
Exact solution for the optimal neuronal layout problem

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Abstract

A key factor in the evolution of brain architecture is the minimization of the wiring cost. This can be used to predict neuronal placement by solving the optimal layout problem, i.e. finding the neuronal placement that minimizes wiring cost for a given connectivity. However, this problem is difficult to solve because the number of possible layouts is often astronomically large. I argue that the wiring cost may scale as wire length squared, reducing the optimal layout problem to a constrained minimization of a quadratic form. For biologically plausible constraints this problem has exact analytical solutions, which give satisfactory approximations to actual layouts in the brain. These solutions make the inverse problem of inferring neuronal connectivity from neuronal layout more tractable.

1 Introduction

Wiring up distant neurons in the brain is costly to an organism [1]. The cost of wiring arises from its volume [2, 3], metabolic requirements [4], signal delay and attenuation [5, 6], or possible guidance defects in development [7]. Whatever the origin of the wiring cost, it must grow with the distance between connected neurons. Therefore, placing connected neurons as close as possible reduces wiring cost and confers selection advantage to an organism. In principle, this evolutionary argument allows one to predict the neuronal placement from the connectivity data by solving an optimal layout problem. In practice, solving this problem for many neurons with non-stereotypical connectivity is difficult because the number of possible neuronal permutations grows exponentially in the number of neurons.

In this paper I argue that the wiring cost may scale approximately as the wire length squared (Section 2). In this approximation, the optimal layout problem reduces to the minimization of a quadratic form (Section 3). The trivial solution is ruled out by biological constraints that can be classified into external and internal. For both classes of constraints, the optimal layout can be found in analytical form (Sections 4,5). To test the quadratic placement optimization I compare its predictions in two cases where both full connectivity and layout are known: prefrontal cortical areas in macaque (Section 6) and *C. elegans* ganglia (Section 7). The solution of the

quadratic optimal layout problem gives a satisfactory approximation to the actual placement of these multi-neuron complexes.

2 Wiring cost may scale as wire length squared

Because the exact origin of the wiring cost is not known, one can only guess its dependence on the distance between neurons. In this section, I consider several plausible hypotheses for the wiring cost function and argue that the wire length squared may serve as a reasonable approximation.

Previous work suggests that the cost function is proportional to the wiring volume [2, 3, 8, 9], which scales with the distance times wire diameter squared. If the wire diameter is fixed then the cost grows linearly with the distance. But if the cost is proportional to volume, why not make all the axons infinitesimally thin? My collaborators and I have argued that the observed axon diameter may result from the trade off between the wire volume cost, which grows with wire diameter, and signal propagation delay cost, which decreases with wire diameter because of increase in conduction speed [8, 10]. Such trade off is captured by the wiring cost function, \mathfrak{C} , that contains two terms, one proportional to the signal propagation delay, T , to power n , the other proportional to the wire volume, V :

$$\mathfrak{C} = \alpha T^n + \beta V, \quad (1)$$

where α and β are unknown constants. If the wires are myelinated axons, then the signal propagation speed, s , scales linearly with the wire diameter, d , $s = kd$, leading to the following expression for the cost function:

$$\mathfrak{C} = \alpha \left(\frac{L}{kd} \right)^n + \beta \frac{\pi}{4} d^2 L, \quad (2)$$

where L is the wire length. The cost function is minimized by the wire diameter that solves the equation $\partial \mathfrak{C} / \partial d = 0$. By substituting this optimal wire diameter into the cost function (2) I get the following dependence of the cost on the wire length, L :

$$\mathfrak{C} = \left(1 + \frac{n}{2} \right) \left(\frac{\pi \alpha^{2/n} \beta}{2nk^2} \right)^{n/n+2} \frac{3n}{L^{n+2}}. \quad (3)$$

If the exponent, $n=1$, then again the wiring cost scales linearly with the wire length. It is possible, however, that the signal propagation delay is a hard constraint ($n = \infty$). Then the wiring cost scales as the length cubed. Halfway between the linear and the cubic functions lives the quadratic wire length cost function:

$$\mathfrak{C} = \frac{3}{4} \left(\frac{\pi^2 \alpha \beta^2}{k^4} \right)^{1/3} L^2. \quad (4)$$

Even if it turns out that the wiring cost does not scale exactly as wire length squared, the quadratic approximation is useful because the layout problem can be solved exactly as demonstrated below. Thus the quadratic layout optimization may serve as “the harmonic oscillator” of optimal layout problems.

3 Optimal layout problem must include constraints

In order to formulate the quadratic optimal layout problem, I represent a neuronal circuit as a non-directed weighted graph. Nodes of the graph correspond to neurons (or multi-neuron complexes), and edges correspond to connections between neurons (or between multi-neuron complexes). The weight of each edge represents the connection strength and is given by the (constant) coefficient in front of the wire length squared (4) times the multiplicity of the connection. In turn, the multiplicity of the connection is given by the number of parallel wires between the given pair of neuronal complexes or, perhaps, by the number of synapses between the given pair of neurons.

The graph is characterized by its adjacency matrix (or the wiring diagram), A , where weights A_{ij} give (non-directional) connection strengths between neurons i and j . This matrix is symmetric ($A_{ij} = A_{ji}$), non-negative ($A_{ij} \geq 0$), with all diagonal elements equal to zero ($A_{ii} = 0$). With the help of the adjacency matrix, the quadratic wire length cost function for the neuronal circuit can be written as:

$$\mathfrak{C} = \frac{1}{2} \sum_{i,j} A_{ij} (r_i - r_j)^2, \quad (5)$$

where r_i, r_j are coordinates of the nodes i and j . The quadratic optimal layout problem is to find the coordinates, which minimize the cost function for given constraints. The constraints exclude the trivial solution, $r_i = 0$, and may be classified by their biological origin into external and internal. External constraints arise from the fact that the brain is not an isolated network of neurons, but is connected with the sensory and motor organs, the placement of which is determined by the functional requirements (Section 4). Internal constraints arise from the volume exclusion by neuron bodies and axons, meaning that no two neurons or axons can occupy the same point in space (Section 5).

The quadratic wire length cost function (5) has a simple physical interpretation. If neurons are connected by stretched rubber bands of zero length at rest, then (5) represents their elastic energy. The weights A_{ij} in (5) represent “elasticity” of connections. Then the minimal energy state is achieved when all neurons are in one location and all rubber bands have zero length. This trivial solution is ruled out by the constraints.

4 Exact solution under external constraints

Because brain’s function requires its communication with sensory and motor organs, there are wires between the brain and those organs. The cost of these wires must be included in the overall cost function:

$$\mathfrak{C} = \frac{1}{2} \sum_{i,j} A_{ij} (r_i - r_j)^2 + \sum_{i,j} B_{ij} (r_i - f_j)^2, \quad (6)$$

where the first term represents the cost of wiring between neurons in the brain and the second term represents the cost of wiring between the brain and sensory and motor organs. B_{ij} represents connection strength between neuron i and organ j , and f_j is the coordinate of organ j . As various functional requirements determine organ placement in the body plan (e.g. frontal eyes, forward nose, muscles attached to bones), it is reasonable to formulate the optimal neuronal layout problem with the organ coordinates fixed. To

solve the optimal layout problem I search for the minimum of the wiring cost function (6), while varying the locations of the brain neurons, r_i . A natural way to do this is by first rewriting the two terms of the cost function in a matrix form.

$$\begin{aligned} \frac{1}{2} \sum_{i,j} A_{ij} (r_i - r_j)^2 &= \frac{1}{2} \sum_{i,j} A_{ij} (r_i^2 - 2r_i r_j + r_j^2) = \\ &= \sum_i r_i^2 \sum_j A_{ij} - \sum_{i,j} r_i A_{ij} r_j = r^T (D - A) r = r^T L r, \end{aligned} \quad (7)$$

where matrix $D_{ij} = \delta_{ij} \sum_k A_{ik}$, and L is called the Laplacian of matrix A .

$$\begin{aligned} \sum_{i,j} B_{ij} (r_i - f_j)^2 &= \sum_{ij} B_{ij} (r_i^2 - 2r_i f_j + f_j^2) = \\ &= \sum_i r_i^2 \sum_j B_{ij} - 2 \sum_{ij} r_i B_{ij} f_j + \sum_j f_j^2 \sum_i B_{ij} = r^T D_B r - 2r^T B f + const, \end{aligned} \quad (8)$$

where matrix $D_{Bij} = \delta_{ij} \sum_k B_{ik}$. The minimum of the quadratic wire length cost function (6) can be found by taking a derivative in respect to r_i and setting it to zero:

$$\frac{d\mathcal{C}}{dr} = 2(L + D_B)r - 2Bf = 0 \quad (9)$$

Then the optimal layout is given by the following matrix equation:

$$r = (L + D_B)^{-1} Bf \quad (10)$$

This solution for the layout problem can be easily generalized to d spatial dimensions. Because the cost function (6) is separable into d terms each containing distances along different dimensions, Eq.(10) gives the projection of the layout vector onto the corresponding spatial dimension.

5 Spectral analysis emulates internal constraints

Finite size of neuronal bodies and axons places constraints on the possible layouts because of volume exclusion. Inclusion of these constraints is, in general, a difficult problem. Here I present an approximate treatment of the internal constraints, which yields an esthetically appealing exact solution [11]. In order to avoid the trivial solution, the norm of vector r is fixed, yielding the following optimization problem (see Eq.(7) for derivation):

$$\text{minimize } \mathcal{C} = \frac{1}{2} \sum_{i,j} A_{ij} (r_i - r_j)^2 = r^T L r, \text{ subject to } r^T r = 1 \quad (11)$$

The solution to this minimization problem is the eigenvector of L corresponding to the lowest eigenvalue. However, the lowest eigenvalue is 0 and the corresponding eigenvector is $\bar{1}/N^{1/2}$, which means that all nodes are at the same point. Therefore, I require the minimization problem solutions to be orthogonal to that eigenvector:

$$r^T \vec{1} = 0 \text{ or } \sum_i r_i = 0 \quad (12)$$

Then the solution to the one-dimensional optimal layout problem is given by the eigenvector of the Laplacian, v_2 , corresponding to the second lowest eigenvalue, λ_2 . If the problem is d -dimensional, then the solution is given by the d eigenvectors, corresponding to the 2nd to $d+1$ st lowest eigenvalues [11].

This formulation also admits a physical analogy. In addition to the elastic force exerted by rubber bands there is a repulsive force proportional to the distance from the origin. The solution is subject to the constraint (12) that places the center of mass at the origin.

The Laplacian spectrum and corresponding eigenvectors may approximate the solution obtained with external constraints if the number of external connections per neuron is less than internal. This relationship between the two formulations can be formalized by rewriting the scalar product between the i th eigenvector, v_i , and the external constraint solution, r :

$$v_i r = \frac{v_i B f}{\lambda_i + \beta_i} \quad (13)$$

where β_i are coefficients of the spectral decomposition of D_B in the projection basis.

6 Application to macaque cortical areas

Cerebral cortex consists of multiple areas whose spatial arrangement and inter-connectivity are reproducible from animal to animal. Previous work suggests that the arrangement of cortical areas is determined by minimizing the total length of the inter-connections between them [3, 12]. Recently, this suggestion has been put to a direct test in the macaque prefrontal cortex [13], where most of the inter-connections and the layout of areas are known [14]. Comparison of the wiring length in the actual layout with each alternative layout reveals that the total wiring length is minimized [13].

Here I test the quadratic wire length approach on the dataset used in [13] by using both external and internal constraints formulation.

In the external constraints formulation, the thirteen areas on the periphery of the prefrontal cortex are treated as fixed organs [13], their locations being actual ones (crosses in Figure 1A). Locations of the remaining eleven areas are continuously varied to minimize the sum of connection lengths squared. Eq. (10) yields the placement shown in Figure 1A with bold text. Although the predicted locations are closer together than in reality, the predicted ordering is close to the actual one. The only exception to the correct ordering is the placement of 14r and 11m, which should be lower. Interestingly this placement corresponds to the close-to-optimal placements reported in [13]. There are two possible explanations for why the areas are predicted to bunch up more than they do in reality. First, we don't take into account volume exclusion, i.e. the fact that the areas have finite size and cannot overlap. Second, there must be connections between the areas that were considered in [14] and the areas that were not considered. In particular, area 32 has a nearest neighbor that was not included into the wiring diagram, and could pull it away from the cluster, thus making the predicted placement closer to the actual.

The internal constraints formulation for the eleven movable areas yields the arrangement shown in Figure 1B. This placement gives the correct ordering of the areas with the

internal constraints formulation in this example because they are unlikely to play a significant role in the placement of ganglia due to the relative sparseness of the *C. elegans* nervous system.

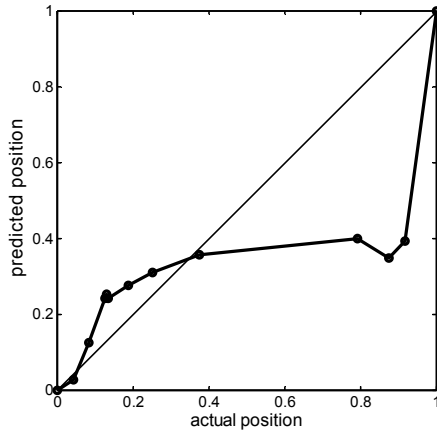


Figure 2. Solid dots (connected in the anterior-posterior order) show predicted vs. actual positions of *C. elegans* ganglia normalized by the distance from head to tail. Deviations from the diagonal line correspond to differences in the actual vs. predicted ganglia positions. Although predicted ganglia positions differ from actual ones, their order is predicted correctly with the exception of the dorsorectal ganglion (actual position: 0.88 of body length).

8 Discussion

In this paper, I argue that the wire length squared may approximate the wiring cost, thus reducing the optimal layout problem to the constrained minimization of a quadratic form. For two types of constraints, external and internal, exact analytical solutions exist allowing straightforward and intuitive analysis. To test the quadratic optimization approach, I revisit two known cases of wire length minimization: prefrontal cortical areas in macaque and *C. elegans* ganglia, where previous solutions relied on brute force complete enumeration. Minimization of wire length squared approximates the actual layouts reasonably well. One problem with external constraint formulation is the bunching of graph nodes in the solution. This happens because the number of internal connections usually exceeds that of the external ones. The bunching does not happen in actual brains because of the “volume exclusion” of multi-neuron complexes, or internal constraints. The spectral method emulates these constraints and eliminates the bunching problem. However, exclusion of the external connections may lead to the overall rotation of the graph or incorrect positioning of some multi-neuron complexes.

Although quadratic cost function is an approximation, it yields optimal layouts reasonably close to those obtained by minimizing total wiring length in realistic situations. While complete enumeration is limited to a small number of movable components, quadratic layout problem yields exact solutions in analytical form for the wiring diagrams as big as computers can handle. These analytical solutions can be readily and intuitively investigated making the inverse problem, i.e. predicting connectivity from neuronal layout, more tractable. Since solving this problem may compliment the existing experimental methods for establishing neuronal connectivity, the quadratic cost function promises to be an important tool for understanding brain design and function.

Acknowledgments

I would like to thank Natarajan Kannan for bringing Hall’s work to my attention, Armen Stepanyants, Anatoli Grinshpan and the members of my group for helpful discussions, and Charles Stevens for making his paper available prior to publication. This work was supported by the Lita Annenberg Hazen Foundation and the David and Lucile Packard Foundation.

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