this model[1], which is functionally desirable: early sensory areas operate on short timescales appropriate for rapid processing of stimuli, whereas higher association areas display slow dynamics suitable for time integration in decision-making. A key notion emerging from this research is that of macroscopic gradients, namely cellular and connection properties vary systematically along certain preferred axis across the entire cortical mantle. This general principle of large-scale cortical organization, supported by analysis of genetic expression patterns in human as well as mice cortex[2], will be highlighted.

The last lecture will cover ongoing research on large-scale brain circuit modeling for understanding distributed dynamics and cognitive functions. First, our model has been expanded to incorporate a laminar structure[4], with layer-dependent projections as well

as synchronous neural population oscillations[8]. This advance will enable us to investigate dynamical interplay between bottom-up information processing and top-down feedback signaling. Second, we re-examined the classic problem of signal propagation along the cortical hierarchy in an anatomically-constrained large-scale cortex model endowed with many feedback loops[3]. Surprisingly, our model displays a thresholding phenomenon for access to the prefrontal cortex and distributed dynamics akin to the global workspace model of conscious report. Third, analysis of densely connected multi-regional cortical circuit urged us to consider how information is routed to the right place at the right time in such a complex system, flexibly according to behavioral demands. I will propose a circuit disinhibitory motif instantiated by three (PV+, SOM+ and VIP+) subtypes of inhibitory neurons as a mechanism for gating inter-areal communication[11]. Fourth, model simulation of a delayed response task revealed working memory representations distributed across cortical areas. The theory of distributed self-sustained persistent activity patterns opens the door for elucidating cognitive processes, as well as their deficits associated with mental illness, in a large-scale multi-regional brain system.

Reading materials :

1. Chaudhuri R, Knoblauch K, Gariel M-A, Kennedy H, Wang X-J (2015). A large-scale circuit mechanism for hierarchical dynamical processing in the primate cortex. *Neuron* **88**, 419-431.
2. Fulcher D, Murray J, Zerbi V, Wang X-J (2018) Multimodal gradients across mouse cortical areas. *Proc. Natl. Acad. Sci.* in press.
3. Joglekar M, Mejias J, Yang GR and Wang X-J (2018) Inter-areal balanced amplification enhances signal propagation in a large-scale circuit model of the primate cortex. *Neuron*, 98, 222-234.
4. Mejias J, Murray J, Kennedy H and Wang X-J (2016) Feedforward and feedback frequency-dependent interactions in a large-scale laminar network of the primate cortex. *Science Advances* **2**: e1601335.
5. Wang X-J (2001) Synaptic reverberation underlying mnemonic persistent activity. *Trends in Neurosci* **24**, 455-463.
6. Wang X-J (2002) Probabilistic decision making by slow reverberation in neocortical circuits. *Neuron* **36**, 955-968.
7. Wang X-J (2008) Decision making in recurrent neural circuits. *Neuron* **60**, 215-234.
8. Wang X-J (2010) Neurophysiological and computational principles of cortical rhythms in cognition. *Physiological Reviews* **90**, 1195-1268.
9. Wang X-J (2013) The prefrontal cortex as a quintessential "cognitive-type" neural circuit: working memory and decision making. *Principles of Frontal Lobe Function*, Edited by DT Stuss and RT Knight, Second Edition, Cambridge University Press, pp. 226-248.
10. Wang X-J and Krystal J (2014) Computational psychiatry. *Neuron* **84,** 638-654.
11. Wang X-J and Yang R (2018) A disinhibitory motif and flexible information routing in the brain. *Current Opinion in Neurobiology*, **49**: 75-83.
12. Wei W and Wang X-J (2016) Inhibitory control in the cortico-basal ganglia-thalamocortical circuit: complex regulation and interplay with memory and decision processes. *Neuron,* **92**, 1093–1105.