*Computational analysis and multi-dimensional modeling uncover hyperbolic geometry in whole brain of C. elegans which aids in discovery of neural network states*

**Background:**

Neural responses are influenced by both external stimuli and internal network states. While

network states have been linked to behavioral and stimulus states, little is known about how

sensory inputs are filtered by whole-brain activity to downstream motor neurons. Using calcium imaging in a Zeiss Airyscan 880, we recorded whole-brain activity of *Caenorhabditis elegans* (*C. elegans)* experiencing bacterial food stimuli and modeled how sensory inputs affect sensory and motor neurons in a network state dependent manner. We classified active neurons into six functional clusters: two sensory neuron clusters (ON, OFF), and four motor/command neuron clusters (AVA, RME, SMDD, SMDV). We proceeded to analyze our multi-dimensional calcium trace data without losing the distance measures between points using a hyperbolic embedding technique, Hyperbolic Multidimensional Scaling (HMDS). We determined that there was a hierarchical structure among the neuronal populations. Bayesian information criteria analysis showed that our data can be optimally represented in 8-dimensional space. These dimensions correspond to the axes of 4 different sets of complementary neurons corresponding to the cell types we identified. Although neural computations performed by sensory neurons are linear due to their direct exposure to stimuli, the downstream neurons are often non-linear as they integrate inputs from multiple neurons. This non-linearity poses a challenge in interpreting downstream neural responses that correspond to their original input stimuli.

**Proposal:**

Our goal is to analyze how input stimuli and sensory neurons affect downstream motor neural populations. We use HMDS and linear and quadratic maximum noise entropy, which recapitulates the nonlinear filter dynamics within neural populations allowing us to identify specific states of the network that links sensory neuron activity with downstream motor neurons. Collectively, we will present an interpretable approach for modeling network dynamics of neural populations, which can be scaled to larger organisms.

**Aim 1: Hyperbolic Multidimensional Scaling Analysis Clusters Neuronal Populations**

The data collection provided a robust dataset consisting of time series calcium traces in each neuron in the whole brain of *c elegans.* The organism was fixated and presented randomized pulses of stimulus. We predict that whole brain dynamics govern the organism’s response to stimulus in a time dependent manner, with the presence of network states. This research aims to prove that there is an innate hierarchical structure among the sensory neurons which serve as primary responders to stimulus and higher order motor neurons which respond to complex non-linear signaling from multiple downstream inputs. This hierarchical structure can aid in the analysis of network states. There are multiple supervised and unsupervised clustering models available to analyze multidimensional data such as this, however HMDS ensures multidimensional data points can be clustered while maintaining original distance information between points. This creates an alternative to PCA, which can be useful for separating data according to principal components, but can obfuscate information such as cell identity, is insensitive to outliers, and assumes linear relationships among variables. Upon running HMDS, we see that there is a hyperbolic geometry present in our system (Fig 1 A-D.) The spherical shape of the system where each point represents a cell, using our entire cohort of organisms, is a hallmark of many hyperbolic systems. The embedding distances in the Sheppard diagram (Fig 1B) scale linearly with the original distances in the data. The distance metric between points was a normalized squared Pearson Correlation. The optimal number of dimensions to represent our data, represented by the Bayesian Information Criterion (BIC) was shown to be 14. (Fig 1). BIC per individual organism it was 6 dimensional. We aim to show that these 6 dimensions correspond to 6 known neuronal clusters: Sensory ON, Sensory OFF, AVA, RME, SMDD, and SMDV. Using a cell data taken from their hyperbolic coordinate system, we map a pair of clusters onto a single axis, the ON and OFF sensory neurons separate using just one dimension (Fig E, F). Altogether we will continue to use hyperbolic embedding coordinates to separate and discover subpopulations of cells within our data, that would not be discoverable using classical dimensionality reduction methods.

**Aim 2: Linear and Quadratic Maximum Noise Entropy (MNE) Uncovers Neuronal Receptive Fields**

Nonlinear dynamics are a hallmark of neuronal systems. Canonically a nonlinear system exhibits behavior in which an input has a nonlinear relationship to the output, in other words, they are not proportional to each other. This makes a system appear chaotic, or unpredicatable. Often times in computational neuroscience, the goal is to be able to decode a neuron’s optimal stimulus ( what is prefers firing to the most) in response to it’s firing rate. The nonlinearity in the case of a neuron stems from the complex dynamics of it’s interactions with neurons it is synapsed to. There may be multiple inputs to its dendrites, and these neuronal inputs may further have multiple inputs on their dendrites, and so on and so forth. This complex and hierarchical structure includes many unknown variables that aid in creating these complex nonlinear dynamics. We aim to use MNE (maximum noise entropy) a technique rooted in elucidating nonlinear dynamics of neurons, to be able to recapitulate their receptive fields. In other words, we use a constrained gradient descent optimization to calculate the unknown terms in a logistic function, to fit it to our data. This function predicts the probability of a neuron firing through the course of several time points, depending on the stimulus it receives. Otherwise known as a time series, one dimensional, receptive field.

**Significance**

This research attempts to bridge the worlds of computational and experimental neuroscience to investigate whole brain dynamics of a complex system. There are often difficulties in obtaining whole brain data, and the analysis of nonlinear dynamics may obfuscate the process entirely. However, methods rooted in information theory can help take a complex, nonlinear multidimensional system, and isolate its most essential informative parts, in an interpretable and scalable manner. This allows us to gain a clearer understanding of the way an organism interacts with its environment and the environmental and internal variables which may be responsible to subsequent actions this organism might take, for. In our case, the motor response initiated by a sensory stimulus.

**Figure 1**

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D

C

B

A

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F

E

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**Figure** Hyperbolic multidimensional scaling analysis of food-stimulated whole-brain calcium activity. (A) 3-dimensional Poincaré embedding coordinates calculated from Pearson correlation distance matrix of all worms (B) single worm distance matrix of normalized squared Pearson correlations. (D) Shepard diagram of respective distance measures. (C) Bayesian Information Criterion show optimal dimension for maximum information (D) Histogram of radii of point embeddings in hyperbolic space (E) Kernel Density Estimate plot of hyperbolic embedding coordinates of ON and OFF sensory neurons mapped in tangent space along single axis (F) Scatter plot of hyperbolic tangent coordinates along single axis shows cluster separation.

**Bibliography:**