WHY ARE MOST NEURONS IN THE HEAD?

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Abstract

We pursue the hypothesis that neuronal placement in animals minimizes wiring costs for given functional constraints. Using available *C. elegans* wiring data, we solve the optimal layout of 280 non-pharyngeal neurons. The solution demonstrates: 1. Neurons in the same ganglion cluster together. 2. Neurons follow actual anterior to posterior order. 3. The coordinates of neurons agree with actual positions. Rare neurons show strong deviations from predictions, suggesting existence of other unknown constraints. Our results not only prove the importance of wiring cost minimization in neuronal placement but also spotlight neurons whose function is not captured simply by the wiring diagram.

Keywords: Neuron placement; Optimization; *C. elegans*

Introduction

The nervous system of animals follows a specific arrangement. For example, most neurons reside in the brain (or ganglia), located in the head of the animal. What rules govern this physical organization? Can the placement or misplacement of neurons help us understand their function? We address these questions by computing the optimal position of neurons through minimization of network wiring.

The farther apart two neurons are, the more costly the connection between them [9]. This "cost" can be attributed to factors such as: wire volume [4,8], signal attenuation [10], metabolic expenditures associated with wire maintenance [2], and guidance during development [11].

Previous efforts have used the "save wire" hypothesis to find the optimal layout of networks with a small number of components [5,7]. These studies calculated the total wire length for all possible arrangements in order to find one that requires the shortest wire. However, since the number of permutation increases

exponentially with the number of components, this approach becomes computationally impractical for finding the optimal layout at the level of individual neurons.

We bypass this computational difficulty by solving the placement problem analytically in the case where cost scales as wire length squared. This quadratic formulation has been argued to be biologically relevant in previous work [6].

Here, we take advantage of the abundance of anatomical information available in the nematode *C. elegans* to calculate neuronal placement. In the worm, the number of neurons, the location of their cell bodies, as well as the wiring diagram have been well-studied and found to be reproducible from animal to animal [12]. Furthermore, the length of the worm is around 10 times greater than its diameter, allowing us to reduce the problem into one-dimension. By minimizing wiring cost, we calculated the placement of 280 non-pharyngeal neurons along the lateral body axis of the hermaphrodite worm.

Model

We start by writing the cost of wiring (E^{tot}) as the sum of an internal (E^{int}) and external (E^{ext}) component:

$$E^{tot} = \sum_i E_i^{\text{int}} + \sum_i E_i^{ext}, \qquad (1)$$

where subscripts denote neuron index and sums are over all neurons in the network.

The internal cost stems from connecting to other neurons in the circuit. We assume the cost of connecting the i^{th} and j^{th} neuron to be a function of the square of the distance between them, $|x_i - x_j|$, where x is position:

$$E^{\text{int}} = \frac{1}{2}\alpha \sum_i \sum_j A_{ij} \left| x_i - x_j \right|^2 . \qquad (2)$$

A_{ij} is an element of the adjacency matrix A, representing the strength of connection between neurons *i* and *j*; α is an unknown coefficient. The adjacency matrix is non-negative ($A_{ij} \geq 0$) and symmetric ($A_{ij} = A_{ji}$). Since wiring cost is attributed to the physical connection between neurons, neither the type of signal (inhibitory vs. excitatory) nor the polarity of signal propagation (from neuron *i* to *j* or vice versa) should impact this function.

The external term of the cost function results from wiring neurons to structures outside the network. It is the total cost of connecting to each external component, *k*, such as sensors and muscles, located at position b_k:

$$E^{ext} = \beta \sum_i \sum_k B_{ik} \left| x_i - b_k \right|^2 \qquad (3)$$

where B_{ik} is the strength of connection between neuron *i* and external component *k*; β can be set to one without loss of generality. Since the placement of organs such as sensors and muscles are under presumably different functional constraints, we assume these positions, b_k, are fixed.

The model approximates connection cost to be proportional to the number of synapses. This assumption is equivalent to having a dedicated wire for each synapse. However, each neuron in the worm, on average, forms 56 synapses from only two processes. *C. elegans* neurons are typically bipolar with one process connecting to the external component (e.g., sensory organ) and a second process making internal *en passant* synapses to other neurons [12]. We take this morphology into account by normalizing each internal connection by the average number of synapses per neurite ($\alpha = 1/28$ or the inverse of 56 synapses per neuron divided between 2 processes). Each external fixed point, by construction, connects to the neuron through a single wire ($\beta = 1$).

The current work utilizes neuronal wiring data compiled by Achacoso and Yamamoto (AY) [1]. Each electrical or chemical synapse makes a unit contribution to the symmetrized adjacency matrix, A_{ij}, such that $A_{ij} = A_{ji}$. A total of 39 external components constrain the network via 161 neurons. These points include 19 sensory organs and 20 segments of neck and body muscles. The locations of sensory organs are measured relative to the most anterior point of the worm using diagrams obtained from the Wormatlas website (www.wormatlas.org). We assume muscle segments to be evenly distributed between positions 25% to 85% down the length of the worm body with neuron-to-muscle mapping according to AY [1]. Neuron-to-sensor mapping is determined by sensory neuron identity [12]. Using formulations from Equations 2 and 3, the optimal layout can be found by minimizing the total wiring cost (Equation 1) with respect to position.

Results

The neuronal layout obtained from minimization of wiring cost agrees well with actual neuron organization in the worm. Figure 1 shows the location of neuronal cell bodies within each ganglion (pharyngeal ganglion excluded). With the exception of lumbar neurons, most neurons belonging to the same ganglion tend to be clustered together in the optimal layout. The order of ganglia placement in the worm also agrees well with actual. However, on an overall level, the neurons from the theoretical layout aggregate in the anterior two-thirds of the worm body. In the actual worm, neurons form clusters in the head and tail of the animal and evenly distributed in the mid-body [12]. These results show that many neurons are clustered in the head due to the large number of connections to sensors located there.

The ordering of neurons that minimizes wiring cost resembles the actual head-to-tail layout in the worm. Cells in the calculated arrangement of 280 neurons have a standard deviation of 43.6 positions from the actual order (Figure 2). Neurons located in the neck of the worm (dorsal, lateral, and ventral ganglion) show larger differences in ordering than other regions, standard deviation of 55 versus 35 positions, respectively. Cell bodies in the neck are tightly packed in a ring around the pharynx whereas neurons in the body and tail of the worm are arranged in a linear fashion [12]. Therefore, our one-dimensional analysis demonstrates a more accurate description of neuronal arrangement in the body and tail.

The location of neurons relative to the worm also agrees well compared to actual positions in the worm (Figure 3). On average, the optimal neuronal location from wire cost minimization deviates 10.2% from their actual coordinates in the worm.

Using neuron coordinates in the optimal layout, we also analyzed the computational results from the cost perspective. In Figure 4, the wiring cost of each neuron is calculated using theoretical and actual positions in the worm. Two classes of neurons, AVA and PVC, show the largest wiring cost difference. Functionally, these neurons are the key interneurons responsible for backward and forward locomotion in the worm, respectively [3]. Instead of positioning at a location that minimizes total wire length, the cell bodies of these neurons are preferentially located closer to their post-synaptic terminals (Figure 4). This unexpected

deviation suggests that there are additional functional constraints on their placement. Such constraints, when understood, should be included in the formulation of the wiring minimization problem.

Conclusion

We found the optimal layout of *C. elegans* neurons that minimizes the quadratic cost function. This optimal layout agrees well with actual neuron locations on three levels 1. Neurons in the same ganglion cluster together. 2. The relative ordering of neurons follows actual anterior to posterior order, especially from the mid-body to tail of the worm. 3. The predicted neuron coordinates agree well with actual positions. Our work also highlighted neurons whose function cannot be described simply by the wiring diagram, and needs to be explored further.

Acknowledgements

The work was supported by The Watson School of Biological Sciences (BLC) and The Swartz Foundation (DBC).

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Figure Captions

Fig. 1: Top: Schematics of ganglia arrangement in *C. elegans*. Middle: Actual placement of neuronal cell bodies in each ganglion in one dimension. Plots are offset vertically to aid the eye. Bottom: Neuronal layout as predicted by minimization of wiring cost. (A: anterior; P: posterior)

Fig. 2: Differences in predicted versus actual neuron order plotted against actual order (0=head; 300=tail). Black line indicates position where predicted and actual neuronal ordering is equal. Dashed lines denote first standard deviation. Colored circles represent cell bodies in the same ganglion as specified in Figure 1.

Fig. 3: Predicted versus actual position plotted against normalized actual position (0=head; 1=tail). Diagonal line represents position where predicted equals actual. Colored circles represent cell bodies in the same ganglion as specified in Figure 1.

Fig. 4: Cost difference (in dimensionless cost units) between actual and predicted layouts plotted against actual positions. AVA and PVC are exclusively postsynaptic in the front and back of the worm, respectively. Dashed lines: neuron location in the predicted layout. Colored circles represent cell bodies in the same ganglion as specified in Figure 1.

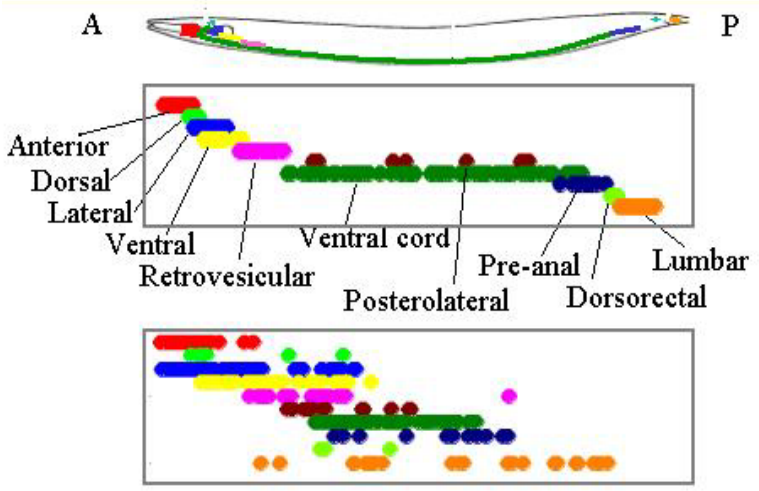
A
P
Anterior
Dorsal
Lateral
Ventral
Retrovesicular
Ventral cord
Posterolateral
Pre-anal
Dorsorectal
Lumbar

Figure 1

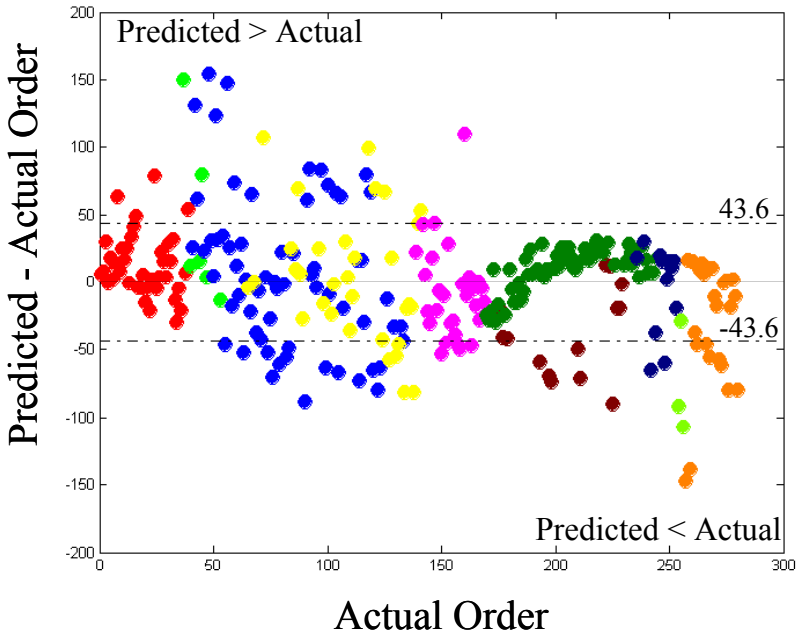
Predicted > Actual
Predicted < Actual
43.6
-43.6
Predicted - Actual Order
Actual Order
200
150
100
50
0
-50
-100
-150
-200
0
50
100
150
200
250
300

Figure 2

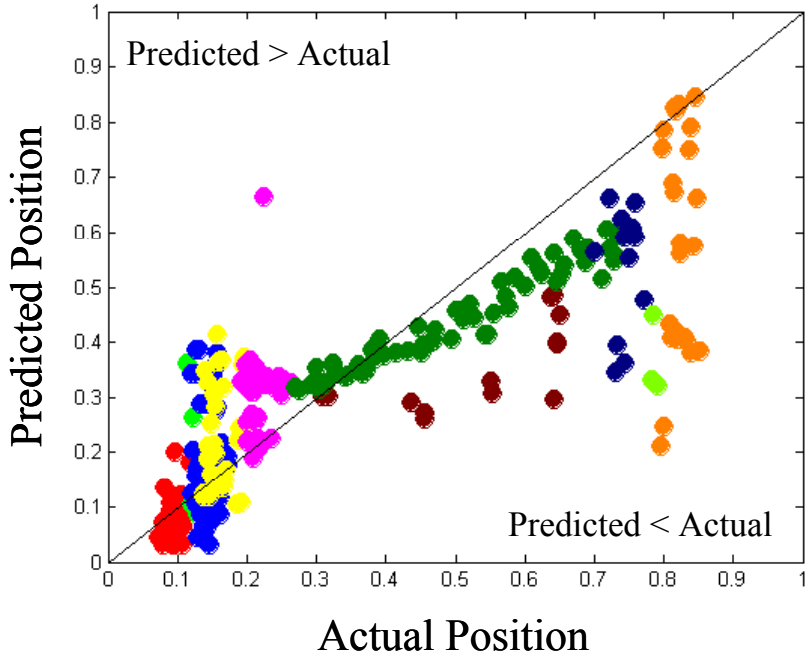
Predicted > Actual
Predicted < Actual
Predicted Position
Actual Position
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1

Figure 3

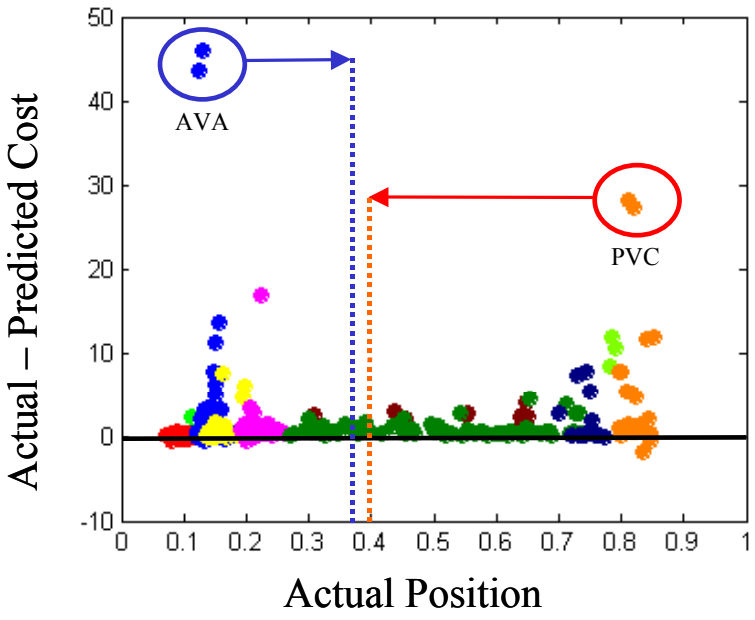
Actual – Predicted Cost
Actual Position
AVA
PVC
50
40
30
20
10
0
-10
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1

Figure 4