Exact Solution for the Optimal Neuronal Layout Problem

Dmitri B. Chklovskii
mitya@cshl.edu
Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724, U.S.A.

Evolution perfected brain design by maximizing its functionality while minimizing costs associated with building and maintaining it. Assumption that brain functionality is specified by neuronal connectivity, implemented by costly biological wiring, leads to the following optimal design problem. For a given neuronal connectivity, find a spatial layout of neurons that minimizes the wiring cost. Unfortunately, this problem is difficult to solve because the number of possible layouts is often astronomically large. We 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 reasonable 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 (Ramón y Cajal, 1899/1999). The cost of wiring arises from its volume (Cherniak, 1992; Mitchison, 1991), metabolic requirements (Attwell & Laughlin, 2001), signal delay and attenuation (Rall et al., 1992; Rushton, 1951), or possible guidance defects in development (Dickson, 2002). 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 the wiring cost and, for a given connectivity, confers selection advantage to an organism. In principle, this evolutionary argument allows one to predict neuronal placement from connectivity data by solving an optimal layout problem. In practice, solving this problem for many neurons with nonstereotypical connectivity is complicated, and often impossible, due to the large number of possible neuronal permutations, which grows exponentially in the number of neurons.

In this letter, we argue that the wiring cost may scale approximately as the wire length squared (see section 2). In this approximation, the optimal layout problem reduces to the minimization of a quadratic form (see 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 (see sections 4 and 5). To test the quadratic placement optimization, we compare its predictions in two cases where both connectivity and layout are known: prefrontal cortical areas in macaque (see section 6) and *Caenorhabditis elegans* ganglia (see section 7). The solution of the quadratic optimal layout problem gives a reasonable approximation to the actual placement of these multineuron complexes. Thus, the quadratic wire length cost function promises to be a powerful tool for solving optimal neuronal layout problems.

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, we 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 of wiring is proportional to its volume (Cherniak, 1992; Chklovskii, Schikorski, & Stevens, 2002; Mitchison, 1991; Stepanyants, Hof, & Chklovskii, 2002), which scales with the distance times wire diameter squared. If the wire diameter is fixed, the wiring cost grows linearly with distance. But if the cost is proportional to volume, why not make all the axons infinitesimally thin? My collaborators and I have argued (Chklovskii et al., 2002; Chklovskii & Stepanyants, 2003) 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 an increase in conduction speed. This trade-off is captured by the wiring cost function, $\mathfrak{C}$, which contains two terms—one proportional to the signal propagation delay, T, to power n, and the other proportional to the wire volume, V:

$$\mathfrak{C} = \alpha T^n + \beta V, \tag{2.1}$$

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

$$\mathfrak{C} = \alpha \left(\frac{L}{kd} \right)^n + \beta \frac{\pi}{4} d^2 L, \tag{2.2}$$

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 2.2, I get the following dependence of the cost on the wire length, L:

$$\mathfrak{C} = \left(1 + \frac{n}{2} \right) \left(\frac{\pi \alpha^{2/n} \beta}{2nk^2} \right)^{n/(n+2)} L^{\frac{3n}{n+2}}. \tag{2.3}$$

If the exponent, $n = 1$, then 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. Intermediate values of the exponent give cost functions that lie between the linear and the cubic dependence on length. Therefore, it is reasonable to approximate the actual wire length cost function by a quadratic expression:

$$\mathfrak{C} = \frac{3}{4} \left(\frac{\pi^2 \alpha \beta^2}{k^4} \right)^{1/3} L^2. \tag{2.4}$$

It is possible that the actual cost function is noticeably different from the quadratic form (e.g., if the exponent, $n < 1$). Still, the quadratic cost function can be very useful due to the exact solvability of the quadratic layout problem, as demonstrated in sections 4 and 5. The validity of the quadratic cost function is established by the comparison of theoretical predictions with experimental data (see sections 6 and 7). Thus, the quadratic cost function may play a role in neuronal layout optimization similar to the harmonic oscillator in physics or the fruit fly in genetics.

3 Optimal Layout Problem Requires Constraints

In order to formulate the quadratic optimal layout problem, we represent a neuronal circuit as a nondirected weighted graph. Nodes of the graph correspond to neurons (or multineuron complexes), and edges correspond to connections between neurons (or between multineuron complexes). The weight of each edge represents the connection strength and is given by the (constant) coefficient in front of the wire length squared (see equation 2.4) 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 directionality of connections can be ignored because the cost of a wire does not depend on the direction of signal propagation.

The graph is specified algebraically by the adjacency matrix (or the wiring diagram), $\mathbf{A}$, where weights A_{ij} give (nondirectional) connection strengths between neurons i and j. This matrix is symmetric ($A_{ij} = A_{ji}$), nonnegative ($A_{ij} \geq 0$), 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

$$\mathfrak{C} = \frac{1}{2} \sum_{i,j} A_{ij} (r_i - r_j)^2, \tag{3.1}$$

where r_i, r_j are coordinates of the nodes i and j. The quadratic optimal layout problem is to find coordinates, which minimize the cost function for given constraints. 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 functional requirements unrelated to wiring (see 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 (see section 5).

The quadratic wire length cost function 3.1 has a simple physical analogy. If neurons are connected by stretched rubber bands of zero length at rest, then equation 3.1 represents their elastic energy. The weights A_{ij} in equation 3.1 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 external or internal constraints. Previously, the rubber band analogy inspired the elastic net algorithm (Durbin & Mitchison, 1990; Durbin & Willshaw, 1987; Goodhill & Willshaw, 1990), whose relationship to the wiring minimization is discussed in Goodhill and Sejnowski (1997).

4 Exact Solution Under External Constraints

The function of the brain is to bridge sensory input and motor output. Communications between sensory and motor organs, on the one hand, and the brain, on the other, require biological wires. The cost of these wires must be included in the overall cost function,

$$\mathfrak{C} = \frac{1}{2} \sum_{i,j} A_{ij}(r_i - r_j)^2 + \sum_{i,j} B_{ij}(r_i - f_j)^2, \tag{4.1}$$

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. Weight 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, we search for the minimum of the wiring cost function 4.1, while varying the locations of the brain neurons, r_i. An elegant way to do this is by first rewriting the two terms of the cost function in a matrix form (Hall, 1970),

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

$$= \sum_i r_i^2 \sum_j A_{ij} - \sum_{i,j} r_i A_{ij} r_j = \mathbf{r}^T(\mathbf{D}_A - \mathbf{A})\mathbf{r}$$

$$= \mathbf{r}^T \mathbf{L} \mathbf{r}, \tag{4.2}$$

where r is a column vector $\{r_i\}$ matrix $D_{Aij} = \delta_{ij} \sum_k A_{ik}$, and $\mathbf{L}$ is called the Laplacian of matrix $\mathbf{A}$,

$$
\begin{aligned}
\sum_{i,j} B_{ij}(r_i - f_j)^2 &= \sum_{i,j} B_{ij}(r_i^2 - 2r_i f_j + f_j^2) \\
&= \sum_i r_i^2 \sum_j B_{ij} - 2 \sum_{i,j} r_i B_{ij} f_j + \sum_j f_j^2 \sum_i B_{ij} \\
&= \mathbf{r}^T \mathbf{D_B} \mathbf{r} - 2\mathbf{r}^T \mathbf{B} \mathbf{f} + const,
\end{aligned}
\tag{4.3}
$$

where matrix $D_{Bij} = \delta_{ij} \sum_k B_{ik}$. The minimum of the quadratic wire length cost function 4.1 can be found by taking a derivative in respect to r_i and setting it to zero:

$$
\frac{d\mathfrak{C}}{d\mathbf{r}} = 2(\mathbf{L} + \mathbf{D_B})\mathbf{r} - 2\mathbf{B}\mathbf{f} = 0.
\tag{4.4}
$$

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

$$
\mathbf{r} = (\mathbf{L} + \mathbf{D_B})^{-1}\mathbf{B}\mathbf{f}.
\tag{4.5}
$$

This solution for the layout problem can be easily generalized to d spatial dimensions. Because the cost function 4.1 is separable into d terms, each containing distances along different dimensions, equation 4.5 gives the projection of the layout vector onto the corresponding spatial dimension.

In the rubber bands analogy, this solution is reminiscent of a cobweb, where the network nodes' location is determined by the forces exerted by external and internal connections. If external connections, B_{ij}, are much stronger than internal, A_{ij}, the location of the nodes is determined mainly by the balance of external forces. For example, if each node makes a strong connection with only one fixed organ, it should be located on that organ. In the opposite limit, when internal connections dominate, all nodes cluster together near the center of mass. Then the optimal layout problem can be broken into two steps. First, the location of the center of mass, r_{cm}, corresponds to the minimum of

$$
\mathfrak{C}_{cm} = \sum_j (r_{cm} - f_j)^2 \sum_i B_{ij}.
\tag{4.6}
$$

Second, coordinates of the nodes relative to the center of mass can be found by using the spectral decomposition of the Laplacian (see the next section). This two-step solution allows one to predict the center of mass location even when the internal connections are not completely known.

5 Spectral Analysis Emulates Internal Constraints

The finite size of neuronal bodies and axons places constraints on the possible layouts because of volume exclusion, or congestion. Inclusion of these

constraints is in general a difficult problem. Here we present an approximate treatment of the internal constraints, which yields an aesthetically appealing exact solution (Hall, 1970). In order to avoid the trivial solution, the norm of vector $\mathbf{r}$ is fixed, yielding the following optimization problem (see equation 4.2 for derivation):

$$\text{minimize } \mathfrak{C} = \frac{1}{2}\sum_{i,j} A_{ij}(r_i - r_j)^2 = \mathbf{r}^T\mathbf{L}\mathbf{r}, \text{ subject to } \mathbf{r}^T\mathbf{r} = 1. \qquad (5.1)$$

This minimization problem is solved by the eigenvector of $\mathbf{L}$ corresponding to its lowest eigenvalue. However, the lowest eigenvalue of $\mathbf{L}$ is 0, and the corresponding eigenvector is $\mathbf{1}/N^{1/2}$, which means that all nodes are at the same point. This led Hall (1970) to introduce an additional constraint by requiring that the minimization problem solution be orthogonal to that eigenvector:

$$\mathbf{r}^T\mathbf{1} = 0 \text{ or } \sum_i r_i = 0. \qquad (5.2)$$

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 (Hall, 1970).

The layout problem with internal constraints also admits a physical analogy. In addition to the elastic force exerted on the nodes by massless rubber bands, there is repulsive force proportional to the distance from the origin. The role of the additional constraint 5.1 is to pin the center of mass to the origin. Alternatively, one can view this problem as finding the configuration with minimum elastic energy for fixed moment of inertia 5.1 and center of mass 5.2.

Unfortunately, the above solution for internal constraints cannot be combined straightforwardly with that for external constraints presented in section 4. For example, the center of mass coordinates is determined by incompatible considerations in the two cases: arbitrary placement at the origin versus force balance depending on external constraints. Yet the Laplacian spectrum and the corresponding eigenvectors may approximate the solution obtained with external constraints if the weights of internal connections dominate that of external. This relationship between the two formulations can be formalized by rewriting the scalar product between the ith eigenvector, v_i, and the external constraint solution, $\mathbf{r}$,

$$\mathbf{v}_i\mathbf{r} = \frac{\mathbf{v}_i\mathbf{B}\mathbf{f}}{\lambda_i + \beta_i}, \qquad (5.3)$$

where β_i are coefficients of the spectral decomposition of $\mathbf{D_B}$ in the projection basis.

6 Layout of Prefrontal Cortical Areas in Macaque

Cerebral cortex consists of multiple areas whose spatial arrangement and interconnectivity are reproducible from animal to animal. Previous work suggests that the arrangement of cortical areas is determined by minimizing the total length of the interconnections between them (Cherniak, 1994; Mitchison, 1991). Recently, this suggestion has been put to a direct test in the macaque prefrontal cortex (Klyachko & Stevens, 2003), where most of the interconnections and the layout of areas are known (Carmichael & Price, 1996; see Figure 1). Brute force enumeration of all possible area layouts shows that the wiring in the actual layout is the shortest (Klyachko & Stevens, 2003).

Here we test the quadratic wire length approach on the data set used in Klyachko and Stevens (2003) by using both external and internal constraints formulation.

In the external constraints formulation, the 14 areas on the periphery of the prefrontal cortex are treated as fixed organs, their locations being the actual ones (the crosses in Figure 1A and 1B). Locations of the remaining 10 areas are continuously varied to minimize the sum of connection lengths squared. Equation 4.5 yields the placement shown in Figure 1B. 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, which should be lower. Interestingly, this placement corresponds to one of the close-to-optimal placements reported in Klyachko and Stevens (2003). There are two possible explanations for why the areas are predicted to bunch up more than they do in reality. First, the external constraint formulation neglects volume exclusion, that is, the fact that the areas have finite size and cannot overlap. Second, there may be connections between the areas that were considered in Carmichael and Price (1996) and the areas that were not considered. Because these areas lie outside the considered fixed areas, their inclusion would pull apart the movable areas.

The internal constraints formulation applied to the 18 areas included in prefrontal orbital and medial networks (Carmichael & Price, 1996) yields the arrangement shown in Figure 1C. This placement has approximately correct ordering of the areas. Moreover, this analysis correctly clusters cortical areas into two clusters distinguished by the sign of the second eigenvector component. These clusters correspond to the known (Carmichael & Price, 1996) subdivisions of the prefrontal cortex orbital (blue labels) and medial (red labels) networks. Thus, the predictions of the internal constraints formulation are consistent with anatomical data.

7 Layout of Ganglia in *C. elegans*

Neurons in the *C. elegans* nervous system are clustered into several ganglia distributed along its body. Most connections between the ganglia are known, making this system a natural choice for testing the wiring optimiza-
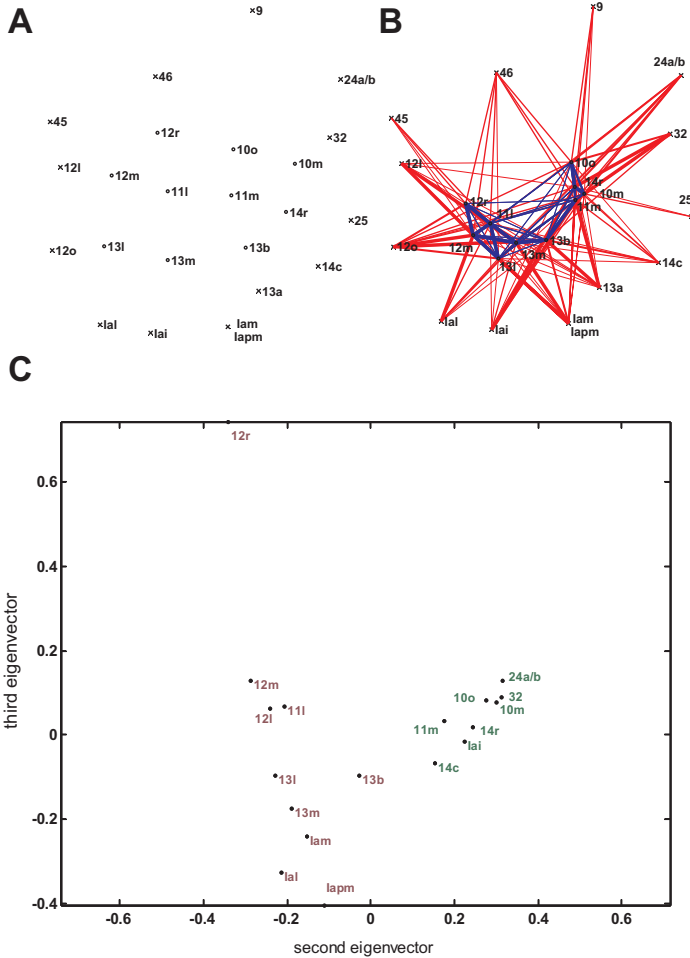
Figure 1: Comparison of the actual cortical area arrangement (A) with the predictions of the quadratic layout optimization under external (B) and internal (C) constraints. (A) Cortical area centers in the coordinate frame of the flattened prefrontal cortex, taken from Klyachko and Stevens (2003) and labeled according to Carmichael and Price (1996). Crosses indicate areas that were fixed in the external constraint formulation, and circles indicate movable areas. (B) Area locations predicted by the external constraint formulation. Blue lines show internal connections (A_{ij}), and red lines external ones (B_{ij}). (C) Area locations predicted by the internal constraint formulation. Areas cluster by the sign of the second eigenvector component (negative versus positive abscissa) in accordance with the known division of the prefrontal cortex into orbital (brown labels) and medial (green labels) networks (Carmichael & Price, 1996).
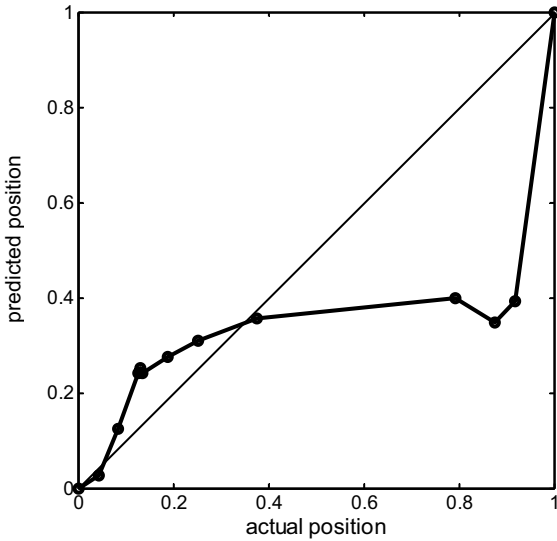
Figure 2: Solid dots (connected in the anterior-posterior order) show predicted versus actual positions of *C. elegans* ganglia normalized by the distance from head to tail. Deviations from the diagonal line correspond to differences in the actual versus predicted ganglia positions. Although predicted ganglia positions differ from the actual ones, their order is predicted correctly with the exception of the dorsorectal ganglion (actual position: 0.88 of body length).

tion approach. The layout problem is essentially one-dimensional because of the large aspect ratio (more than 10:1) of the worm body. Brute force enumeration of all permutations of 11 movable components (including nerve ring in addition to ganglia; Cherniak, 1994) shows that the actual ordering minimizes the total wire length.

Here I show that solving a quadratic placement problem can largely reproduce the actual order of ganglia. In the external constraints formulation, the locations of ganglia are given by equation 4.5, where the wiring diagram and fixed locations of sensors and muscles are the same as in Cherniak (1994). Figure 2 shows the predicted positions of *C. elegans* ganglia versus the actual ones. The predicted order agrees with the actual one with the exception of a single ganglion. This is a reasonably good agreement considering that there are 11! alternative orderings. However, predicted ganglia locations deviate from the actual ones. These deviations may be due to missing information in the wiring diagram (e.g., the lack of neuromuscular connections); deviations of the cost function from the quadratic form; or

other factors that should be included in the cost function. Future work will determine which of these factors are responsible for the disagreement.

Internal constraints are unlikely to play a significant role in the placement of ganglia due to the relative sparseness of the *C. elegans* nervous system. Therefore, I skip this analysis.

8 Discussion

In this letter, 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, where previous solutions relied on brute force complete enumeration. Minimization of wire length squared approximates the actual layouts reasonably well. One recurring 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 multineuron 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 multineuron complexes.

As in any other theoretical analysis, the optimal neuronal layout solution relies on several simplifying assumptions. The central assumption, the quadratic form of the cost function, is supported by the argument in section 2, showing that quadratic cost function may be a reasonable approximation. The utility of this approximation is due to its exact solvability (see sections 4 and 5). The validity of this approximation is supported by the fact that its predictions are consistent with experimental data (see sections 7 and 8). Another assumption is that wiring consists of point-to-point (nonbranching) axons. This assumption is valid for connections between cortical areas and can serve as a first-order approximation in other cases. Future work will analyze the impact of the axonal branching and the presence of dendrites on brain design. Also in the real brain, axonal branches are not exactly straight lines. Their curvature is itself a result of internal constraints, which are included here only on the mean-field level (see section 5). A more detailed treatment of internal constraints, or congestion, will be presented elsewhere.

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 of possible layouts 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 (predicting connectivity from neuronal layout) more tractable. Since solving this problem may complement 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

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