Short Time-Scale Dynamics in a Computational Model of Signal Propagations in a Cerebellar Neural Network

Proposal by Zan Ahmad
Advised by Dr. Charles S. Peskin

The goal of this project is a mathematical model for the propagation of signals in a neuronal network. The focus of this model will be the basic cerebellar circuit and the transfer of information through a small portion of this network, centered around the purkinje cell (PC). The cerebellum is involved in adaptive motor learning and motor control. It helps to facilitate the maintenance of balance and posture and the coordination of voluntary movements [3]. It is a structure located in the back of the brain behind the top part of the brainstem, underlying the temporal and occipital lobes of the cerebral cortex[1].

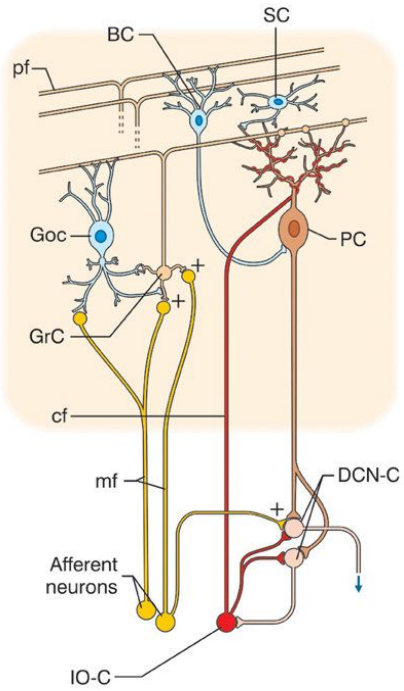

Figure 1: Circuit diagram of cerebellar network; (+)=excitatory, (-)=inhibitory; image reproduced from [2]

The neural network that will be modeled consists of a small portion of the system outlined in Figure 1. The scope of the model will include the excitatory output from granular cells (GrC) that form parallel fibers (pf) leading to the dendrites of PCs and the climbing fiber (cf) outputs sent from the inferior olive cells (IO-C) that target the PC as well as purkinje cell synapsing onto the deep cerebellar nucleus (DCN)[2]. The small network essentially consists of some of the information received and outputted by the PCs.

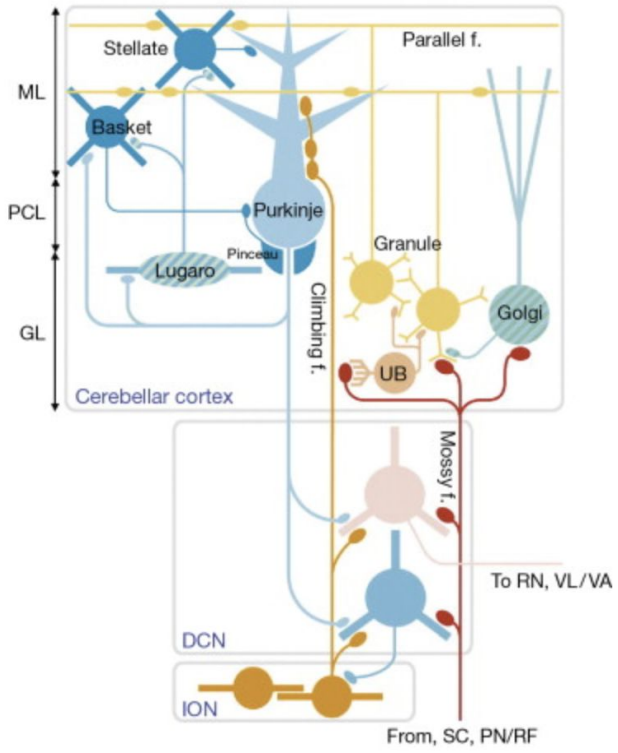

Figure 2: Three layers of the cerebellar cortex depicted; image reproduced from [4].

The cerebellar cortex consists of three layers as can be seen in Figure 2. The granular layer is situated below the purkinje cell and contains many small granule cells. The large cell body of the purkinje neuron forms the purkinje layer., and lastly the molecular layer contains the parallel fibers as well as the dendrites of the purkinje cell. [4]

The afferent input of the cerebellar cortex consists of signals from mossy fibers (mf) and climbing fibers (cf). Granular cells (GrC) receive input from four mossy fiber units that synapse onto short, claw-like dendrites. GrC's have unmyelinated axons that ascend to the molecular layer and bifurcate into many parallel fibers that are orthogonal to the dendritic tree of the purkinje cell. A climbing fiber originating in the inferior olive cells (IO-C) terminates within the main dendrite of the PC where it forms many synapses on short spines. The main efferent output of the cerebellar cortical process is the purkinje cell which has axons that target neurons in the deep cerebellar nucleus (DCN). [4]

The parallel fiber to purkinje cell synapse as well as the climbing fiber to purkinje cell synapse involves the release of excitatory neurotransmitter Glutamate. The PC to DCN synaptic transmission is inhibitory, involving the neurotransmitter GABA. [4]

Our methodology consists of two parts. The first part is to model the propagation of signals in individual neural cells. This will be done using Hodgkin Huxley partial differential equations for electrical signaling in axons and dendrites and a numerical methodology that solves equations like these on an arbitrary tree of cables will be employed. The steps to this method are outlined in Dr. Peskin's online lecture notes from

the course “Mathematical Aspects of Neurophysiology: Hodgkin Huxley equations” [16]. The HH PDEs are a continuous-time dynamical system of nonlinear differential equations used for approximating electrical properties of cells with excitable nature such as how action potentials in neurons are initiated and propagated [17]. In order to construct this model, the geometry of the cells need to be determined. In particular, the diameters and lengths of each axon and dendrite of each of the cell types in question (purkinje, granular, inferior olive, deep cerebellar nucleus) need to be known parameters for the model. The channel types that each cell has, how these channel types are distributed throughout different parts of the cell, along with a quantitative description of the gating properties of each of the channel types need to be determined. We will use data from literature perhaps including data from existing mathematical models of these individual cells. [5] contains information about the channel types of the purkinje cell. Relevant information regarding the dendrites of the Purkinje cell can be found in [6]. Parameter values essential to HH PDE’s for the granular cell, parallel fibers, climbing fibers and deep cerebellar nuclei are available in [7] and [10]. Data on inferior olive cells and climbing fiber connectivity and morphological characteristics are detailed in [14]. The details of the geometric parameters and network connectivity in the stomata of the purkinje cell can be found in [8], [13], as well as in the supporting materials section of [9]. Detailed information on the trajectories of a single climbing fiber and mossy fiber are found in [11]. Connectivity information involving the granular layer of the cerebellar circuit can be found in [12].

Once we have this information to model the individual cell in the network, the second part is to couple the individual neuronal cells with model synapses that incorporate stochastic vesicle release which is a mechanism of short-term synaptic depression leading to enhanced transmission of contrast and depressed transmission of steady signals. The probabilistic nature of neurotransmitter vesicle release in synapses makes it a significant source of noise in the circuit. We can construct a pre-synaptic model of this phenomenon and analyze its effects on the short-term dynamics of the synapse. Although there is a lot that remains uncertain about synaptic vesicle release, a probabilistic math model that covers the essential stochastic docking, undocking, and release of neurotransmitters can be incorporated to create a functional network model that connects the individual cells in question. [15]

Some interesting characteristics that we hope to observe in the dynamic model include the emission of a complex spike discharge after PC activation by climbing fibre inputs in addition to the simple spike discharge with the waveform of a typical action potential.

Overall, this project will provide training in the analysis of neuroscientific data, the application of mathematical models to physiological systems, as well as develop experience in numerical methods and computational skills and is thus well-suited for a student in the TPCN program.

References

[1]“Cerebellum (Section 3, Chapter 5) Neuroscience Online: An Electronic Textbook for the Neurosciences: Department of Neurobiology and Anatomy - The University of Texas Medical School at Houston.” *Cerebellum (Section 3, Chapter 5) Neuroscience Online: An Electronic Textbook for the Neurosciences | Department of Neurobiology and Anatomy - The University of Texas Medical School at Houston*, nba.uth.tmc.edu/neuroscience/m/s3/chapter05.html.

[2]D'Angelo, Egidio & Casali, Stefano. (2012). Seeking a unified framework for cerebellar function and dysfunction: From circuit operations to cognition. Frontiers in neural circuits. 6. 116. 10.3389/fncir.2012.00116.

[3]Yamazaki, Tadashi, and Jun Igarashi. “Realtime Cerebellum: A Large-Scale Spiking Network Model of the Cerebellum That Runs in Real Time Using a Graphics Processing Unit.” *Neural Networks*, vol. 47, 2013, pp. 103–111., doi:10.1016/j.neunet.2013.01.019.

[4]“Cerebellar Circuits.” *Neural Circuit Development and Function in the Brain: Comprehensive Developmental Neuroscience*, Academic Press, 2013.

[5] Wehenkel, Marie, and Rodolphe Sepulchre. “Cellular Regulation Mechanisms : Case Study of up and down States in the Purkinje Cell.” *University of Liège Faculty of Applied Sciences Department of Electrical Engineering and Computer Science*, 2013.

[6] Kitamura, Kazuo, and Masanobu Kano. “Dendritic Calcium Signaling in Cerebellar Purkinje Cell.” *Neural Networks*, vol. 47, 2013, pp. 11–17., doi:10.1016/j.neunet.2012.08.001.

[7] Saarinen, Antti, et al. “Stochastic Differential Equation Model for Cerebellar Granule Cell Excitability.” *PLoS Computational Biology*, vol. 4, no. 2, 2008, doi:10.1371/journal.pcbi.1000004.

[8] Shelton, D.p. “Membrane Resistivity Estimated for the Purkinje Neuron by Means of a Passive Computer Model.” *Neuroscience*, vol. 14, no. 1, 1985, pp. 111–131., doi:10.1016/0306-4522(85)90168-x.

[9] Genet, Stéphane, et al. “Dendritic Signals Command Firing Dynamics in a Mathematical Model of Cerebellar Purkinje Cells.” *Biophysical Journal*, vol. 99, no. 2, 2010, pp. 427–436., doi:10.1016/j.bpj.2010.04.056.

[10]Casali, Stefano, et al. “Reconstruction and Simulation of a Scaffold Model of the Cerebellar Network.” *Frontiers in Neuroinformatics*, vol. 13, 2019, doi:10.3389/fninf.2019.00037.

[11] Shinoda, Y., et al. “The Entire Trajectory of Single Climbing and Mossy Fibers in the Cerebellar Nuclei and Cortex.” *Progress in Brain Research Cerebellar Modules: Molecules, Morphology and Function*, 2000, pp. 173–186., doi:10.1016/s0079-6123(00)24015-6.

[12] Maex, Reinoud, and Erik De Schutter. “Synchronization of Golgi and Granule Cell Firing in a Detailed Network Model of the Cerebellar Granule Cell Layer.” *Journal of Neurophysiology*, vol. 80, no. 5, 1998, pp. 2521–2537., doi:10.1152/jn.1998.80.5.2521.

[13] De Schutter, Erik, and J M Bower. “An Active Membrane Model of the Cerebellar Purkinje Cell.” *JOURNAL OF NEUROPHYSIOLOGY*, vol. 71, no. 1, 1994, pp. 375–400.

[14] Sugihara, Izumi, et al. “New Insights on Vertebrate Olivo-Cerebellar Climbing Fibers from Computerized Morphological Reconstructions.” *Bioarchitecture*, 1 Mar. 2013, pp. 38–41., doi:https://dx.doi.org/10.4161%2Fbioa.24062.

[15] Zhang, Calvin, and Charles S. Peskin. “Analysis, Simulation, and Optimization of Stochastic Vesicle Dynamics in Synaptic Transmission.” *Communications on Pure and Applied Mathematics*, vol. 73, no. 1, 2019, pp. 3–62., doi:10.1002/cpa.21847.

[16] Peskin, Charles S. “Mathematical Aspects of Neurophysiology .” Hodgkin Huxley Equations. 2000.

[17] “Hodgkin–Huxley Model.” *Wikipedia*, Wikimedia Foundation, 25 July 2020, en.wikipedia.org/wiki/Hodgkin%E2%80%93Huxley_model.