A novel causal modeling algorithm uncovers predictive coding properties of c. elegans

Background

Predictive coding is a theory in theoretical and cognitive neuroscience which aims to prove that the core function of the brain is to minimize prediction error. The central idea is that the brain is organized in a hierarchy of layers. Each layer takes makes a prediction about the activity of the layer below it. The downward predictions are compared to the activity of the layer, the difference is called prediction error (Friston, 2003). In other words, at each layer there is activation information that is received and a pre-existing expectation of what is to be received. The difference, prediction errors, at each level is what is fed to the level above it. As a result, there is an efficient hierarchy of perceptual errors which gets passed up. These predictions happen on a variety of scales ranging from fine grain sensory level details such as simple shapes or features of objects, to whole scenes and whole objects, to higher level thinking. The goal of the system is to minimize the difference between actual activity and predicted activity at each level, in other words minimize prediction error, the act of doing this minimization results in inference and learning (Millidge, 2021). This is accomplished by performing a procedure called variational inference. Predictive coding can be used to explain phenomena such as end-stopping, bi-stable perception, and learning and adaptation. Focusing on learning and adaptation, predictive coding can help explain how an organism can learn to anticipate sensory stimuli in its environment that it has not yet experienced but learned from previous instances to expect. This anticipation can be viewed as a predictive response. In other words, can the organism anticipate future environmental factors based on the information and inference it has accumulated in the past?

The existence of predictive coding in this capacity has been investigated predominantly in mammalian systems, with the first proposed model explaining perceptual phenomena in the human retina (Srinivasan, 1982). In recent years there has been a growing interest in investigating the existence of it in smaller organisms, some which do not exhibit spiking or a cortical structure, such as *c. elegans* (Leifer 2014). However, **there is a lack of evidence that predictive coding is used by *c. elegans* to anticipate the onset of a sensory stimulus.**

Convergent cross-mapping (CCM) is a method used in time series analysis to detect causal relationships between variables (Sugihara 1990). It is particularly useful for identifying nonlinear interactions and can provide insights into whether one time series can predict another, and thereby establishes a causal relationship between the two. The ability to make an accurate prediction about the future instance of a variable based on the time series generated manifold of another variable is what determines a causal relationship between the two.

Proposal

Using calcium imaging in a Zeiss Airyscan 880, I have recorded whole-brain activity of *Caenorhabditis elegans* (*C. elegans)* experiencing bacterial food stimuli and which models how sensory inputs affect sensory and motor neurons in a network state dependent manner. I have classified active neurons into six functional clusters: two sensory neuron clusters (ON, OFF), and four motor/command neuron clusters (AVA, RME, SMDD, SMDV). In my proposal I identify a computational method not commonly used to investigate this specific application of predictive coding, convergent cross mapping (CCM). I further attempt to expand on this method by optimizing it, to recognize similar structural motifs regardless of magnitude within time series data encompassed by E. I will use this novel method to create a shadow manifold of calcium trace data from a neuron and used this to predict the causal relationships between neurons in the *c. elegans* brain and investigate how the organism can anticipate the onset of a stimulus as evidence my modulations of its calcium activity. I believe that if I find that establishing a strong causal link from a neurons response data to the stimulus signal can make a case that the neuron is anticipating stimulus, as theorized by predictive coding.

Specific Aims

Aim 1 - Optimization of the Simplex Algorithm for Convergent Cross mapping (CCM)

Convergent Cross Mapping Model is a type of tool for short range forecasting of chaotic time series data. The algorithm it uses is called Simplex. Simplex works by reconstructing the system dynamics of a model based on Takens' Theorem. In which a single time series: $\{X_t, X_{t-1\tau}, X_{t-2\tau},\ldots,X_{t-(E-1)\tau}\}$, where E is the dimensionality of a system, and T is some time lag tau. The original time series is the sequence for which we choose to make a prediction. This creates a shadow manifold. The forecast for the prediction can be denoted as:

$Y(t_k) =\{Y(t_k),Y(t_{k-1}),\ldots,Y(t_{k-E+1})\}$ is made using the projections of its neighbors in the state space from the library set, $\{X_{(1)},X_{(2)},\ldots,X_{(E+1)}\}$, where $\|X_{(1)}-Y(t_k)\|=min(\|X-Y(t_k)\| = min(\|X - Y(t_k)\|)$ for all X≠YX. So a time prediction one step forward into the future is $Y^{\wedge}(t_{k+1})$ is the average of all of the projections of all of its neighbors in this

shadow manifold: $\{X_{(1)}(t_{1+1}), X_{(2)}(t_{2+1}), \ldots, X_{(E+1)}(t_{E+1+1})\}$ (Chang 2017). This method can be used to reconstruct manifolds which can predict the future activity of multiple variables in a single system, based on the time series of a single variable.

However, I believe there are certain repetitive motifs within the time series data that are not utilized by the algorithm and may therefore lead to less than accurate inferences about the nature and strength of causal relationships among datasets. In addition, this may lead to a weaker predictive ability and therefore a weaker causal link between the two variables being studied. Establishing causality between variables is crucial.

I will create a modified version of this algorithm to consider repetitive motifs of the same shape but various magnitudes. (Fig 1a) Shows calcium recording of two neurons in the *c. elegans* brain and the corresponding stimulus. One can see that although there are repetitive peaks with similar shapes, they may not be of the same magnitude. With the simplex algorithm as is, these points will lie in further positions on the shadow manifold, than they should be expected to. However, I believe by normalizing each vector $\{X_{(1)}, X_{(2)}, \ldots, X_{(E+1)}\}$ according to its first term, this would account for these structural similarities.

Aim 1.2 - Testing additional Causality models to investigate the optimal model for the system

There exists an abundance of other models which seek to predict behavior, and thereby establish a causal relationship between two variables throughout the course of time. Techniques such as mixtures of structural causal models (MSCD) proposed by (Varambally 2023) rely on the use of multiple predictive models in a single system to explain its causal dynamics. It would be wise to use multiple models to determine the degree of causality in my system.

Aim 2 - Establishing causal relationships among neuronal subtypes within *c. elegans* time series dataset using modified Simplex Algorithm

In Figure 1, there is an outline of the analysis procedure that one normally does using the current CCM method. I anticipate having better predictive capabilities with my altered simplex algorithm; however the workflow will remain unchanged. Once the data (Fig 1a) is cleaned and normalized, one time series from a neuronal calcium response to a stimulus will be chosen. Simplex creates a shadow manifold which predicts the future time points of a time series, one half of the data is withheld as ground truth to test these predictions (Fig 1b). Based on trial and error a dimensionality E will be chosen. This is the dimensionality that yields the highest Pearson correlation between actual data and predictions. Multiple variables can then be tested, using CCM the causal relationship between one variable is determined based on the accuracy of the predictions that it makes for another variable's future activity. (Fig 1c) shows how the SMDV motor neuron predicts the AVA motor neuron, blue line, with the y-axis indicating Pearson coefficient between prediction and ground truth. The orange line shows the inverse condition, indicating SMDV has a stronger causal influence of AVA than the other way around. The algorithm can be run on an entire dataset of neurons (Fig 1d), and causal relationships can be between each variable within the whole system. Fig 1e demonstrates the degree to which using this method to infer future activity of a neuron is better than using autocorrelation within the data. The time point at which the method is the most useful is beyond 150 time points into the future. I anticipate with the change to simplex, my Pearson coefficients will be higher, and there will be a greater benefit to using this algorithm than autocorrelation at earlier than 150 time points into the future. Most importantly, I anticipate that I can **find a causal link between a single neuron and the stimulus time series itself.** This would show that the neuron is predicting the stimulus, as predictive coding postulates would happen. There various degrees of strength of causality between neuronal subtype (sensory or motor) and stimulus, and this can be investigated as well.

Aim 2.1 – Using Modified Simplex on Additional Time Series Data

I will use additional time series datasets to test the robustness of my method and investigate the same organism and others using resources such as Allen Brain Atlas, OpenNeuro, CRCNS (Collaborative Research in Computational Neuroscience).

<u>**Significance**</u>

The advantages and impact of using this modified method in this unique way cannot be understated. Although predictive coding as a phenomenon has been characterized in more complex mammalian systems such as the human visual cortex, its presence has not been investigated to the same extent in less complex, non-mammalian, and non-spiking organisms. There is of publicly available time series data The use of nonlinear forecasting has predominantly been in ecological systems. Not only can this modified simplex method could be used on time series data in nonlinear complex systems, but it would be more suitable to the specific motifs that are found in c. elegans calcium traces, and other less complex organisms. Altogether this research can shed light into the predictive capabilities of the brain in anticipating future stimuli in accordance with the theory of predictive coding.
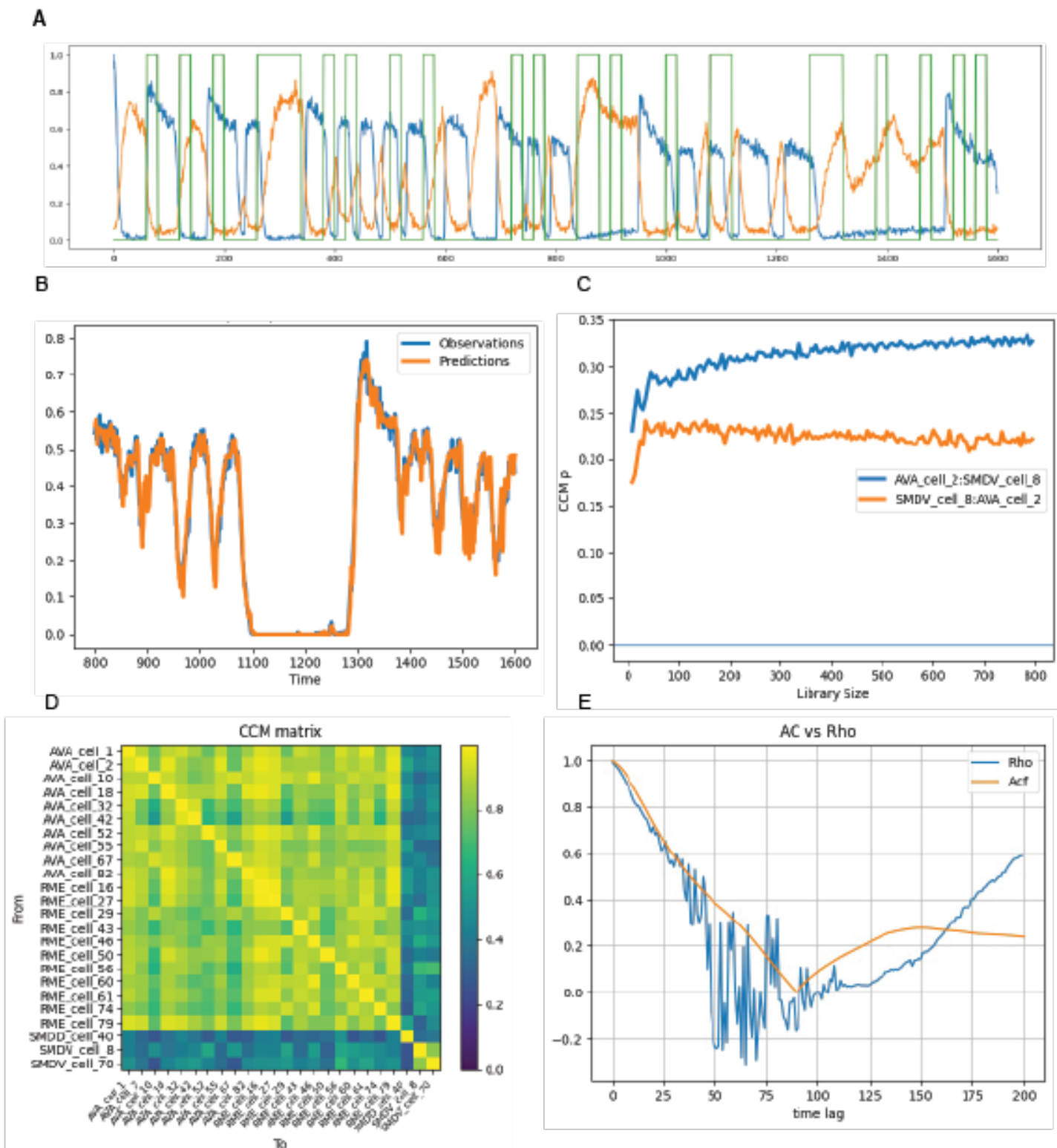
Figure 1 A) Time series calcium trace data from whole brain of c. elegans. Two traces (blue and orange) and the stimulus (green). B) Predictions (organge) created using the simplex algorithm of a single neuron's activity pattern, one 800 time points into with the future, using preciding 800 time points, with an embedding dimension size of 5, and a Tau prediction interval of 1. Overlayed against ground truthdata observations (blue). C) Convergent Crossmaping results showing the strength of the causal relationship based on predictive power between 2 neurons, AVA and SMDV. SMDV has better predictive power onto AVA than vice versa. D) Convergent Cross Mapping matrix of a series of AVA, RME, SMDD, and SMDV motor neurons in a single c. elegana shows strongest causal relationships between AVA and RME. E) Predicitive capability of the autocorrelation (orange) versus predicitive capability using simplex (blue) method shows advantage of using simplex past 160 time points.

References

1. Chang, C.-W., Ushio, M., & Hsieh, C.-H. (2017). Empirical dynamic modeling for beginners. *Ecological Research, 32*(6), 785-796. https://doi.org/10.1007/s11284-017-1469-9

2. Friston, K. (2005). A theory of cortical responses. *Philosophical Transactions of the Royal Society B: Biological Sciences, 360*(1456), 815–836. https://doi.org/10.1098/rstb.2005.1622

3. Golkar, S., Tesileanu, T., Bahroun, Y., Sengupta, A. M., & Chklovskii, D. B. (2022). Constrained predictive coding as a biologically plausible model of the cortical hierarchy. In S. Koyejo, S. Mohamed, A. Agarwal, D. Belgrave, K. Cho, & A. Oh (Eds.), *Advances in Neural Information Processing Systems* (pp. 14155-14169). Curran Associates, Inc. https://doi.org/10.48550/arXiv.2210.15752

4. Golkar, S., Tesileanu, T., Bahroun, Y., Sengupta, A. M., & Chklovskii, D. B. (2023). CUTS+: High-dimensional causal discovery from irregular time-series. *arXiv*.

5. Leifer, A. M., Fang-Yen, C., Gershow, M., Alkema, M. J., & Samuel, A. D. (2014). Optogenetic manipulation of neural activity in freely moving Caenorhabditis elegans. *Nature Methods*, 8(2), 147-152. https://doi.org/10.1038/nmeth.1554

6. Millidge, B., Seth, A., & Buckley, C. L. (2021). Predictive coding: A theoretical and experimental review. *arXiv*. https://arxiv.org/abs/2107.12979

7. Sugihara, G., & May, R. M. (1990). Nonlinear forecasting as a way of distinguishing chaos from measurement error in time series. *Nature, 344*(6268), 734-741. https://doi.org/10.1038/344734a0

8. Varambally, S., Ma, Y.-A., & Yu, R. (2023). Discovering mixtures of structural causal models from time series data. *arXiv*. https://doi.org/10.48550/arXiv.2310.06312