Daniel Strouse **Proposed Plan of Research**

Title: The Functional Role of Spine Plasticity in Learning and Memory
Keywords: spine plasticity, dendritic spines, wiring plasticity, silent synapses, Alzheimer's disease, Down's syndrome, Fragile-X syndrome
Outline: I propose to investigate the role of spine formation and elimination (referred to as "spine plasticity" henceforth) in learning and memory. In particular, I will investigate how spine-related disorders such as Alzheimer's disease, Down's syndrome, and Fragile-X syndrome (FXS) disrupt the brain's ability to learn and, conversely, examine to what extent these mechanistic disruptions explain the behavioral symptoms. To do so, I will mathematically model the interaction between neural activity and spine plasticity, simulate learning tasks using biophysically realistic neural network models (such as compartmental models built with the Neuron simulation package), and verify the predictions of my simulations through collaborations with experimentalists. I intend to pursue this project at the University of California-San Diego mainly in collaboration with computational and experimental neuroscientist Terry Sejnowski.
Motivation: A lifelong love of learning and a fascination with the links between biophysical mechanisms and behavior[1] has guided my research interests towards the biological mechanisms of learning and memory. The brain's repertoire of biophysical learning mechanisms may be roughly divided into two categories: "weight plasticity" (i.e. those modifying the effectiveness of existing neural synapses) and "wiring plasticity" (i.e. those forming connections between previously uncoupled neural subunits or eliminating existing connections).[2] While weight plasticity has received a great amount of attention from both experimentalists and theorists, wiring plasticity is not as well understood. Imaging studies indicate that wiring plasticity via spine formation and elimination remains an active process throughout life and thus may play a significant role in learning and memory.[3] Evidence also indicates a connection between reduced spine number in Alzheimer's and Down's syndrome patients and an imbalance of mature and immature spines in FXS patients.[4] Thus, while spine plasticity may be important in both normal and abnormal brains, its exact role remains a mystery. What advantage does wiring plasticity offer on top of weight plasticity? For what tasks is wiring plasticity essential? I intend to focus my graduate studies on investigating this important gap in our scientific understanding of the biophysical mechanisms of learning and memory.
Previous Work: With Professor Bartlett Mel at USC, I am presently researching the mechanisms by which neurons select their presynaptic partners from the dense forest of nearby neurons. We hypothesize that immature or "silent" synapses may serve as trial connections for the correlation-based sorting of inputs onto dendritic subunits.[5] That is, we hypothesize that (1) the dendritic subunit is the fundamental computational unit of the neuron, (2) there is a computational advantage in having highly correlated groups of presynaptic neurons forming connections to the same dendritic subunit,[5] and (3) immature or "silent" synapses provide a mechanism for carrying out this correlation-based sorting. Past work has provided support for the first two hypotheses,[5] and we are beginning to investigate the third. Thus, my current work focuses on *how* neurons find appropriate connections while my future work will focus on *why* connections are altered and *what* happens when the process is disrupted.

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[1] See "Personal Statement" for further discussion.
[2] Chklovskii D, Mel B, Svoboda K. 2004. "Cortical rewiring and information storage." Nature 431:782–788.
[3] Alvarez V, Sabatini B. 2007. "Anatomical and physiological plasticity of dendritic spines." Annual review of neuroscience 30:79-97.
4 Bhatt D, Zhang S, Gan W-B. 2009. "Dendritic spine dynamics." Annual review of physiology 71:261-82.
[5] Poirazi P, Mel B. 2001. "Impact of active dendrites and structural plasticity on the memory capacity of neural tissue." Neuron 29:779-96.

Research Plan: My approach will combine mathematical analysis, computer simulations, and collaborations with experimentalists. Through statistical models and information-theoretic tools, I will examine the optimal balance between spine formation and elimination during a variety of learning and memory tasks. Through compartmental models of neurons integrated with simulations of diffusible factors, I will investigate the optimal biological conditions for the activity-dependent formation and elimination of spines during these same learning tasks. Optimal network parameters will provide experimentally verifiable predictions of biological variables (such as relative rates of spine formation and elimination). Incorrect predictions will necessitate further iterations between calculation, simulation, and experiment. In addition, I will examine the sensitivity of task performance to suboptimal network parameters in an attempt to model the connection between the biological and behavioral abnormalities associated with Alzheimer's disease, Down's syndrome, and FXS. By exploring changes in complementary network parameters that correct system performance, I hope to suggest potential new treatments, such as the application of chemical signals that modify spine plasticity.
Proposed Institution: UCSD and the Salk Institute form one of the largest and most well-integrated communities of computational and experimental neuroscientists in the world. Among these researchers, Professor Sejnowski is uniquely suited to advise my proposed project. Professor Sejnowski oversees the Computational Neurobiology Lab and shares my interest in connecting biophysical mechanisms to the functional properties of neural systems. His group combines computational and experimental methods and is well-versed in electrical and chemical monitoring techniques capable of measuring changes in the connections among nerve cells. Conditional upon my acceptance at UCSD, Professor Sejnowski has already offered to allow me to rotate in his laboratory. The Salk Institute is also home to dozens of experimental neuroscientists studying Alzheimer's as well as genetic abnormalities (such as Down's syndrome and FXS). As Professor Sejnowski has an appointment at Salk and plenty of collaborations with experimentalists there, I will also have access to experts on the disorders I aim to model.
Broader Impacts: According to the WHO, there are currently 18 million people with Alzheimer's disease while Down's syndrome occurs in about 1 in 800 newborn babies and FXS in about 1 in 4000. Thus, any advances in our understanding of these disorders or suggestions for treatments have the potential for widespread impact on society. Furthermore, in order to maximize the accessibility and impact of my research and promote a better understanding of the scientific process among the public, I will maintain an active research blog with non-technical summaries of ongoing projects and obstacles, a practice I have already begun.[6] In order to maximize the accessibility and impact of my research among my scientific colleagues, I will also make available all simulation code, neural data, and lab notes for full transparency and reusability, a practice that I am actively promoting.[1]
Personal Qualifications: Though past and present coursework in information theory, optimization, and statistical mechanics as well as previous work in the statistical modeling and optimization of neural networks,[7] I am familiar with the mathematical tools of analysis I propose to use. I have experience constructing compartmental models using the simulation package Neuron as well as experience with computational models of chemical diffusion in neural communication. Moreover, I have a working knowledge of known learning mechanisms and relevant biophysical variables through my current research. Finally, I have previously collaborated with experimentalists to guide theoretical and computational modeling efforts.

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[6] http://www.djstrouse.com
[7] See "Previous Research Experience" for further details on all research mentioned in this paragraph.