Neural component placement

Christopher Cherniak

A range of neuroanatomical results supports the idea that 'save wire' is an organizing principle of brain structure: that the theory of combinatorial optimization of networks applies to the anatomy of the nervous system. In particular, optimization of the placement of components operates at several hierarchical levels in the nervous system, from gross to microscopic anatomy, and from invertebrates to primates. That is, when anatomical positioning of interconnected neural components is treated like a problem of wire minimization in microchip layout, a hypothesis of 'best of all possible brains' is consistent with the observed siting of brains, ganglia, and even somata of individual neurons that minimizes the length of interconnections. In the case of the positioning of ganglia of *Caenorhabditis elegans*, optimization predictions of one-in-a-million precision can be verified.

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A MINIMUM-WIRING INTERPRETATION for neuroanatomy can already be discerned in Ramón y Cajal's qualitative 'laws of protoplasmic economy' (see Ref. 1), and continues to receive attention to the present time[2,3]. A 'save-wire' hypothesis of minimization of connections for computational neuroanatomy can be derived from a general methodological framework of bounded resources in cognitive neuroscience: that is, from focusing attention upon the perspective that the mind/brain is an object of stringently limited resources[4,5]. Such a resource-realistic framework is linked to concrete neuroanatomy via some of the formalisms of scarcity of the theory of combinatorial optimization of networks in computer science, which deals with problems of efficient use of wire (that is, of minimization of connectivity)[6,7]. A working hypothesis thereby emerges that, because connections in the brain are a scarce resource both in volume and in signal-propagation delay, minimizing the costs of the required connections drives significantly the anatomy of the nervous system. Hence the empirical question, if brain connections are in short supply, is their configuration optimized in this way? The theory of optimization of networks might yield general principles that characterize compactly aspects of the neural wilderness, and which form a 'generative grammar' of the nervous system.

The theory of optimization of networks deals with a variety of connection-minimization problems with neuroanatomical applicability, for example, Steiner-tree optimization[8] of dendritic and axonal arbors[3,9,10]; however, this review concerns component-placement optimization (CPO). The problem has received attention recently in the design of very large-scale integrated (VLSI) microcircuits[11]. It can be simply stated as: given the interconnections among a set of components, find the layout (the physical positioning) of the components that minimizes total connection costs, for example, wire length. Sites for components are often restricted to a matrix of permissible positions, or legal slots (see Fig. 1). Many of the most important problems of the optimization of networks in the real world (for example, the traveling-salesman problem[6]) have been proved to be non-deterministic polynomial-time (NP)-complete[12]. Problems that are NP-complete are strongly conjectured to be intrinsically computationally complex: that is, they are not generally solvable without exhaustive search of an exponentially exploding number of possible solutions. In particular, CPO is of this type, having been proved, like the Steiner-tree problem, to be NP-hard, that is, at least as difficult as NP-complete problems[13] (J. Frankle, PhD Thesis, University of California, 1987). The computational costs for an exact general solution of problems of CPO should be emphasized: for n components, the number of alternative possible placements is $n!$ Consider the approximately 50 areas of the human cerebral cortex: a mere 50-component problem has 50! ($= 3.04 \times 10^{64}$) possible configurations, far more than the number of picoseconds in the 20-billion-year history of the universe since the Big Bang. So-called 'quick but dirty' heuristic procedures that only approximate optimal solutions can be carried out much faster than a total brute-force search, but their performance (for example, how close to optimal they are likely to come) is not well understood at present[14].

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Placement of the brain

Can a connection-minimization hypothesis explain why the brain is in the head? Positioning of the entire brain in the body constitutes a problem of one-component placement (see Fig. 2). The simplest measure of the cost of connection is the total length of individual fibers in all sensory and motor tracts leading to and from the brain. The locations of all sensors and effectors are treated as fixed edge constraints. The complete published information necessary to calculate numbers of fibers in all nerve tracts appears to be available only at two phylogenetic extremes, for the nervous systems of the human[18] and the nematode[19]. Taking into account the flexures of the human CNS, the number of nerve fibers leading to and from locations forward of the brain exceeds the number of fibers leading to and from locations to the rear of the brain; a similar consideration applies to the brain of *Caenorhabditis elegans* (or a predominant concentration of its nervous system). Consequently, the wire-minimizing placement of these brains will be as far forward as possible. And the actual positioning of the human and nematode brains on the longitudinal body axis is in fact consistent with this simplest wire-minimization prediction. [Inspection of drawings of gross anatomy suggests that, more approximately, whenever anterior connections exceed posterior ones, as in the case of all vertebrates (for example, see Ref. 20) and most invertebrates[21], the brain is placed as far forward on the body axis as possible.]

Placement of cerebral cortex areas

On a finer scale, an account of minimization of connections can be thought of as a kind of plate tectonics of the cortex. Schemes of the Brodmann or von Bonin and Bailey types parcel the human cortex into over 50 cytoarchitectonically and functionally distinct areas[22,23]. The simplest hypothesis of optimization of placement for these components is that they are positioned on the two-dimensional cortical sheet to minimize the total length of their interconnections. (The more difficult question of three-dimensional positioning on the actual configuration of the folded cortex ought also to be examined.) As mentioned above, a search of all possible alternative layouts of even 50 components in order to verify optimization would require resources of a greater than cosmic scale. However, if cortical components are in fact placed to minimize interconnection lengths, one would expect a quite tractable statistical confirmation of an adjacency rule: if components are interconnected, then they are positioned contiguously to each other, other things being equal[15,16]. (In Ref. 24, a similar rule is proposed as a nearest-neighbor rule[17].)

At present, incomplete information on connections and contiguities can be compiled from published data on the cortical anatomy of the visual systems of the macaque[25-27] and the cat[28], and the olfactory system of the rat[29]. And in fact, when evaluated by simple χ^2-type tests, each of these very diverse systems departs strongly from random placement in favor of the adjacency rule (see Table 1)[15,16]. Clearly, the rule ought to be checked for other neural systems. However, while this simple rule is a powerful predictor of anatomy, a caution is in order: satisfying an adjacency rule cannot be sufficient in itself to entail optimality. For example, the rule does not specify how best to allocate contiguity where there are too many interconnections for all connected pairs to be contiguous. In addition, the rule takes no account of the use of branching to economize connection costs, for example, via Steiner-tree structures[8,10]; a significant proportion of intracortical connections in the visual systems of the monkey and cat appears to be of this type[27].

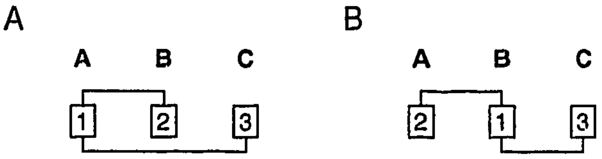


Fig. 1. *A simple combinatorial problem of placement of components.* (A and B) *Diagrams of two out of six possible configurations of components 1, 2 and 3 in positions (legal slots) A, B and C. For the connections shown among the components, the placement of the components in A requires the greatest total length of connections, and that in B the least.*

Fig. 2. *The simplest problem of placement of components, the one-component case. As a biological example, the brain of verebrates, and of most invertebrates, makes more anterior than posterior sensor-motor connections. To minimize the total length of peripheral nerve fibers, the brain should be placed as far forward as possible, as is in fact the case*[15-17].

Placement of ganglia of *C. elegans*

For only one species, *C. elegans*, does approximately complete neuroanatomy now exist. During the 1970s and 1980s, the *C. elegans* group at Cambridge University published about 1000 pages of drawings of the 302 neurons of the nervous system of this species[19,30-32], a measure of the intricacy of even so simple a brain. Motivated by the good performance of the adjacency rule observed above, we compiled a database from the diagrams of *C. elegans* (with supplementation from a draft of Ref. 33), listing for each neuron its location and all known connections; from the database, a connectivity matrix was in turn computed.

TABLE 1. Connections and contiguities between neural components

	Macaque visual-cortex areas (19)[26]			Cat visual-cortex areas (18)[28]			Rat olfactory-cortex areas (21)[29]			Ganglia of *C. elegans* (11)[30-32]		
	Contiguous pairs			Contiguous pairs			Contiguous pairs			Contiguous pairs		
	Yes	No	Total	Yes	No	Total	Yes	No	Total	Yes	No	Total
Connected pairs												
Yes	30	61	91	70	108	178	19	10	29	31	40	71
No	14	237	251	0	128	128	61	330	391	9	59	68
Total	**44**	**298**	**342**	**70**	**236**	**306**	**80**	**340**	**420**	**40**	**99**	**139**
Significance of effect	$P < 0.0001$			$P < 0.0001$			$P < 0.0001$			$P < 0.0001$		
Magnitude of effect	$r_\phi = 0.35$			$r_\phi = 0.46$			$r_\phi = 0.32$			$r_\phi = 0.34$		

There is a tendency to conform to the adjacency rule: for each of a wide variety of systems, a significantly greater proportion of connected than non-connected pairs are contiguous. (Compiled from Refs 15 and 16; see Ref. 16 for connection-counting conventions.)

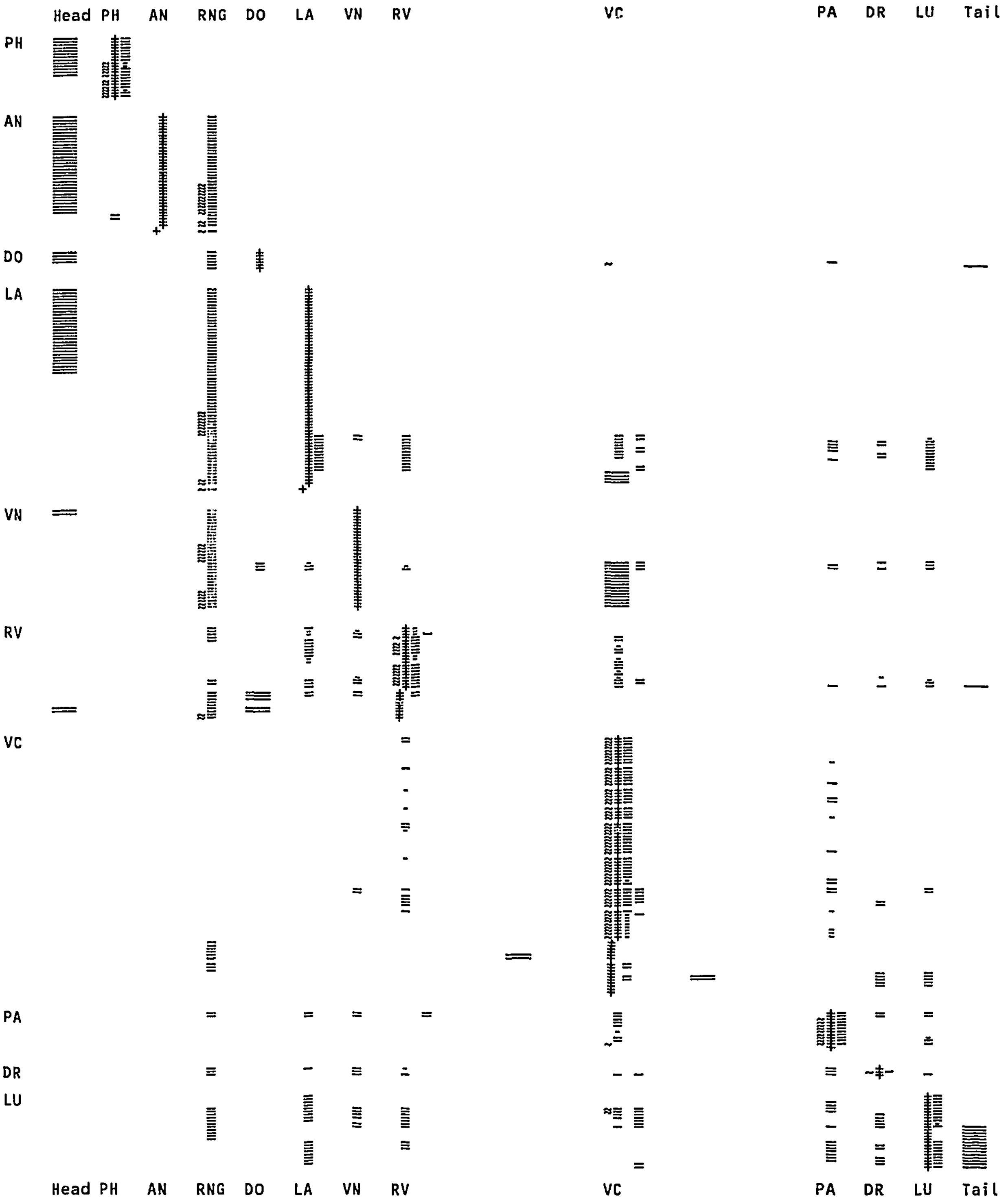


Fig. 3. *Total ganglion-level connectivity map for the nervous system of* Caenorhabditis elegans. *The actual layout conforms to the wire-saving adjacency rule. Each partially superimposed horizontal micro-line represents one of the 302 neurons: +, soma; –, asymmetrical (chemical) synapse; -, symmetrical (gap) synapse; ~, muscle connection; —, sensor. (Non-ganglionic somata appear below and one space to the left of the somata of the nearest ganglion.) PH, AN, and so on are codes for the ganglia. Horizontal scaling, approximately 100×. See Ref. 16 for connection-counting rules.* Reproduced, with permission, from Ref. 16.

Figure 3 represents that matrix, showing synoptically all connections of all neurons. This appears to be one of the first complete depictions of an entire nervous system, at synapse-level detail, in a single image. A clustering of connections along the diagonal from top left to lower right is immediately apparent, and confirms the validity of the adjacency rule, in this case for positioning of the ganglia of *C. elegans* (see also Table 1).

One account of the ganglia of *C. elegans* is that they are merely clusterings of somata caused by extraneous mechanical factors, without functional significance[32,34]. However, stronger evidence can be obtained that suggests that placement of these components conforms to a save-wire rule. The problem of ganglion-level optimization can be treated as involving 11 movable components, with 11! (= 39 916 800) possible orderings. All of these placements can be searched exhaustively in about 24 h using an SGI R4000SC workstation[16]. The actual placement turns out to be the ideal, or optimal, one. The actual ganglion layout of *C. elegans* in fact requires the least total length of connecting fiber of any of the millions of possible layouts. For comparison, the last-place, 'pessimal' layout would require about four times as much total connecting fiber as the optimal one (see Fig. 4).

The scale of such a one-in-a-million search of all orderings of ganglia is worthy of emphasis: in effect, the search approximates a simulation of the maximal possible history of the evolution of an aspect of the nervous system of the worm. If each layout is described in a single alphanumeric line, just listing them all would fill about one mega-page (a million pages). Or, again, suppose that 2000 alternative layouts had turned out instead to require less connectivity than the actual layout: if each of the ~40 000 000 possible layouts that the actual one undercosted represented a 1-mm increment along a darwinian racetrack in a possible-worm race, then the actual layout would still have covered all but the last 2 m of the total 40-km distance. One natural interpretation of such a finish in 2001st place would then be to consider the possibility that, after beating the rest of the millions of alternative layouts, failure of the actual layout to beat the last 2000 was merely apparent (for example, suspected to arise plausibly from some type of small-scale error of measurement). One implication of this search result is as a calibration of the much more easily applied adjacency principle: while the actual layout of ganglia conforms highly significantly to the adjacency rule, it includes some violations of the rule. These demonstrate that, for moderately high densities of connectivity, there may be no possible arrangement where every pair of interconnected elements can in fact be contiguous.

Placement of individual *C. elegans* neurons

There is also evidence that optimization of placement is so sensitive that it fine-tunes even the positioning of individual somata in the roundworm. Of course, an exhaustive search of all relevant placements of the 302 neurons would require resources on a far greater than cosmic scale. However, the following special case of the wire-saving adjacency rule is strongly confirmed: if two neurons are interconnected, then they are placed near each other – in particular, clustered in the same ganglion – other things being equal. In addition, even positioning of somata within a ganglion tends to conform to a prediction of connection-minimizing placement of components: there is a highly significant trend for cell bodies that make exclusively anterior extra-ganglionic connections to be located in the front half of the ganglion, while cell bodies with external connections only to sites posterior to the ganglion tend to be placed in the rear half of the ganglion (see Fig. 5). Even at the level of the individual cell, internal structuring of ganglia appears skewed toward optimization of layout.

Mechanisms

Good network optimization of neuroanatomy raises questions about the mechanisms by which the optimization actually arises. A first point is that the mechanisms can be conjectured not to be perfectly correct and complete procedures. As mentioned, execution by natural selection of a simple brute-force search for a solution to the 50-component problem of ordering of the human cortical areas would require, even with unrealistic speed and parallelism, more than the age of the universe. Indeed, this same limitation also confronts attempts of human investigators to identify perfect neural optimization – even if it is present, it might not be feasible to verify this. Therefore, instead of exact general solutions, attention turns to 'quick but dirty', approximate and probabilistic wire-saving heuristics that evolution might have hit upon blindly. (Perhaps such wiring heuristics are shared widely across species, like the recently reported master-control gene for eye morphogenesis that appears common to both invertebrates and vertebrates[35].) One of the simplest candidates is of a tug-of-war type; weight-table analog machines of this sort were in fact used a century ago to solve problems of real-world one-component placement[36]. Correspondingly, for the brain-positioning problem, each sensory and motor nerve fiber can be represented as acting over generations like a microscopic weight-and-pulley device (such an account has affinities with Kappers' principle of neurobiotaxis[20]). However, one must hasten to add that a similar procedure for combinatorial, multiple-component problems in design of VLSI chips, known as the mesh-of-springs heuristic, behaves problematically because of local-minima traps[37,38]. More generally, in evaluating imperfect procedures known to fail in some

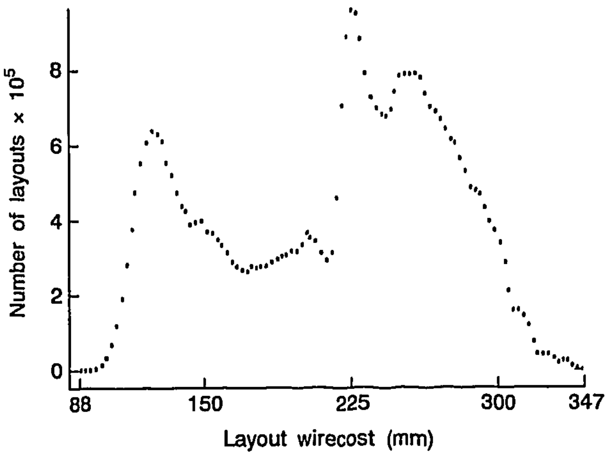
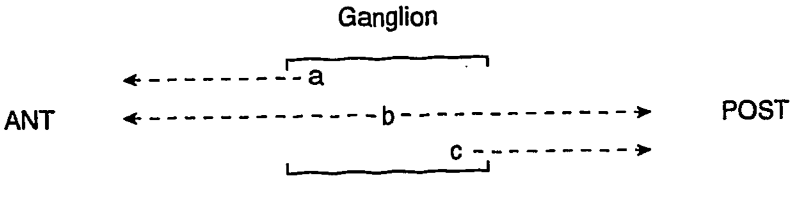


Fig. 4. *Distribution of wirecosts of all possible layouts of ganglia of* **Caenorhabditis elegans.** *Data were compiled from an exhaustive search of all 39 916 800 alternative orderings of ganglia. The least- and the most-costly layouts are rarest. (Besides its rough approximation to a normal distribution, other features of the observed distribution, for example, the three main peaks, have no known significance.)*



Soma		Placement
a: anterior-only connections	⇒	front of ganglion
b: ant & post connections	⇒	-----
c: posterior-only connections	⇒	rear of ganglion

Fig. 5. *Intra-ganglionic positioning of somata of* Caenorhabditis elegans. *A hypothesis of minimization of connection costs entails anatomical predictions within a ganglion. The observed cell-body placement in fact conforms significantly to these predictions.*

relevant cases (for example, for the adjacency rule as well as such energy-minimization procedures) there is a methodological problem in characterizing clearly how good an approximation of the optimal solution can be expected, how often, and when[14].

Of course, over evolutionary history, the sensorimotor connections of the brain cannot, in fact, behave literally as springs. It is, therefore, useful to distinguish between such abstract models and, at more concrete explanatory levels, actual implementations of those models (compare with the distinction in linguistic theory between, respectively, abstract competence and biologically realistic performance grammars[39]). For example, the co-ordination of placement of components and connections described by the adjacency rule in turn raises questions about the direction of causation: whether connections, in fact, lead to optimal positioning of components, or vice versa. Indeed, direction of causation might diverge in different cases. Another conjecture about biological reality is that there might be a significant division of labor in minimization of connections between phylogenetic and ontogenetic processes.

The good optimization of placement of the ganglia of *C. elegans* suggests that some of the wire-saving procedures must fall, in a sense, between the adjacency rule and brute-force search. A biological heuristic for optimization of neural wiring must not only run fast enough to evade paralysis, but also not be so dirty or inaccurate as to preclude the sort of good performance that has been observed for ganglia of *C. elegans*. Another constraint on the process of refining wiring heuristics is the familiar point in evolutionary theory that, at every stage, the heuristic will be a prisoner of its prior history[40]: natural selection improves upon inherited designs, and cannot begin anew from a blank slate. This is yet another hint about the nature of the mechanisms of optimization that awaits interpretation.

Recently, Adleman has described the physical construction of a 'DNA computer', which found, by a virtually exhaustive search, the shortest-path solution of a small-scale instance of a traveling-salesman type of problem of combinatorial network optimization[41]. Adleman's result converges with the evidence of placement of neural components that has been reviewed here: it constitutes a demonstration of the feasibility, at least in principle, of the use of DNA-based mechanisms to solve small-sized problems of combinatorial network optimization, a category that includes CPO. One question that Adleman's device raises concerns the scale of the problem that such biomolecular computation could solve in naturally occurring systems. As mentioned above, in populations of organisms, a darwinian process of optimization by a brute-force search seems too slow; but within a single cell, the genetic machinery seems insufficient for the number of alternative CPO layouts to be checked in parallel. A mere 25-component CPO problem has 10^{25} alternative layouts, a number greater than Avogadro's constant.

Another issue concerns how widespread the phenomenon of CPO is: does CPO also occur in non-neural systems? The presence or absence of similarly fine-grained CPO in other biological systems would provide additional clues as to the mechanisms involved in CPO. In the case of another concept of network optimization, Steiner tree, small-scale or local minimization of connecting structures can be observed not only for dendritic and axonal arbors, but also for arterial and venous vasculature, and even for non-biological systems such as networks of river drainage[9,10]; similar elementary vector-mechanical mechanisms might operate in all these cases. In addition, evidence is now emerging of aspects of large-scale or global minimization in some types of tree structures (C. Cherniak, unpublished observations). Both the neural and the non-biological arbors again appear to optimize comparably well, raising the possibility that global optimization of neuronal arbors might exploit the same mechanisms as the physical systems.

Finally, robust phenomena of optimization of connections turn one's attention from anatomy to physiology: why should saving wire have such a distinctive importance, in competition with the many other natural desiderata, in designing a brain? The evidence of good wire-saving optimization of dendritic and axonal arbors of neurons, as well as of neural component placement, further emphasizes this question. While instances of biological optimization approaching even absolute physical limits are known (such as the light sensitivity of the dark-adapted human retina) these cases stand out against a broad background of more familiar, merely 'good-enough' biological design. Of course, shorter connections mean lower volumes of tissue and shorter delays in propagation of signals[5], but an especially high priority to the minimization of connection costs might be a more specific clue to how the brain functions. Indeed, an understanding of these physiological roles might in turn contribute to an understanding of the means by which minimization of connections arises.

Selected references

1 Ramón y Cajal, S. (1909, 1911) *Histologie du Système Nerveux de l'Homme et des Vertébrés* (Translated by L. Azoulay), Vol. I, Ch. 5, Maloine
2 Durbin, R. (1990) *Nature* 343, 644–647
3 Mitchison, G. (1991) *Proc. R. Soc. London Ser. B* 245, 151–158
4 Cherniak, C. (1986) *Minimal Rationality*, MIT Press
5 Cherniak, C. (1990) *J. Cognitive Neurosci.* 2, 58–68
6 Lewis, H. and Papadimitriou, C. (1978) *Sci. Am.* 238, 96–109
7 Stockmeyer, L. and Chandra, A. (1979) *Sci. Am.* 240, 140–159
8 Bern, M. and Graham, R. (1989) *Sci. Am.* 260, 84–89
9 Cherniak, C. (1990) *Local Network Optimization in the Brain*, University of Maryland Institute for Advanced Computer Studies Technical Report No. 90–90
10 Cherniak, C. (1992) *Biol. Cybern.* 66, 503–510
11 Soukup, J. (1981) *Proc. IEEE* 69, 1281–1304
12 Garey, M. and Johnson, D. (1979) *Computers and Intractability: A Guide to the Theory of NP-Completeness*, W.H. Freeman
13 Sahni, S. and Bhatt, A. (1980) *Proc. 17th Design Automation Conference*, 402–411
14 Cherniak, C. (1988) *Commun. ACM* 31, 402–412
15 Cherniak, C. (1991) *Component Placement Optimization in the Brain*, University of Maryland Institute for Advanced Computer Studies Technical Report No. 91–98
16 Cherniak, C. (1994) *J. Neurosci.* 14, 2418–2427
17 Cherniak, C. (1994) *Philos. Studies* 73, 89–107
18 Blinkov, S. and Glezer, I. (1968) *The Human Brain in Figures and Tables: A Quantitative Handbook*, Plenum
19 Wood, W., ed. (1988) *The Nematode* Caenorhabditis elegans, Cold Spring Harbor Laboratory
20 Kappers, C., Huber, G. and Crosby, E. (1967) *Comparative Anatomy of the Nervous System of Vertebrates*, Hafner
21 Bullock, T. and Horridge, G. (1965) *Structure and Function in the Nervous Systems of Invertebrates*, W.H. Freeman
22 Jouandet, M. *et al.* (1989) *J. Cognitive Neurosci.* 1, 88–117
23 Krieg, W. (1963) *Connections of the Cerebral Cortex*, Brain Books
24 Young, M. (1992) *Nature* 358, 152–155
25 Van Essen, D. and Maunsell, J. (1980) *J. Comparative Neurol.* 191, 255–281

26 Van Essen, D. (1985) in *Cerebral Cortex* (Vol. 3) (Peters, A. and Jones, E., eds), pp. 259–329, Plenum
27 Felleman, D. and Van Essen, D. (1991) *Cereb. Cortex* 1, 1–47
28 Rosenquist, A. (1985) in *Cerebral Cortex* (Vol. 3) (Peters, A. and Jones, E., eds), pp. 81–117, Plenum
29 Price, J. (1987) in *Neurobiology of Taste and Smell* (Finger, T. and Silver, W., eds), pp. 179–203, Wiley
30 Albertson, D. and Thomson, J. (1976) *Philos. Trans. R. Soc. London Ser. B* 275, 299–325
31 White, J. *et al.* (1976) *Philos. Trans. R. Soc. London Ser. B* 275, 327–348
32 White, J. *et al.* (1986) *Philos. Trans. R. Soc. London Ser. B* 314, 1–340
33 Achacoso, T. and Yamamoto, W. (1992) *AY's Neuroanatomy of C. elegans for Computation*, CRC Press
34 Chalfie, M. and White, J. (1988) in *The Nematode Caenorhabditis elegans* (Wood, W., ed), pp. 337–391, Cold Spring Harbor Laboratory
35 Halder, G., Callaerts, P. and Gehring, W. (1995) *Science* 267, 1788–1792
36 Francis, R. and White, J. (1974) *Facility Layout and Location*, Prentice-Hall
37 Kuh, E. and Ohtsuki, T. (1990) *Proc. IEEE* 78, 237–263
38 Kirkpatrick, S., Gelatt, C. and Vecchi, M. (1983) *Science* 220, 671–680
39 Chomsky, N. (1965) *Aspects of the Theory of Syntax*, MIT Press
40 Gould, S. (1980) *The Panda's Thumb*, Norton
41 Adleman, L.M. (1994) *Science* 266, 1021–1024

Striatal interneurones: chemical, physiological and morphological characterization

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The neostriatum is the largest component of the basal ganglia, and the main recipient of afferents to the basal ganglia from the cerebral cortex and thalamus. Studies of the cellular organization of the neostriatum have focused upon the spiny projection neurones, which represent the vast majority of neurones, but the identity and functions of interneurones in this structure have remained enigmatic despite decades of study. Recently, the discovery of cytochemical markers that are specific for each of the major classes of striatal interneurones, and the combination of this with intracellular recording and staining, has revealed the identities of interneurones and some of their functional characteristics in a way that could not have been imagined by the classical morphologists. These methods also suggest some possible modes of action of interneurones in the neostriatal circuitry.

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RECENT YEARS have seen major advances in the understanding of the circuitry of the basal ganglia. The key to these advances was the recognition that the most common type of neostriatal cell, the medium-sized spiny neurone, was also the source of the major efferent-fibre systems of the neostriatum, innervating the globus pallidus and substantia nigra[1–7]. Anatomical studies also showed that these neurones are the synaptic targets of the vast majority of striatal afferents, including those from the cerebral cortex, intralaminar thalamic nuclei, the dopaminergic neurones of the substantia nigra, and the serotonergic fibres from the dorsal raphé nucleus[1,2]. Thus the spiny projection neurones represent over 90% of cells in the neostriatum, give rise to nearly all the outputs of this structure, and receive nearly all of the synapses from inputs. Some of the intrinsic synaptic interconnections formed among neostriatal neurones were found to arise from the spiny projection cells as well, owing to the dense arborizations formed by their local axonal collaterals[1,2]. These findings highlighted the importance of a single cell type, the spiny projection neurone, as the main circuit element in the neostriatum, and focused much research on the discovery of the properties and interactions of this neuronal type. While it had been known since the time of Ramón y Cajal that there are a variety of other neuronal types in the neostriatum, these interneurones were few in number and highly variable in morphology, and so defied all attempts to categorize them using the classical method of somato-dendritic morphology[8–11]. Given the large numerical advantage enjoyed by the projection neurones, it was difficult to imagine how interneurones could have more than an ancillary function within the neostriatal circuitry.

Chemical identification

One result of the explosion of research on the spiny projection cell was the discovery that, while they are identical in somato–dendritic morphology, not all spiny projection neurones are alike. At least two subtypes have been identified on the basis of differences in their axonal projections[12]. One cell type projects mainly to the external pallidal segment (simply called globus pallidus in non-primates), while the other has its main projections to the substantia nigra and internal pallidal segment (called entopeduncular nucleus in non-primates). These two cell types can also be identified on the basis of cytochemical differences. While both cell types are GABAergic, spiny projection