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Wiring optimization can relate neuronal structure and function

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We pursue the hypothesis that neuronal placement in animals minimizes wiring costs for given functional constraints, as specified by synaptic connectivity. Using a newly compiled version of the Caenorhabditis elegans wiring diagram, we solve for the optimal layout of 279 nonnpyral neurons. In the optimal layout, most neurons are located close to their actual positions, suggesting that wiring minimization is an important factor. Yet some neurons exhibit strong deviations from “optimal” position. We propose that biological factors relating to axonal guidance and command neuron functions contribute to these deviations. We capture these factors by proposing a modified wiring cost function.

Caenorhabditis elegans | optimal placement

Because brain structure is intimately related to its function, understanding structure should provide important clues to brain function. Traditionally, structural features of the brain are explained from the perspective of development, a complex process including such events as cell migration (1, 2), axonal guidance (3–5), cellular signaling (6), and synaptogenesis (7–10). Although much progress has been made in understanding the mechanisms of neural development, many unanswered questions remain. In particular, it is not known what determines the placement of neurons and synapses in the body, a question to be addressed in this paper.

Our approach for understanding neuronal structures complements neural development and relies on the existence of general principles governing the architecture of a mature brain. Specifically, we exploit the wiring economy principle proposed by Ramón y Cajal more than 100 years ago (11). This principle postulates that, for a given wiring diagram, neurons are arranged in an animal to minimize the wiring cost. The evolutionary “cost” can be attributed to factors such as wire volume (12–14) and signal delay and attenuation (15–17), as well as metabolic expenditures associated with signal propagation and maintenance (18, 19). Although the exact origin of the wiring cost is not known, the farther apart two neurons are, the more costly is the connection between them. The wiring cost can therefore be expressed as a function of distance between neurons and consequently minimized (12, 20–25).

Despite many successful applications of the wiring minimization principle (refs. 12–14 and 20–27, but see ref. 28), it has never been tested on the level of individual neurons for an entire nervous system. Such testing was precluded by the lack of wiring diagrams and by the computational complexity of the optimization problem. Previous works have shown that wire length minimization can explain the layout of small systems by tabulating the amount of wire required for every possible permutation of components in the network. The actual ordering of ganglia in Caenorhabditis elegans (20) and the arrangement of areas in the prefrontal cortex in the macaque (27) were found in this manner to have the shortest total wiring. Unfortunately, this brute force method is impractical for all but the smallest networks (number of components of order 10), because the number of permutations increases exponentially with the number of components. In addition, the results provide only the relative ordering of components and not their exact positions in an actual animal.

In this paper, we solve for the neuronal layout of an entire nervous system of the nematode C. elegans using the updated wiring diagram and powerful placement algorithms borrowed from computer engineering (29–33). We consider 279 neurons (pharyngeal and unconnected neurons excluded) of the hermaphrodite worm, whose identity, locations of cell bodies, sensory endings, and neuromuscular junctions, as well as the wiring diagram, have been well studied and found to be largely reproducible from animal to animal (34, 35). The length of the worm is >10 times greater than its diameter, allowing us to reduce the problem into one dimension.

By minimizing the cost of connecting the nervous system, our solution predicts the position of most neurons along the anterior–posterior (AP) body axis of the nematode worm. This result suggests that wiring minimization is a good general description of the relationship between connectivity and neuron placement. A comparison of the cost-minimized layout with actual neuron positions revealed groups of outlier neurons with distinct structural characteristics. Interestingly, neurons within each group have been shown in experiments to play similar roles in the worm nervous system: developmental pioneering and signal integration for motor control. We suggest that the results obtained from cost minimization can be used in a number of ways to infer neuron function.

Wiring Cost Minimization in the Dedicated-Wire Model

We start by modeling the nervous system (see Fig. 1B Inset for example) as a network of nodes that correspond to neuronal cell bodies, connected by wires that represent synapses (Fig. 1C Inset). We call such model “dedicated wire,” because each synapse has its own wire (similar to point-to-point axon design in ref. 14). Additional wires connect neurons to sensory endings and muscles. Assuming that the placement of these structures is subject to constraints independent of neuronal organization, their positions are fixed.

The total wiring cost, $C^\text{tot}$, can be expressed as the sum of an internal cost to connect neurons to each other ($C^\text{int}$) and an external cost to attach neurons to the fixed structures ($C^\text{ext}$):

$$C^\text{tot} = C^\text{int} + C^\text{ext}. \quad [1]$$

We assume that the cost of wiring the $i$th and $j$th neurons is proportional to some power, $\xi$, of the distance between them. Then the total internal wiring cost is:

$$C^\text{int} = \frac{1}{2\alpha} \sum_i \sum_j A_{ij} |x_i - x_j|^\xi, \quad [2]$$

where $x_i$ is the neuron position, and $\alpha$ is an unknown coefficient. $A_{ij}$ is an element of the adjacency matrix $A$, representing the total number of synapses between neurons $i$ and $j$ in both directions. Because the wiring cost is assumed to be independent of the directionality of synapse (i.e., signal propagation from neuron $i$ to...
yet, in the actual worm, the majority of neurons are nonbranching and bipolar, making an average of 58.6 \emph{en passant} synapses and neuromuscular junctions with only two neurites (or two wires). this morphology can be taken into account by normalizing each neuron-to-neuron and neuron-to-muscle connection by the average number of synapses per neurite (α = 29.3 or 58.6 synapses per neuron divided between two neurites). sensory neurons, on the other hand, typically send one specialized neurite to the sensory organ (34), which, with a few exceptions, does not make synapses with other neurons or muscles. thus each sensory fixed point, by construction, connects to a neuron through a dedicated wire and needs not be normalized. an alternative way to incorporate this neuronal morphology is by using a “shared-wire” model (Fig. 1E Inset), which will be introduced later.

We find the optimal neuronal placement that minimizes the wiring cost function defined by Eqs. 1–3. Initially, we assume that the cost of connecting two neurons increases as the square of the distance between them (ξ = 2 in Eqs. 2 and 3). the quadratic cost function can be minimized analytically and the position of neuronal cell bodies is given by (26, 29, 30):

\[
x = Q^{-1} \left[ Sx + \frac{1}{\alpha} Mm \right]
\]

\[
Q_{ij} = \delta_{ij} \left( \frac{1}{\alpha} \sum_{p} A_{ip} + \sum_{k} S_{ik} + \frac{1}{\alpha} \sum_{i} M_{ij} \right) - \frac{1}{\alpha} A_{ij}.
\]

Minimization of the quadratic cost function is mathematically identical to finding the equilibrium placement of objects connected with elastic rubber bands (minimum elastic energy of rubber bands with zero length at rest).

Comparison of the Minimum-Wiring Placement with Actual Layout

Using the complete connectivity diagram of the C. elegans nervous system, we calculate neuron positions that minimize the quadratic cost function (ξ = 2 in Eqs. 2 and 3, 1 < ξ < 4 to be considered later). Data sets are available at http://www.wormatlas.org/handbook/nshandbook.htm#swiring.htm. Fig. 1C shows optimal neuronal layout in the one-dimensional worm, where neurons from the same ganglion are represented by the same color, offset vertically for clarity.

We compare this result to actual locations of neuronal cell bodies projected into one dimension along the anterior–posterior axis of the worm (Fig. 1B). Neurons belonging to the same ganglia are clustered (positioned near each other) in the actual layout. Wiring-cost minimization predicts somewhat more dispersed clusters of neurons located in the anterior two-thirds of the worm and no clustering for neurons in the tail ganglia (see Ganglia Distribution in Supporting Text and Fig. 5, which are published as supporting information on the PNAS web site). Later we will discuss possible causes for such discrepancies. Because a large number of the sensory organs are located in the tip of the head (34), aggregation of neurons in the anterior region of the animal is consistent with minimization of cost required to connect these sensors (20). The predicted anterior–posterior order of the first five ganglia, as defined by the median of neuron positions, agrees with the actual order. The actual ganglia ordering was previously obtained by Cherniak via brute force enumeration of all possible permutations (20). However, as mentioned previously, the method used to obtain Cherniak’s result cannot be applied at the level of individual neurons.

Next, we plot predicted positions of individual neurons as a function of actual positions in the worm (Fig. 2). Neuron locations in the animals are scaled between 0 and 1, where 0 is the head and 1 is the tail. The majority of neurons in the network lie along the diagonal of the plot, where predicted position equals actual posi-
The actual system is not fully optimized. 

**Robustness of Optimization Results to Small Variations of Parameters**

To determine the robustness of the wire-minimized solution, we explored several aspects of the cost function and assessed their impact on the ability to predict neuronal layout.

First, we analyze the sensitivity of the wire-minimized layout to the normalization coefficient $\alpha$ and the exponent $\zeta$. As mentioned, our cost formulation accounts for multiple synapses on a given neurite by normalizing connection weights by the average number of synapses per neurite ($\alpha = 29.3$). We test how the predicted layout changes by varying $\alpha$ between 1 and 45. Because the choice of the quadratic form of the cost function may seem arbitrary, we also varied the power of wire length in the cost function, $\zeta$ in Eqs. 2 and 3 between values of 1 and 4. As argued previously, the wiring cost is likely to scale supralinearly ($\zeta > 1$) with distance between neurons (26). If so, the minimization problem is convex and can be efficiently solved numerically. The lowest mean deviation, 9.71%, is achieved by using the cost function with normalization coefficient $\alpha = 27$ and exponent $\zeta = 2$ (see General Power-Law Cost Function in Supporting Text and Fig. 6, which are published as supporting information on the PNAS web site). Interestingly, these values are close to those chosen from biological considerations and validate the quadratic cost function.

Second, we test the importance of synaptic multiplicity between neurons. Instead of a wire dedicated to each synapse between cells (Fig. 1C Inset), we use a single wire to connect a given pair of neurons regardless of the number of synapses (Fig. 1D Inset). In other words, we minimize the quadratic cost function with a binary connection matrix (only 0 or 1 elements in the matrix $A$ from Eq. 2). Using $\zeta = 2$, the lowest mean deviation between predicted and actual position (9.82%) is higher than the result from a synapse-number weighted cost function and was found at $\alpha = 8$. In the actual worm, the average number of synaptic partners (as opposed to individual synapses) per neurite is 12.2, close to the optimal value of $\alpha$ obtained from the binary connection matrix.

To summarize, we find that various reasonable cost functions predict neuronal placement incomparably better than the random one. Although mean deviations vary somewhat between different cost functions, they are not far from the best known solution. Thus the wire length minimization approach is rather robust. Because the quadratic cost function can be solved exactly and is reasonably close to the best-known solution, it may serve as the reference predicted layout. Although the predicted placement is only approximately correct, we recall that the problem was solved in one dimension. Such dimensionality reduction may introduce errors on the order of the inverse aspect ratio of the worm, just under 10%. Because the mean deviations we report approach this range, wiring optimization results are encouraging.

**What Causes Discrepancies Between Predicted and Actual Neuronal Layouts?**

Several reasons may account for the deviation between positions predicted by wiring-cost-minimized and actual neuron positions. (i) The actual system is not fully optimized. (ii) The wiring diagram is still somewhat incomplete. (iii) The wiring cost function does not fully represent costs associated with neuronal placement, or constraints other than connectivity need to be taken into consideration. Although reason (i) remains a possibility, its exploration lies beyond the framework of the optimization approach (38). Reason (ii) can be
addressed by future reconstructions. Here, we explore the merit of
Fig. 3.

Directionality of Synapses Along the Neuron May Bias the
Location of Cell Bodies
Because analysis of synapse position relative to the cell body does not account for all outliers, such as AVA and PVC where synapses
developmental pioneers of the ventral cord currently known in C.
 elegans: AVG, PVPL/R, and PVQL/R. By comparing the positional
tensions of known pioneers with the deviations of the rest of the
neurons in the system, we find that all pioneers are outliers in the
wire-minimized layout (significant for pioneers as a group, $P = 0.002$ from Student’s $t$ test). The most prominent anterior
outlier, AVG, is in the head (39). During development, the
neuron sends the first posterior-directed projection into what
eventually becomes the right ventral cord, pioneering a path for
other anterior neurons to follow (Fig. 2). Along the way, AVG
makes synapses with neurons in the midbody and the tail. Neurons
PVP and PQV, the biggest outliers in the tail, behave similarly but
in the reverse direction: they are born in the tail and send pioneering
processes forward. Ablation of these pioneer neurons results in
disorganization of ventral cord fascicles, although a nerve cord is
still formed (39). All of these pioneer neurons are characterized by
long processes that span the entire length of the worm with the
majority of synapses situated outside of the soma region.

Another key player in neural development, PVT, also has
synapses mostly on the opposite end of the worm from the soma.
The previously published wiring of PVT (34) was later amended (O.
Hobert and D.H.H., unpublished work). Interestingly, only after
these changes are incorporated does PVT emerge from this outlier
analysis. Functionally, PVT acts as a guidepost cell for neurons
located in the posterior region of the worm to grow forward (40, 41)
and maintains the organization of ventral cord fascicles (42).
Without PVT, axons in the lumbar ganglia fail to enter the ventral
cord in a single bundle, and axons already in the ventral cord cross
the ventral midline in an aberrant manner.

The remaining neurons with asymmetry factor $>75\%$, DVC and
PVR, are also outliers in the wire-minimized solution and, based on
their structural characteristics, we propose that DVC and PVR may
also play pioneering or developmental roles. PVR, an interneuron
located in the lumbar ganglion, is a putative tail sensory neuron,
with some animals displaying microtubule bundles in the posterior
process (34, 35). The pioneering role of DVC has been previously
postulated by Durbin (39) by using independent data. However, this
hypothesis was not fully verified by experiments (39).

Directionality of Synapses Along the Neuron May Bias the
Location of Cell Bodies
Because analysis of synapse position relative to the cell body does not account for all outliers, such as AVA and PVC where synapses
are evenly distributed, we hypothesize that the directionality of synapses might be important. We found an asymmetry in the spatial distribution of pre- and postsynaptic terminals for AVA and PVC (Fig. 4). Specifically, the region containing cell bodies of these neurons contains more inputs or postsynaptic terminals. This unexpected result suggests that the distance between cell bodies and pre- vs. postsynaptic terminals invokes different connection costs. Because the dedicated-wire model does not distinguish between the location of individual synapses or the type of synaptic terminals, the failure of our cost minimization to predict the actual position of these neurons is not surprising.

By examining the type of synapses near the soma of neurons with long projections and >25% of head/tail synapses near the cell body (101 neurons), we find a small group of 12 neurons with predominately postsynaptic terminals (>75%) near the cell body (above the red line in Fig. 3C). With the exception of AVEL/R, all of these neurons are either outliers (AVAL/R, DVA, and PVC) or very close to being outliers (AVBL/R, AVDL/R, and AVL). Within this group, AVEL/R are the only neurons that do not have neurites spanning the entire length of the worm; their cell bodies are in the head, and neurites project halfway down the worm, terminating anterior to the vulva. The shorter span might be the reason why AVEL/R do not emerge as outliers.

The directionality of synapses (input or output) near the cell body is a structural property capable of identifying neurons important for integrative signaling in motor control. The collection of neurons with mostly inputs near the soma includes all, except PVC, of the command interneurons (nine neurons) functionally identified as responsible for worm locomotion (43, 44). Wild-type worms, when touched on the head, respond by moving backwards. Without AVA, AVD, and AVE, worms no longer exhibit this behavior. AVB and PVC are responsible for the exact opposite response: they mediate forward movement when worms are stimulated at the tail.

Although neurons in C. elegans appear isopotential and do not generate classical Na$^+$ action potentials (45), command neurons may have special requirements to reach an activation threshold near the cell body before a command signal can be passed along the process to distant targets. Physiological study will be necessary to understand the underlying mechanism for the position of pre- vs. postsynaptic terminals relative to the cell body.

The analysis of asymmetry in directionality of synapses revealed noncommand neurons that appear to mediate motor functions. DVA, presynaptic to command interneurons and forward locomotion motor neurons, is involved in mechanosensory responses (46). When subject to a diffused mechanical stimulus, such as a disturbance (e.g., tap) of the substrate on which the worm is resting, the worm responds by moving either forward or backward. Without DVA, the acceleration of such movement is diminished. AVL, acting in conjunction with neuron DVB, is critical for activating muscle contraction for defecation (47). RID has unknown function although both AVL and RID make neuromuscular connections to body muscles.

### Wiring Optimization Using the Shared-Wire Model

To incorporate the importance of synapse location and directionality into theory, we propose an anatomically more accurate shared-wire model (Fig. 1E Inset). In this model, each neuron is represented by a wire with multiple synapses. If a pair of neurons is synaptically connected, the corresponding wires must overlap. Similarly, if a neuron makes an external connection, the corresponding wire must include the location of that fixed point. Given these constraints, minimization of total wiring length (31, 33) yields the optimal placement of each synapse as well as the front and back ends of each neuron.

Because the actual locations of most synapses in the worm are not currently known, comparison with data requires predicting cell body positions. One possibility is to assign the cell body position to the center of mass of synaptic locations for each neuron. If connections are treated equally (analogous to the binary dedicated-wire model), the mean deviation of the predicted cell body location is 10.6% from actual. If connections are weighted by their multiplicity (number of synapses per connection analogous to the weighted dedicated-wire model), the mean deviation is 10.7%. In either case, the accuracy of the shared-wire model is no better than the dedicated-wire model.

However, the shared-wire model allows us to apply the results from outlier analysis by adopting different rules for the placement of cell bodies in neurons with specialized functions. First, we incorporate the observation that cell bodies of command interneurons gravitate toward postsynaptic terminals. For these neurons, the cell body is placed at the end of the neuron closest to the center of mass of postsynaptic terminals. Second, we incorporate the observation that cell bodies of neurons important in developmental pioneering are located on the opposite end of the neuron from the majority of synapses. For these neurons, we consider only the synapse-containing region (excluding connections to external structures). The cell body is placed at the end of this region most distant from the synaptic center of mass. Applying these rules for specialized neurons to the distribution of synapses obtained in the shared-wire model, we obtain a placement (Fig. 1E, Shared-Wire Model in Supporting Text and Fig. 7, which are published as supporting information on the PNAS web site) with mean deviation of 9.41%, better than predictions from the quadratic dedicated-wire model.

Wiring optimization using the shared-wire model makes an interesting prediction where a large fraction of all synapses congregates in a single anterior location along the worm (Fig. 7 Lower). It is natural to associate this location with the nerve ring. Of course, because our model is 1D, the actual 3D structure of the nerve ring could not emerge. Yet, this congregation of synapses is an unexpected demonstration of the predictive power of wiring optimization.

### Discussion

Here we show that wiring minimization can establish a relationship between neuronal structure and function. We found that, for given connectivity, wiring optimization predicts the layout of many neurons in the animal despite some uncertainty about the exact form of the wiring cost. Thus, wiring optimization is a constructive approach for relating wiring diagram and neuron placement. Detailed comparison of the wiring optimization prediction and actual layout reveals neurons with special structural properties that have
specialized function. Therefore, wiring optimization may also be used for predicting neuronal function.

Although wiring optimization establishes a structure–function relationship, there could be other factors affecting neuronal placement. In particular, the positions of certain neurons, such as the tail ganglia, may be influenced by non-neuronal factors, such as mechanical forces or chemical signals. For example, the tail ganglia in C. elegans are positioned such that they are far from the head, which may be due to mechanical constraints or chemical gradients.

In conclusion, we show that neuronal layout can be largely predicted by minimizing the wiring cost for given synaptic connectivity. The discrepancy between optimized and actual placement is mainly due to neurons with stereotypical roles in the nervous system. Although wiring optimization may not be the only factor in neuronal placement, it is the only one that has been quantified and has predictive power to relate neuronal structure and function.

Note added in proof. After completion of this work, we became aware of two related studies (57, 58).

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