Harvard Medical School Research (Ready)

The brain’s fundamental role in adaptive behavior lies in its capacity to coordinate effector organs in response to environmental demands. The timing of muscle activations, for example, can drastically affect behavioral outcomes in classic fight or flight contexts. However, as the environment becomes more complex, the decision for immediate action often relies on past sensory states no longer present to the animal. Foraging rodents need to remember which patches were already searched to conserve energy, and humans need to remember where they last placed their car keys. Both humans and animals demonstrate the ability to use past experiences to plan and simulate future actions, which are essential characteristics for higher-order brain function and flexible decision-making.

My work at Lee Lab models these tasks to study memory recall and imagination in the rodent model system. We train mice and rats to perform spatial navigation tasks that require them to either actively recall past experiences or imagine potential future trajectories. During behavior, we record from them using multisite silicon probes and population calcium imaging methods. With our group’s strong background in engineering and mathematics, we apply a range of analytical approaches from simple firing-rate analysis to RNN-based experiment variable decoders.

My current project employs a T-maze-based DNMTS (delayed nonmatch-to-sample) task to study how working memory is maintained through long delay periods in rodents. The task requires the subject to remember a sample stimulus over a long delay and then choose a novel nonmatching option when presented with the sample and the new alternative. In the T-maze implementation, both the sample stimulus and the new alternative are navigation targets equipped with reward ports. We record large-scale electrophysiological activity in freely moving animals and examine consistent patterns that emerge during delay as signatures of the maintained sample stimulus.

To analyze high-dimensional neural population data, I developed a novel LSTM (long short-term memory) decoder incorporating a custom loss function termed GICEL (Geometry-Informed Cross-Entropy Loss). This architecture processes population vector trajectories to classify animal location, task phase, and movement direction with a few technical innovations. Feature-gating mechanisms in early layers help to selectively emphasize informative neural signals (e.g., place cell activity) while suppressing noise from less relevant cell types. Additionally, the vanishing gradient tendency of LSTM, which is traditionally a limitation of RNN architectures, is leveraged to naturally prioritize more recent PVs in the sequence over earlier ones. The custom loss function, GICEL, further enhances performance by making the model aware of the consequences of different classification errors that reflect the maze’s spatial geometry. Unlike conventional cross-entropy loss that optimizes based solely on the target class probability, GICEL incorporates information from the entire prediction distribution. These technical designs achieved a 2.4-fold improvement in evaluation metrics and accelerated training convergence compared to standard methods.

I am currently applying the model to both delay phase data and task phase data to detect nonlocal representations: population activity patterns that do not reflect the animal’s immediate sensory state. During the delay period, we search for representations of either recently visited locations (retrospective coding) or future goal locations (prospective planning). During task execution, we track the emergence of target location representations to identify the moment of decision commitment. This work is ongoing and continues to provide insights into the neural dynamics of working memory and decision-making. Complementing this empirical work, I am developing reinforcement learning simulations of the behavioral task to generate testable predictions about the computational demands of working memory maintenance (see the Simulation page for more information).

UCLA Summer Research (Ready)

Knowing the structure of the brain is essential for understanding how neural circuits give rise to complex behavior. In recent years, we have seen many examples where connectomics datasets reveal previously uncharacterized pathways and motifs that help to explain population-level neural dynamics and circuit function.

In 2023 summer, I was awarded the UCLA Neuroscholar Scholarship for an undergraduate research opportunity at the Dong Lab (Dr. Hongwei Dong). Dong Lab, or UCLA B.R.A.I.N. (UCLA Brain Research & Artificial Intelligence Nexus), is dedicated to constructing a comprehensive, mesoscopic mouse connectome employing multidisciplinary approaches including genetics, 3D imaging, artificial intelligence, and advanced histology.

Under the mentorship of Dr. Nicholas Foster, my project used viral tracing methodologies to investigate the connectivity of the STN (subthalamic nucleus). The basal ganglia circuit is highly recurrent with very specialized input-output relationships. STN occupies a strategic position within the basal ganglia circuit as the primary modulator of basal ganglia output and a critical target for basal ganglia DBS (deep brain stimulation) therapeutics. In our literature review, we found that previous studies of STN afferent projections using chemical tracers were prone to inconsistent results, where retrogradely labeled regions failed to demonstrate reciprocal connectivity when examined with anterograde chemical tracers.

To address this non-specificity, we used a viral tracing construct known as TRIO (Tracing the Relationship between Input and Output), targeting STN and its main postsynaptic target SNr (substantia nigra pars reticulata). This system integrates a clever combination of a modified viral vector with the Cre expression system to restrict the expression of the fluorescence reporter to a specific path of projection. The approach enables precise trans-synaptic input mapping from defined neuronal populations based on both projection targets and cell-type identity, attenuating false-positive signals from injection site artifacts.

In the end, our results helped address the inconsistencies in the existing literature and additionally identified novel anatomical connections to the STN that had not been previously characterized. We also found initial evidence of internal topographical organization in several key structures, including GPe (globus pallidus external segment) and caudoputamen. Specifically, anatomically adjacent regions within these structures exhibited distinct connectivity patterns, suggesting functional subdivision at a finer spatial scale than previously appreciated. These results contribute to our current models of basal ganglia organization and have implications for understanding both normal circuit function and the mechanisms underlying movement disorders. These findings were presented in an abstract at a department event at the conclusion of the research program.

Cornell Undergraduate Research (Ready)

During undergraduate research at Bass Lab (Professor Andrew Bass), I contributed to establishing Danionella dracula as a pioneering model organism for system neuroscience. This miniature teleost fish species is a close relative of zebrafish that not only remains transparent throughout its lifetime but also lacks a skull roof, making it an attractive model for optical neuroimaging studies of intact brain circuits. My undergraduate research experience encompassed three complementary projects investigating their social behavior, developmental neuroanatomy, and sensory system organization.

The first project I contributed to was a neurobehavioral study to characterize the species’ social interactions, through which we hoped to establish behavioral paradigms for intraspecific aggression. During aggressive displays, males exhibit a stereotyped behavioral pattern including hypertrophied jaw extension and coordinated acoustic signaling. We analyzed the interactions between Danionella adult males to score how often an individual directed or received aggression from another male. We were able to demonstrate that Danionella exhibits a sophisticated hierarchical social relationship in which aggressive “higher-ranking” individuals receive less aggression and gain more frequent access to spawning sites than “lower-ranking,” less aggressive conspecifics.

In the summer of 2022, I investigated developmental trajectories of different brain regions in Danionella dracula using advanced optical methods. Working with Dr. Rose Tatarsky, we employed three-photon microscopy to perform comprehensive volumetric imaging of the entire central nervous system in intact, living Danionella specimens. This approach required no physical intervention other than simple mechanical stabilization, which allows for longitudinal studies of nervous system development. We identified the boundary between different brain regions in 3P imaging data using established neuroanatomical landmarks. This then enabled us to track regional growth trajectories with contour tracing and volumetric estimation methodologies. A particularly interesting result we were able to demonstrate was that the emergence of behavioral patterns like the aggressive displays correlates with the rapid growth of certain brain regions, providing quantitative evidence for structure-function relationships during neural development.

My final project investigated sensory responses in the Danionella dracula telencephalon to construct a sensory map for the Danionella brain, relying on the fact that sensory representation is often topographically organized in teleost sensory systems. I was initially contributing to viral vector injection protocols that aimed at establishing transgenic lines expressing pan-neuronal GCaMP. However, achieving uniform expression across diverse brain regions presented significant technical challenges that could confound activity measurements. To circumvent this limitation, we adopted an alternative endogenous activity marker known as pERK (phosphorylated extracellular signal-regulated kinase). Previous studies in larval zebrafish demonstrated robust correlations between pERK expression levels and GCaMP-derived activity measurements, validating this approach for our application. Through systematic pERK immunohistochemistry following controlled sensory stimulation (visual, acoustic, and lateral line modalities), we identified discrete telencephalic regions responsive to each sensory domain, contributing to the first comprehensive sensory map for this emerging model system.

High School Research (Ready)

My early interest in biological science was more general, and I was involved in research projects on very diverse topics, including molecular genetics of neuronal regeneration, animal courtship behavior, and ecological wildlife conservation.

At Sichuan University, I investigated how metformin, a widely prescribed antidiabetic medication with a nuanced profile of therapeutic benefits, affects the nervous system repair of a highly regenerative flatworm species called planaria. With a team of three high school researchers, we conducted controlled experiments exposing planarian populations to graded metformin concentrations and quantified neural repair responses using immunohistochemical visualization. To further explore metformin’s operating mechanism, we consulted literature and identified the GSK3β/Wnt signaling pathway as a potential mediator of metformin's regenerative effects. To test this hypothesis, we implemented pharmacological pathway inhibition experiments and demonstrated metformin's neural repair enhancement is abolished when GSK3β/Wnt signaling is blocked. This evidence suggests that GSK3β/Wnt plays a major role in metformin-mediated neural regeneration.

In the Emei Mountains, the habitat of the Rana Daunchina frog, I assisted two graduate students in investigating the species’ courtship behavior. The research project employed controlled playback experiments to determine female preferences for specific male call characteristics and examine the evolutionary pressures shaping acoustic communication. To ensure the experiments coincided with the species’ natural mating period, I adopted a nocturnal cycle. I captured the frogs for use in the experiments each morning before I went to sleep, and I woke up in the late afternoon to prepare for the experiments at midnight. Our results showed that not only are the females highly selective in their mating call preference, the structure of male-built nests acoustically modifies the male's mating call to match the female's preferred frequency profile.

In Tangjiahe National Reserve, I joined a government-funded research expedition as a volunteer with the National Department of Biology. The purpose of the trip was to analyze how local animal populations had changed their navigation patterns and spatial distribution in response to local tourist activities. We used mapping software to survey how the population distribution of indicator species like reptiles and snakes had changed due to human constructions. In parallel, we installed infrared cameras to trace keystone species like the local takin population, a gentle animal that looks like a sheep with a buffalo head. Our comprehensive analysis provided park officials with quantitative data on habitat fragmentation effects and population displacement patterns. These results were used to inform park management decisions regarding protective barrier placement and tourism-impact mitigation strategies.

POMDP Research (Ready)

Navigation-based DNMTS task (delayed nonmatch-to-sample) is the classic behavioral paradigm to study working memory, decision-making, and cognitive flexibility in rodent model systems. One approach to understanding how the brain solves such tasks is to employ reinforcement learning (RL) agents as mathematical proxies for neural computations, under the premise that any agent—biological or artificial—must share core computational characteristics to successfully perform the same cognitive task.

To this end, I implemented a custom simulation environment to model our T-maze-based DNMTS task and am currently training an RL agent within it. This custom environment, which I named TMazing (the “amazing T-mazing”), extends the OpenAI Gymnasium framework, a standard API for RL research.

To be consistent with the DNMTS paradigm, I formalized the task as a POMDP (partially-observable Markov decision process), reflecting the fact that the agent has limited access to the full environment state and must rely on past sensory experiences to perform correctly. The observation space encompasses three primary information channels: spatial position, auditory cues, and gustatory feedback. Auditory signals indicate gate opening during phase transitions, while gustatory information provides immediate reward detection. Spatial representation, which was initially implemented as one-hot positional encoding, was subsequently refined to simulate place-cell (gaussian bump model) or grid-cell (cosine interference model) population activation. This refinement followed the realization that one-hot vector encoding represents an extreme case of place-cell activity characterized by extremely sharp, non-overlapping place fields.

The agent obtains reward from successfully navigating to the target reward location, explorative behavior, thigmotaxis, and receives a penalty for timing-out and energy expenditure. The environment also incorporates robust error-handling protocols for any atypical agent behaviors. In a “time-out” scenario, which is when the agent has prolonged episodes of actions without achieving the phase transition criterion (e.g., not returning to the delay box after obtaining sample reward), the agent will be forced into ITI (inter-trial interval) with a time-out penalty plus opportunity cost of missed food reward. In a “wrong-choice” scenario, which is when the agent chooses the wrong arm at task phase, the opposing gate locks and the agent will face the opportunity cost of task food reward. The environment can be executed without rendering for training, but it has implementation for graphics with the Pygame lightweight game engine. This allows visualizing the behavior of trained agents and human interaction with the environment.

To solve this simulated DNMTS task, I am implementing a custom recurrent architecture which I termed “DORA” (delayed option reinforcement agent, “DORA the explorer”). DORA is a LSTM-based (long short-term memory) DRQN (deep recurrent Q-network) algorithm, designed to capture the task’s temporal dependencies for effective decision-making. TMazing’s POMDP formulation violates standard Markov assumptions, precluding the application of traditional RL algorithms that rely on Bellman equation frameworks designed for fully observable environments. The DRQN approach extends DQN (Deep Q-Network) methodologies to the partially observable domain by incorporating recurrent neural network architectures capable of maintaining internal state representations across temporal sequences. The LSTM implementation provides dual information processing pathways—long-term cell state and short-term hidden state—that enable systematic analysis of how the agent maintains task-relevant information throughout delay periods. Agent training is currently still in progress, and iterative modifications are being made to the training loop design and agent architectural components. In the end, we hope this work gives us the opportunity to see what representation the agent maintains to track cue information. This enables us to form testable hypotheses about the neural mechanisms underlying working memory in vivo, and to directly compare representations in artificial agents with those observed in our animal experiments.

Undergraduate Projects (Ready)

During undergraduate studies at Cornell, I pursued diverse programming projects spanning computational neuroscience, reinforcement learning, natural language processing, machine learning theory, and computer architecture. These experiences helped develop my ability to bridge theoretical concepts with practical implementations, and the skills I've acquired directly contribute to my current research.

In the computational neuroscience domain, my simulation projects involved using standard SNN (spiking neural network) paradigms—such as LIF (leaky integrate-and-fire) and MCP (McCulloch–Pitts) neurons—to construct canonical network motifs including Hopfield networks and oscillatory circuits. The Hopfield network, for example, is a recurrent artificial neural network that models auto-completion and content-addressable memory functionality of the hippocampal circuit. It demonstrates robust pattern recovery, where corrupted input patterns are recovered to their corresponding stored representations. The first figure on the right demonstrates the simulated Hopfield network recovering patterns of digit “0” and “1” from noisy inputs.

In the reinforcement learning domain, I developed agents to solve relatively simple MDP (Markov Decision Process) problems such as the Lunar Lander environment. The OpenAI Gym Lunar Lander environment represents a classic continuous control benchmark task that requires agents to execute controlled landings through thrust and rotational control. My implementation used a simple feed-forward architecture with the DQN (Deep Q-Network) training scheme, which is a Q-learning algorithm that relies on a neural network to approximate optimal action-value functions (Q functions). The second figure on the right is a rendered frame of the agent attempting landing in the environment. This experience has built the foundation for my current reinforcement learning project, where I implement a custom environment to simulate our animal experiment and train agents within it.

In the natural language processing domain, I developed a text summarization model using a pre-trained transformer (BERT-light). The model employs an extractive summarization approach where BERT first processes input sentences and generates sentence-level representations through its "sentence essence" CLS token. A binary classification head then analyzes these CLS token outputs to determine whether each sentence should be included in the final summary. We trained the model on a news dataset where the input documents were news articles, and the ground truth summaries were derived from the handy accompanying bullet points. Our model performed well on ROUGE-N evaluation metrics, which measures the overlap of n-grams (a sequence of n consecutive tokens) between the prediction and the reference.

In ML theory, I implemented a basic backpropagation engine that performs automatic differentiation on computational graphs. Backpropagation is the backbone (pun intended) of deep learning. It automates the process of calculating gradients of the loss function with respect to model parameters using the chain rule. My implementation follows PyTorch's reverse-mode design, where the algorithm dynamically constructs a computational graph during the forward pass and subsequently traverses the graph in reverse to compute gradients. This project provided me with a comprehensive understanding of the mathematical foundations underlying machine learning and helped me grow proficient with the PyTorch framework.

In the computer architecture domain, I designed a complete CPU circuit based on the 32-bit RISC-V instruction set architecture, an open-source processor specification. The processor was constructed entirely from fundamental logic gate components (NOT, AND, OR, etc.) and simulated using Logisim, an open-source digital circuit design platform. Shown on the right is the circuit design of the RCA (ripple-carry adder) unit, which implements binary mathematical addition/subtraction in the ALU (arithmetic logic unit, a CPU component). The ripple-carry adder is called so because the “carry output” from each stage must "ripple" through to the next stage sequentially (notice the one->two->four->…sixteen progression in the figure). This project provided me with a comprehensive understanding of how high-level computations are translated into fundamental Boolean operations at the hardware level, demystifying the seemingly magical inner workings of computers.

About Me Introduction (Ready)

I am Lucas Wang (Ke Wang), and I am currently serving as a research assistant at the Lee Laboratory (Dr. Albert Lee) at Harvard Medical School. I graduated from Cornell University with dual B.A. degrees in Biological Sciences and Computer Science, where I concentrated my studies in neuroscience and machine learning respectively. My interdisciplinary approach was profoundly inspired by Frank Rosenblatt, the Cornell neuroscientist who, despite lacking formal computer science or mathematics training, developed the perceptron—the foundational algorithm of modern deep learning—purely from his neurophysiological insights. His work demonstrates how biological and artificial neural systems converge on similar computational principles to solve learning problems.

My research experience spans both experimental and computational aspects of neuroscience, and topics include hippocampal & prefrontal cortical dynamics, artificial agent mechanistic modeling, viral genetic connectomics, multiphoton imaging, endogenous activity markers, conspecific aggression, and neurodevelopment. Please navigate to the Research page to learn more about my experimental work and the Simulation page to explore my computational modeling projects.

Research Area Introduction (Ready)

In my current role at the Lee Laboratory (Dr. Albert Lee), I investigate the neural mechanisms underlying working memory maintenance and decision-making in rodents using large-scale electrophysiological recordings from hippocampus and prefrontal cortex. Complementing this empirical work, I develop a task-matched reinforcement learning agent that performs the identical task to generate new hypotheses about the in vivo neural mechanism of working memory maintenance. At Cornell's Bass Laboratory (Dr. Andrew Bass), I contributed to establishing Danionella dracula (a zebrafish relative) as a novel multiphoton imaging model system for studying brain circuits. My projects included characterizing conspecific aggressive behaviors, demonstrating non-invasive three-photon imaging capabilities in adult specimens, and mapping telencephalic sensory representations using endogenous activity markers. Through the UCLA Neuroscholar summer research program at the Dong Laboratory (Dr. Hongwei Dong, UCLA B.R.A.I.N. Center), I employed viral tracing methodologies to investigate basal ganglia connectivity patterns, contributing to refined identification of subthalamic nucleus afferent sources.