Spatial Embedding of Edges in a Synaptic Generative Model of *C. elegans*

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Abstract

The human brain is poorly understood. Although insufficient, investigating its structure is necessary to discern how it operates. This structure on a microscale can vary wildly between individuals. Understanding how these networks form would help in explaining this variability. To do so, we need to develop computational models that simulate the processes involved. With a relatively small and (near) completely reconstructed connectome, *C. elegans* is an ideal subject for this research. A previous attempt at this used stochastic methods, where connections are assigned randomly and weighted by the distance between soma. While useful, this model failed to predict particular network attributes of the *C. elegans* connectome. We aimed to develop a minimal model that incorporates the spatial embedding of neurites to approximate the process of neurite growth and synapse formation in Euclidean space, examining the impact of neurites on network structure. We found that networks that incorporate the spatial embedding of neurites resulted in particular attributes consistent with connectomes of *C. elegans*.

Introduction

Despite tremendous computational power, no person has been able to create an algorithm as capable as the human brain. With its approximately 86 billion neurons (Azevedo et al., 2009), the human brain is an organ so complex that charting its synaptic connections alone is a monumental task (Van Essen et al., 2012). Tremendous time and effort are being invested in the creation of a complete human connectome. However, there is little justification for how this data would explain the functioning of the human brain (Ceylan et al., 2022; Rheault et al., 2020). Accurate mapping of these connections in living brains alone proves difficult given modern technological limitations (Rheault et al., 2020). With a neuronal network that is approximately 0.01% the size of a human's (Azevedo et al., 2009), *Caenorhabditis elegans* has the most complete connectome mapped at the cellular level (White et al., 1986). One might expect the neural functions of *C. elegans* to be well understood. However, the dynamics and behaviors of the *C. elegans* neuronal network (CENN) have not been accurately replicated. While the topology of synaptic connections cannot predict the dynamics of a neuronal network, it does restrict what sort of dynamics are possible (Prinz et al., 2004). To truly understand how a brain works, a model replicating the structure and dynamics of said brain is essential (Izquierdo, 2019).

Synaptic variability is a major roadblock to understanding the structural organization of brains. Even with just 302 neurons, the neuronal network of the hermaphrodite *C. elegans* exhibits tremendous variability. With over half of all its synaptic connections found to vary between healthy individuals, recording every possible *C. elegans* connectome morphology is untenable (Witvliet et al., 2021). Moreover, a complete knowledge of when and where synaptic connections occur does not necessitate an understanding of how and why this variability occurs. We cannot expect to understand the nature of *C. elegans*'s connectomic structure from large sets of data alone.

Generative models are a promising method for understanding network formation and the parameter space where particular connectomes lie. Generative network models create networks from a set of rules defining where and how connections are created (Betzel and Bassett, 2017). By focusing on how networks form and not on a complete list of nodes and edges, generative models can apply to many brains, not just a single instance of one.

Itzhack and Louzoun (2010) developed a generative model that produces networks similar to the *C. elegans* connectome in the average length of connections, average connectivity, and the total number of bidirectional links. Their model (i.e. the Random Distance Dependent Attachment Model (RDDAM)) randomly forms connections with a probability that logarithmically decreases with an increase in spatial distance between two neurons, expressed as $p(i \rightarrow j) = c(d)^{-\alpha}$. This aligns with the observations of neuronal organization in *C. elegans* (Pérez-Escudero and Polavieja, 2007). While several generative models attempt to accurately predict the network topology of *C. elegans* (Costa et al., 2007; Khajezade et al., 2019; Nicosia et al., 2013), the RDDAM's simple rules make it an excellent candidate for comparison against future generative models. An essential aspect of the RDDAM is the spatial embedding of each neuron. Neurons exist in physical space, interacting

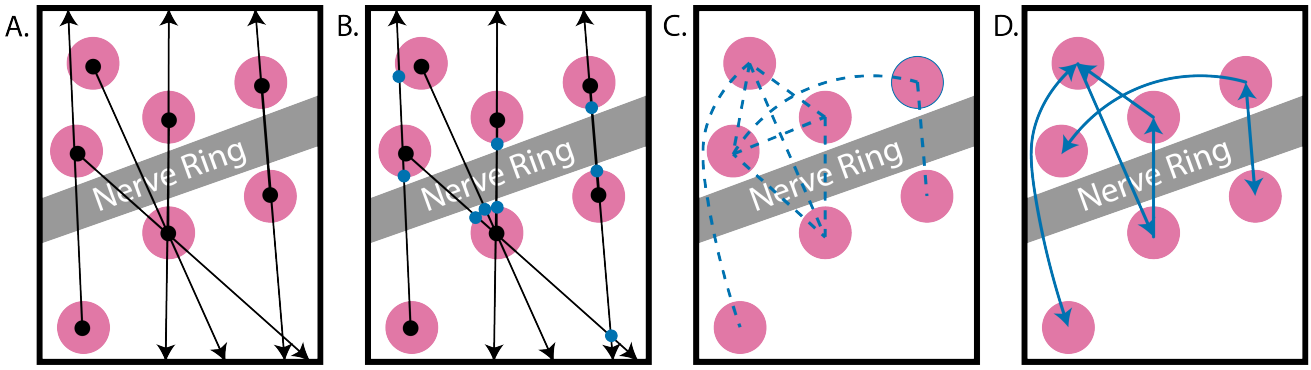

Figure 1: Visual depiction of the Spatially Embedded Edge Model (SEEM) algorithm. **(A)** For each neuron, SEEM finds the neuron whose soma is closest to it and opposite the Nerve Ring (i.e. the neuron's "penpal"). The algorithm then draws a line segment in 3D space, representative of a neurite, originating in the neuron's soma, extending through the soma of the "penpal," and terminating at the boundaries of the body of *C. elegans*. The boundaries are calculated as a range from the minimum coordinate - ε to the maximum coordinate - ε for each dimension (x,y,z). ε is defined as the width of a neurite ($3\mu m$). **(B)** If two of these "neurites" are $\leq \varepsilon$ away from one another, **(C)** the two neurons of these neurites form a potential connection. **(D)** A random subset of these potential connections are chosen equal to the number of total connections found in the *C. elegans* network to which it is being compared.

chemically and electrically with their surroundings. What connections neurons make are in part a result of their location relative to other cells (Hentschel and Ooyen, 2000; Kaiser and Hilgetag, 2006; Pérez-Escudero and Polavieja, 2007).

Spatial embedding is not only relevant for the somas (the center of the neuron) but for the neurites (the extensions of the neuron) as well. Neurites take up physical space within the body of *C. elegans*, limiting how many connections are physically possible within the organism. The majority of neurons in *C. elegans* each have one or two neurites that are a single process, forming most of their connections as "en passant" synapses (i.e. synapses that do not form at the tip of the axon) (Durbin, 1987; White et al., 1986). This pattern of neuronal connectivity is not accounted for in existing models of *C. elegans* neuronal connectivity (Costa et al., 2007; Itzhack and Louzoun, 2010; Khajezade et al., 2019; Nicosia et al., 2013). Constraining connectivity to intersections along the path of a neurite may result in a network that is more similar to CENN than the results of existing generative models. This leads us to the question: How much of the *C. elegans* neuronal network structure is explained by the spatial embedding of its neurites?

Model and Methods

We sought to understand how the spatial embedding of neurites might explain the neural organizational structure of *C. elegans*. We developed a model to create sets of networks that attempt to recreate the process of neurite growth and synapse formation in Euclidean space. Although not biologically precise, this model serves as a tool to analyze the structure of the *C. elegans* neuronal network. Our aim with this model is to examine how neurites impact the structure of a network while keeping the number of assumptions to as few as possible.

Data

The length and organization of neural processes in *C. elegans* are highly variable, particularly in the pharyngeal nervous system. To simplify this, this research focused on the neurons in the frontal ganglia, due to the length of their connections being less variable.

The synaptic connections of a single newborn/L1 ($\sim$ 0 hours old) and two adult/L5 *C. elegans* were acquired from Witvliet et al. (2021). A third adult/L5 connectome was acquired from Durbin (1987)'s N2U, an updated version of the original White et al. (1986) connectome. 3D positions of the neurons were taken from Skuhersky et al. (2022).

Model

We developed a generative model which spatially embeds edges as well as nodes. It replicates the process of neurite growth and synaptogenesis while keeping the number of assumptions and parameters to a minimum. Doing so allows us to better understand how spatial embedding of neurites alone impacts the makeup of the connectome.

This model will be referred to as the Spatially Embedded Edge Model (SEEM). SEEM iterates over every node. Each node locates the node closest to it that is on the opposite side of the nerve ring, a region that contains more than half of all neural processes (Altun, 2017). We refer to these target nodes as the source node's "penpal." A line segment is drawn from the source node through the target node, terminating at the surface of the bounding box of the network (see

fig 1). The bounding box is defined as the smallest 3D box that can hold all nodes in the network. These line segments are intended to represent a single neurite. Since most neurons in *C. elegans* only have 1-2 neurites, we chose for each neuron to exhibit a single neurite in our model.

After all "neurites" have been drawn, the minimum distance between any two line segments is recorded. Given these neurons have a diameter of 2-3 microns (Schafer, 2006), a distance less than or equal to 3 microns (ε) between any two lines will be considered an overlap. All possible edges in the model have now been determined. To generate a network, a random selection of directed edges is selected from the set of all possible edges. The number of edges selected can be adjusted. For these experiments, we used as many edges as were in the comparable *C. elegans* neuronal network. The code for this algorithm can be found at the link listed under *Data and Code Availability*.

Additional Model

Our model assumes a particular algorithm for determining the direction in which its neurites extend. To account for what effects this assumption might have on the results, we created a second model for comparison. The Randomly Embedded Edge Model (REEM) is created in the same way as our other model (SEEM) with one key difference. Rather than passing through the closest neuron opposite of the nerve ring, this model's neurites form in random directions. This model can explain our algorithm for determining how neurite direction influences the results.

Networks for Comparison

In addition to our models, we chose two other sets of networks to compare. The first is a set of networks resulting from the Random Distance Dependent Model (RDDAM) from Itzhack and Louzoun (2010). This network will allow us to see the role that distance between soma alone plays in the network structure. This model determines whether or not to form a connection with the probability function $p(i \rightarrow j) = c(d)^{-\alpha}$. Keeping in line with the original implementation, we kept α to 2.5 and adjusted c so that the resulting number of connections would roughly match the number in the compared *C. elegans* frontal ganglia.

The second set of networks chosen for comparison is a set of random networks. We determined the Erdős-Rényi random network (ERN) to be a suitable random network for our analyses. This network is one where a given number of nodes are connected with a given number of randomly-assigned edges (Erdős et al., 1960). These random networks will allow us to understand what results are a result of chance and what results are meaningful.

Network Comparison Methods

We compared the four chosen *C. elegans* connectomes with the resulting networks of our model, the Spatially Embedded Edge Model (SEEM). To better assess the insights from our model, we also compare the results from a model from the literature, the Random Distance Dependent Attachment Model (RDDAM), and with two null models: the Randomly Embedded Edge Model (REEM), and a set of Erdos-Renyi networks (ERN). For each connectome, each model was run for 100 iterations, resulting in 100 possible graphs. Each metric was run over every instance of the graph and the average value was recorded.

To compare these networks, we selected four distinct graph-theoretic properties: the average clustering coefficient, the average edge distance, the average connectivity, and the total number of bidirectional links. These measures are useful means of understanding the general structure of the networks in question and were used when comparing the RDDAM to *C. elegans* (Itzhack and Louzoun, 2010).

The clustering coefficient measures the number of instances where two neighbors of a node are connected divided by the total number of instances possible ($k(i)(k(i)-1)$ in a directed graph where k(i) is the degree of node i) (Watts and Strogatz, 1998). As the name suggests, it helps us to understand how clustered a network is and get a better idea of how interconnected all nodes in the network are on average.

The average edge distance measures the average length of each link/edge in Euclidean space. Given that many of these models account for Euclidean space when forming connections, this measure is relevant. It gives us an idea of how long these connections are, providing a simple understanding of how these networks compare with *C. elegans*.

The average connectivity measures the average local node connectivity between all pairs of nodes in the network. Local connectivity is defined as the minimum number of nodes needed to be pruned to result in no paths connecting a pair of neurons, resulting in 2 or more connected components (Esfahanian, 2013). The average connectivity of the network can provide us with an idea of the network's redundancy, which can coincide with its metabolic efficiency and its resilience to perturbation.

The total number of bidirectional edges is the number of instances where two nodes are connected to each other in a directed graph. When comparing graphs with a similar number of edges, this property can help us to understand if nodes prefer to connect with their neighbors. A large number of bidirectional edges can also indicate a large amount of symmetry in the network.

For a better understanding of how these networks are distributed, we compared two distributions for all networks: degree distribution and edge distance distribution. Degree distribution gives us a general idea of the network's structure. The edge distance distribution shows us how these connections project into Euclidean space.

To see how descriptive these models are of the *C. elegans* frontal ganglia, we plotted a random network from each of

these models in 3D Euclidean space. We also calculated the overlapping edges of each network to conclusively understand how close any of these models were to replicating a *C. elegans* connectome.

Results

To answer the question of whether spatially embedding edges is an important factor in the formation of the *C. elegans* Neural Network (CENN), we compared networks from our initial model (SEEM) and our randomly-directed model (REEM) with *C. elegans*. We also compared these networks with the Random Distance Dependent Attachment Model (RDDAM) from Itzhack and Louzoun (2010) and a set of random networks (Erdős-Rényi networks / ERN) to gauge how close our model is to the *C. elegans* network. To rule out development as a factor, we made comparisons to both a single L1 connectome ($\sim$ 0 hours) and a set of 3 adult (L5) connectomes. We measured these generative network models from a set of 100.

L1	SEEM	RDDA	ERN	REEM	CENN
Clustering Coefficient	0.08	0.15	0.03	0.07	0.12
Edge Distance	16.23	6.69	19.17	16.36	15.11
Average Connectivity	2.12	2.58	2.89	2.57	1.68
Total Bidirectional Links	26.62	94.81	8.38	44.44	95.00

Table 1: Average network statistics of 100 networks from models when compared with newborn *C. elegans* (L1, $\sim$ 0 hours)

L5	SEEM	RDDA	ERN	REEM	CENN
Clustering Coefficient	0.19	0.25	0.07	0.16	0.22
Edge Distance	16.25	7.58	19.20	16.38	14.94
Average Connectivity	17.00	20.98	23.08	20.27	5.58
Total Bidirectional Links	146.76	288.59	44.84	236.49	283.33

Table 2: Average network statistics of 300 networks from models when compared with the average of 3 adult *C. elegans* (L5)

Network Statistics

Comparing these networks can be done in several different ways. As an initial comparison, we chose to use network statistics to compare essential aspects of these graphs. We chose to compare the average clustering coefficient, average edge distance, average connectivity, and average total number of bidirectional links. These network statistics were chosen as they were used by Itzhack and Louzoun (2010) in their paper on the RDDAM, providing an initial point of comparison with previous work. We plotted the results of the network measures of all 100 instances of each model (see fig 2) and compared them with the results of these measures on the CENN. For the newborn (L1), we compared it to a single graph, but, for the adults (L5), this was three graphs.

In general, there were not many significant differences between the results of L1 and L5 networks. One difference of interest was that the networks of Witvliet et al. (2021) had noticeably different clustering coefficients and total number of bidirectional links when compared with the N2U connectome (Durbin, 1987). It is difficult to determine what might be causing this discrepancy, whether it is a result of different environmental conditions or if this is indicative of flaws in the recording methods of some or all of the connectomes. Rather than averaging the results of the connectomes, we chose to show all three individually (see fig 2).

Clustering Coefficient Our initial model and RDDAM were the closest to *C. elegans* in this statistic, with our model performing better in adults and RDDAM performing better in the L1 connectome. Given these results, proximity alone might explain the clustering patterns of the *C. elegans* connectome.

Edge Distance The average edge distance found that our two models were closest to *C. elegans* in this regard. RDDAM had much shorter edges on average than any of the other networks. Given that it prioritizes proximity when making connections, this result is unsurprising. Our random model (REEM) had edge distances that were slightly longer. It is unclear why this is the case. One possible explanation is that the neurites of this model were less likely to cross paths with their neighbors given the random directions they take. Since both of our models were most similar to *C. elegans* in edge distance, this suggests that spatial embedding of neurites and soma alone mostly explains this characteristic of the network.

Compared with the results from Itzhack and Louzoun (2010), ranging from 3-4 microns, our results are noticeably higher, ranging from 6-20 microns. The increase in distance can likely be explained by the dimensionality of the embedded space. Given that our tests incorporated three-dimensional data of soma body locations from Skuhersky et al. (2022) while Itzhack and Louzoun (2010) only used the one-dimensional position data from WormAtlas (2009), the distance in our analysis between any two soma will always be equal to or greater than what one would find using one-dimensional positions.

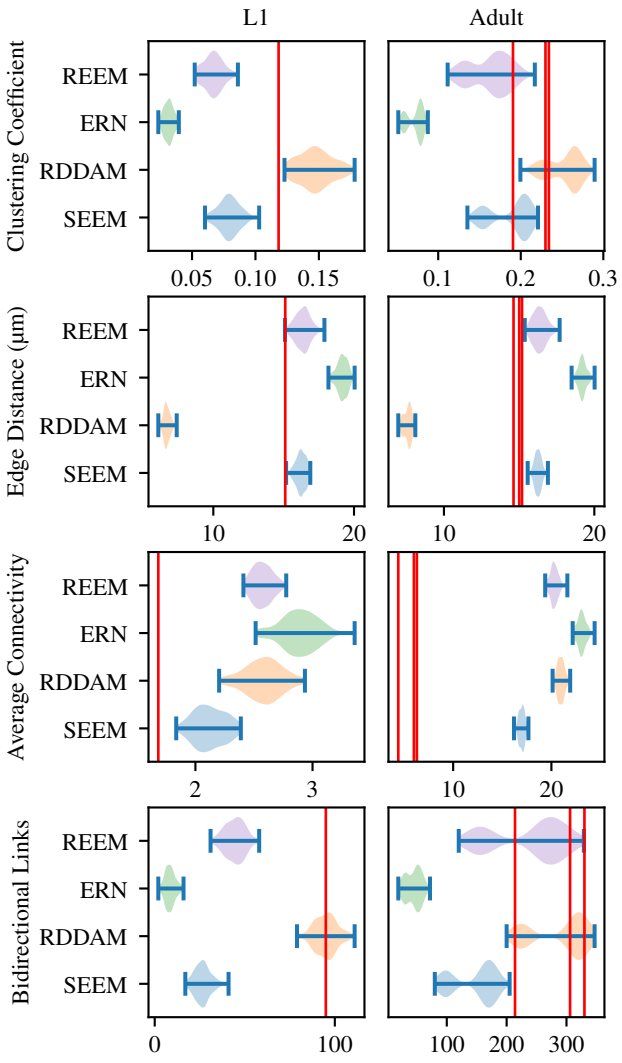

Figure 2: Plots of network statistics which were averaged in Table 1. Red lines denote the values of the *C. elegans* connectomes for comparison. L1 results (left) used 100 networks from each model. Adult results (right) used 100 networks sampled from all 3 adult *C. elegans*, resulting in 300 networks total for each model.

Connectivity Average connectivity was found to be much lower than any of the tested models would predict. In the L1 worm, our initial model appears to somewhat accurately predict this low connectivity. However, in the adult worms, this discrepancy becomes much larger. These results show that the network structure of *C. elegans* connectomes is much more sensitive to perturbation than any of our other networks. This indicates that the connections of neural networks of *C. elegans* are not as redundant as most networks. This is in line with previous work finding the connectome of *C. elegans* contains a "rich club" (i.e. a cluster of nodes all of which have a relatively high degree) and that its connectome is metabolically efficient (Pérez-Escudero and Polavieja, 2007; Towlson et al., 2013).

Bidirectional Links The number of bidirectional links in *C. elegans* was shown to be most similar to the number found in RDDAM. Given how accurate it is in predicting this metric, it is likely that spatial proximity explains the number of bidirectional edges in *C. elegans*.

It is interesting to note that these models have fewer bidirectional links in L1 and more bidirectional links in L5 when compared with *C. elegans*. Given that there are a greater number of connections in the L5 networks, more bidirectional links should be expected just from random chance alone, as we see in the results of our Erdős-Rényi networks. Although, the results of Erdős-Rényi networks show that random chance alone cannot explain the amount of growth in the number of connections between the two ages.

Another simple explanation for this growth could be a result of the smaller number of connections possible under our model. One is more likely to flip two heads with a coin than one is to roll two 1's with a die, given the same number of flips/rolls. Our random model (REEM), on average found fewer potential connections compared with our initial model (SEEM). Given RDDAM's preference for short connections, an even smaller subset of possible connections are most likely to be made in the model, which is direction agnostic. This would explain why RDDAM has so many bidirectional links. These results indicate that the spatial proximity of soma alone can explain the network structure of *C. elegans*.

What does this tell us? Looking at these statistics, it appears that the *C. elegans* connectome clusters are in line with what one might expect from such a spatially embedded graph. The number of long-distance connections suggests that the connectome of *C. elegans* does not prioritize close connections. It is more likely that short connections are just a result of neurites being more likely to come into contact with nearby neurons. Average connectivity points to a network that is more efficiently organized and far less redundant than any other networks examined. Our measures of bidirectional links show that *C. elegans* does appear to have a strong preference for bidirectional edges, in line with what RDDAM predicts. Our model (SEEM) appears to capture many of these network attributes reasonably well except for total connectivity and total number of bidirectional links.

Distributions

While these statistics give us an idea of how some of the attributes of these networks in describing the underlying structure of the CENN, it does not give us a picture of how the edges in any of these networks are distributed. Network distributions can give us a better insight into the shape of these networks. We had two questions: 1) What is the structural makeup of these networks? (Are they scale-free, small-

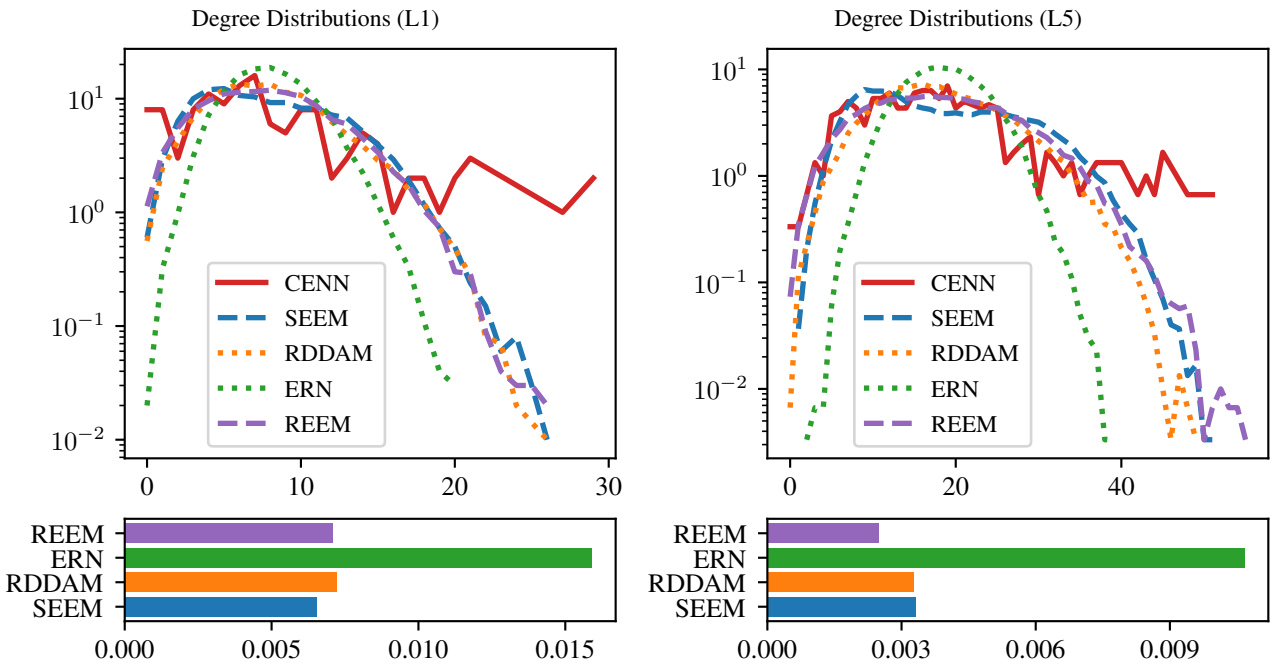

Figure 3: Average degree distributions of all models and *C. elegans* frontal ganglia connectome in log scale (top) and the Wasserstein distances between the average distribution of each model and *C. elegans* frontal ganglia (bottom)

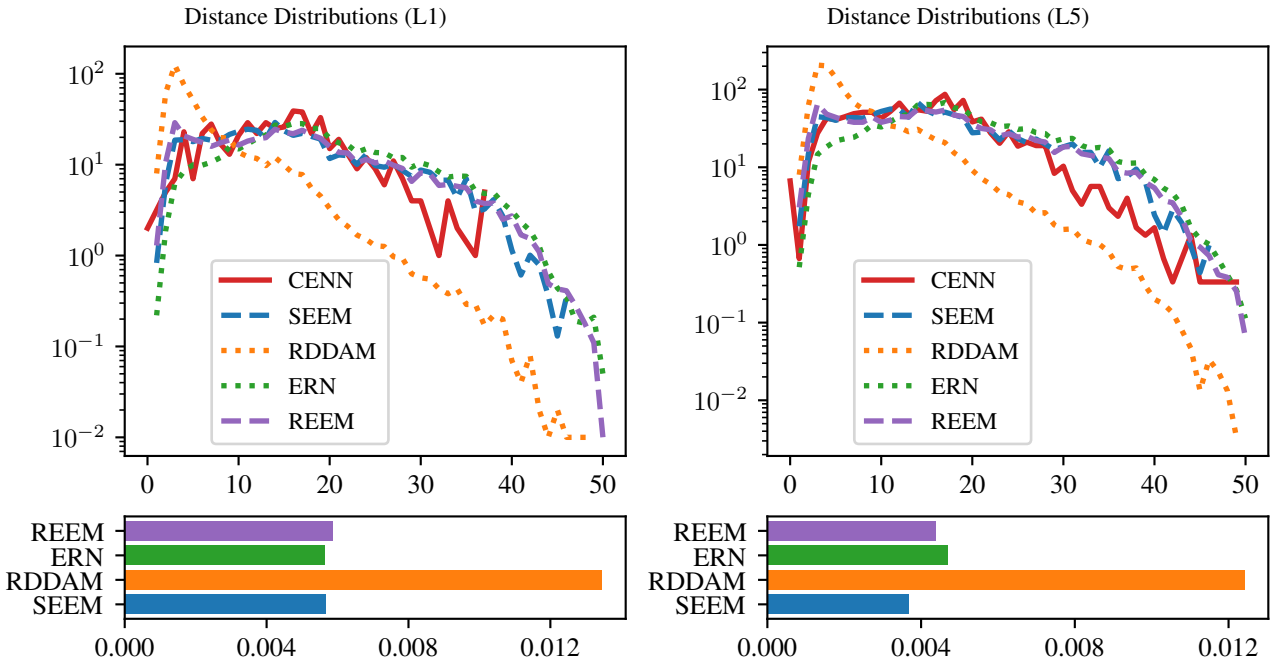

Figure 4: Average distance distributions of all models and *C. elegans* frontal ganglia connectome in log scale (top) and the Wasserstein distances between the average distributions of each model and *C. elegans* frontal ganglia (bottom)

world, etc.?) 2) What is the physical makeup of these networks?

To answer these questions, we compared the degree distributions of these networks to examine their network structure (see fig 3) and the distance distributions of these networks to examine their physical structure (see fig 4). To get a better idea of how similar these distributions were, we also measured their Wasserstein Distances from the *C. elegans* distribution. For the adults, these distributions were averaged.

Degree Distributions We found that our models and RDDAM have degree distributions closest to *C. elegans*, with RDDAM being slightly closer. These models result in networks that appear to have more variability in degree than random networks. Since both rely on the spatial proximity of nodes, which are not evenly distributed, it would be expected for their degree distributions to favor nodes that are closer to many others. This could explain why we see these results. Notably, the degree distributions of CENN have much longer tales. This means that *C. elegans* connectomes are more centralized than any of the other networks This falls in line with the results measured from Average Connectivity.

Distance Distributions The edge distances of each model show an issue with RDDAM: its proclivity for short connections. We see that our model is most like *C. elegans* in this distribution, the same as what we found when comparing average edge distances. This indicates that the *C. elegans* frontal ganglia are not particularly distance dependent as indicated in Itzhack and Louzoun (2010). Given the similarity in the distributions, the spatial embedding of neurites could explain the edge distance distribution of *C. elegans*.

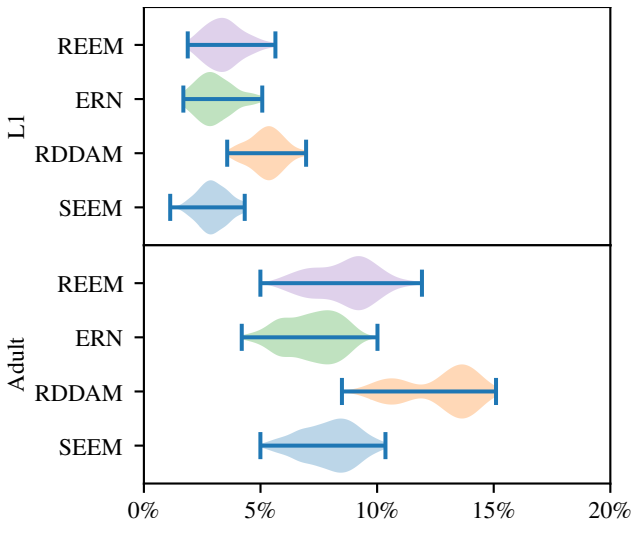

Figure 5: The percentage of connections in the *C. elegans* frontal ganglia which are also found in the model's networks.

Overlaps

Looking at the edges shared by the models and *C. elegans*, we find that none of the models' resulting networks contain a significant portion of the edges found in *C. elegans* (see fig 5). These results are unsurprising given the results of their average connectivity and their spatial embedding. Despite the network similarities that SEEM has in common with the *C. elegans* frontal ganglia, it is not an accurate approximation of it.

Spatial Embedding

Examining the makeup in Euclidean space, we observe varying connection patterns between each model (see fig 6). Our random examples, ERN and REEM, appear to not have any skewed distribution in their preferred connections. On the other hand, our model (SEEM) and RDDAM paint a different picture. SEEM appears to prefer connections that do not span the center (pharynx). RDDAM appears to have connections mostly localized to the most clustered areas. From these observations, the *C. elegans* frontal ganglia form connections around the entire pharynx more often than our model would expect. Given that our model is unable to "wrap" around the pharynx, such a result is unsurprising.

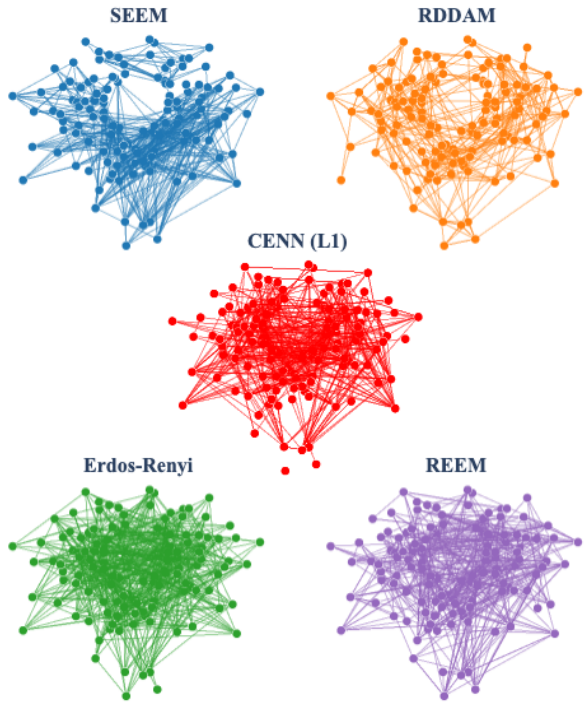

Figure 6: A posterior-facing, coronal view of the L1 networks in Euclidean space looking directly through the center (pharynx)

Conclusion

While significant experimental progress is made to understand the developmental process of *C. elegans*, a computational modeling approach allows us to test what assumptions in our thinking are more and less important for the process. To date, there's only been one model of the synaptogenesis of the *C. elegans* connectome that has aimed at predicting the connections between its neurons. In their work, they based their predictions on the distance between neurons alone. In this work, we found that embedding neurites are an important factor in explaining certain network aspects of the *C. elegans* frontal ganglia. Although geometry is an important factor in determining connection in *C. elegans*, it is not the only factor that matters. All models tested failed to effectively replicate average connectivity, implying these biological neurons create networks that are much more metabolically efficient than typical networks. The results of spatial embedding and comparing edge overlaps show that despite the similarities our model has with the *C. elegans* frontal ganglia they are not representative of the *C. elegans* neuronal network.

Future Directions

The results of this study have resulted in many potential avenues for future research. None of the models presented could replicate the average connectivity found in the *C. elegans* frontal ganglia. It would be interesting to see how a generative model could replicate this network attribute. A simple heuristic to locally enforce low local connectivity in each node could be one way in which this could be possible. It is unclear what biologically realistic mechanism could explain such an effect. A generative model with low connectivity might further uncover the underlying mechanisms of the *C. elegans* neuronal network.

While these generative models have proved useful in understanding *C. elegans*, it is unclear if they can be generalized across species. Applying these models to the larval microconnectomes of *Ciona intestinalis* (Ryan et al., 2016), *Platynereis dumerilii* (Verasztó et al., 2020), and *Drosophila melanogaster* (Winding et al., 2023) would reveal whether these network features are species-specific.

Another potential direction for this work would be to incorporate more biological mechanisms into the system. One option would be to change the connectome during development. For example, adding nodes to the network over time or adjusting the node locations as the worm grows. It might also be interesting to add genetic factors in determining connectivity patterns.

Data and Code Availability

All scripts and files used to generate all figures are available at `https://github.com/Zach-Attach/SEEM.git`

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