

Global optimization of cerebral cortex layout

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Functional areas of mammalian cerebral cortex seem positioned to minimize costs of their interconnections, down to a best-in-a-billion optimality level. The optimization problem here, originating in microcircuit design, is: Given connections among components, what is the physical placement of the components on a surface that minimizes total length of connections? Because of unfeasibility of measuring long-range “wire length” in the cortex, a simpler adjacency cost was validated. To deal with incomplete information on brain networks, a size law was developed that predicts optimization patterns in subnetworks. Macaque and cat cortex rank better in this connection optimization than the wiring of comparably structured computer chips, but somewhat worse than the macroeconomic commodity-flow network among U.S. states. However, cortex wiring conforms to the size law better than the macroeconomic patterns, which may indicate cortex optimizing mechanisms involve more global processes.

Simple “save wire” generative principles from combinatorial network optimization theory predict layout of sensory areas of macaque and cat cerebral cortex. The areas appear to be positioned on the cortex to minimize interconnecting wiring, in some cases to current limits of detectability. This picture of large-scale component placement optimization in the cortex resembles earlier findings for ganglion layout in the nervous system of *Caenorhabditis elegans* (1, 2) and for optimization of neuron arbors (3, 4), but to orders of magnitude finer optimality (5, 6). Computer searches of all of the tens of millions of alternative possible roundworm ganglion placements indicated that the actual layout of the nematode requires the least total wire length for the nervous system’s 1,000 connections. On the model of these worm ganglion searches, we have worked out methods for optimality searches of layouts of cerebral cortex areas. To avoid difficulties of wire length measurement, a more manageable adjacency cost was calibrated as a surrogate. To detect optimization of subnetworks when the complete network is inaccessible and to distinguish local from larger-scale optimization mechanisms, a size law was articulated (ref. 7 and www.cs.umd.edu/Library/TRs).

We present evidence that the cortex areas appear optimally placed, down to the limits of present computing resources. If these types of results are confirmed, they constitute a predictive success story of recent quantitative neuroanatomy. This is a much finer degree of neuro-optimality than previously reported (e.g., refs. 3, 5, and 6). We have also analyzed nonneural networks (a benchmark computer microchip and macroeconomic patterns among U.S. states) as a calibration of these methods. Some chip layouts minimize connection costs better than chance, but worse than the cortex layouts. The economic network performs even better than the cortex, but apparently only via simple local processes.

Component placement optimization (also characterized as a quadratic assignment problem) has been a research focus in computer science for design of large-scale integrated circuits (8, 9). Briefly defined, the problem is: Given connections among a set of components, find the spatial layout of the components that minimizes total connection costs. This task, like many other network optimization problems (e.g., traveling salesman), is nondeterministic polynomial (NP)-time hard. The formal concept of NP-hardness, and the related concept of NP-

completeness, need not be defined here (10–12); they have long been conjectured to be linked with a problem being intrinsically computationally intractable, i.e., not generally solvable without exhaustive search of all possible solution-candidates.

Of course, a cerebral cortex is vastly more complex than the 300-neuron *C. elegans* nervous system; it is also molded by experience much more extensively. And, even when connections are reported between two cortex areas, connection lengths and densities are usually not available. In addition, the 2D cortical sheet is intricately folded, so that measuring distance between two areas becomes a 3D problem. Observing the actual course of an axon bundle in the white matter is yet another layer of difficulty. Finally, widespread axonal bifurcation of corticocortical connections in cat and monkey visual systems has been reported, with estimates of branching ranging >30% for some populations of projecting neurons (13). Such a bifurcation can save ≈10% of the corresponding length of two separate connections (4, 14). However, cerebral connection compendia only describe links between pairs of areas (15, 16); they therefore cannot systematically represent these branchings, and so remain inaccurate as a basis for computing wire costs. Is optimization still discernable through so many barriers?

Adjacency Rule Costing

The adjacency rule is: If two components *a* and *b* are connected, then *a* and *b* are adjacent. Two components are adjacent if immediately contiguous topologically (as are, e.g., the United States and Canada). The rule is a candidate for a network wire-minimizing heuristic (17); in fact, it is also extensively confirmed for macaque and cat visual cortex areas, rat olfactory areas, and *C. elegans* ganglia (1, 2, 18, 19). Conformance of a cortex layout to such a “myopic” adjacency rule is much more feasible to compute than its total wire length cost: Just compare interconnections and contiguities of the layout’s areas and score how many rule-violations occur. [For example, in Table 1, the seventh row VOT is {0, 2, 0, 2, 0, **1**, 0}; it adds 2 to the total cost of the actual layout, because two areas are connected (i.e., value >0) but not adjacent (i.e., not bold).]

How useful would such adjacency costing be? The basic point remains, that component placement optimization is a computationally intractable, NP-hard problem; hence, a quick and dirty heuristic like the adjacency rule cannot provide a general solution to such a problem. [In fact, as noted elsewhere (18, 20), most of the worm’s interganglionic connections are not to adjacent ganglia, but rather to more remote loci. Similarly for the majority of connections in macaque and in cat cortex. See Table 2, which is published as supporting information on the PNAS web site.]

So a first question would be, how closely correlated here in fact are layout wire costs and adjacency performance? As explained, we cannot expect to have accurate wire length data for cerebral cortex. However, another strategy is to use our earlier *C. elegans* databases as a test bed for such queries; a positive picture for the worm would motivate exploring a similar working hypothesis for

Abbreviation: NP, nondeterministic polynomial.

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Table 1. Combined connection and adjacency matrix for macaque visual cortex

	V1	V2	V3	VP	V3a	V4	DP	VOT	V4t	MT	MSTd	MSTl	FST	PITd	PITv	CITd	CITv
V2	<u>2</u>																
V3	2	<u>2</u>															
VP	0	<u>2</u>	1														
V3a	2	2	<u>2</u>	2													
V4	2	<u>2</u>	<u>2</u>	<u>2</u>	<u>2</u>												
DP	0	0	0	0	<u>2</u>	<u>2</u>											
VOT	0	2	0	2	0	<u>1</u>	0										
V4t	1	1	2	0	0	<u>2</u>	0	0									
MT	2	2	2	2	2	<u>2</u>	0	0	<u>2</u>								
MSTd	0	2	2	2	2	0	2	0	1	<u>2</u>							
MSTl	0	2	0	0	2	0	1	0	1	<u>2</u>	<u>0</u>						
FST	0	1	2	1	2	2	1	0	2	<u>2</u>	2	<u>2</u>					
PITd	0	0	0	0	0	<u>2</u>	0	<u>1</u>	<u>0</u>	<u>0</u>	1	0	<u>1</u>				
PITv	0	0	0	0	0	2	0	<u>1</u>	0	0	1	0	1	<u>0</u>			
CITd	0	0	0	0	0	2	0	0	0	0	0	0	0	<u>0</u>	<u>0</u>	1	
CITv	0	0	0	0	0	2	0	0	0	0	0	0	0	0	1	<u>2</u>	<u>0</u>
PO	2	<u>1</u>	<u>1</u>	1	1	0	2	0	1	1	2	2	0	0	0	0	0
PIP	2	<u>1</u>	<u>2</u>	2	<u>0</u>	2	2	0	0	2	0	0	0	0	0	0	0
LIP	0	0	2	1	1	2	<u>2</u>	0	0	2	1	2	0	1	0	0	0
7a	0	0	0	0	0	<u>0</u>	<u>2</u>	0	0	<u>0</u>	<u>2</u>	0	1	0	0	0	0
STPp	0	0	0	0	0	0	0	0	0	0	<u>2</u>	<u>2</u>	<u>2</u>	0	0	1	1
STPa	0	0	0	0	0	0	0	0	0	0	0	0	<u>0</u>	0	0	0	0
AITd	0	0	0	0	0	0	0	0	0	0	0	0	<u>0</u>	1	1	<u>1</u>	2
AITv	0	0	0	0	0	2	0	0	0	0	0	0	0	1	2	1	<u>2</u>
TF	0	<u>0</u>	2	<u>2</u>	0	<u>2</u>	0	<u>0</u>	0	0	1	0	2	0	<u>1</u>	0	<u>1</u>
TH	0	<u>0</u>	0	0	0	2	0	0	0	0	0	0	0	0	1	1	1

The series of 17 core visual areas shown in Fig. 3 are listed (V1–CITv), in the order in which they are successively added to the analysis. They are followed by the set of 10 edge areas for the total core (PO–TH). Connections of an area to itself are excluded. 0 indicates no known connection between the area of that row and of that column; 1 indicates connection in one direction between the two areas; 2 indicates two-way connection. Bold cell values designate topological contiguity of the two areas on the cortex sheet, as in Fig. 3 (ref. 25, www.psychology.ncl.ac.uk/jack/gyri.html, and ref. 26). Adjacencies are from Felleman and Van Essen (15). Adjacencies do not include diagonals, where only corners of two areas are contiguous (e.g., V3a and LIP in Fig. 3); similarly for all analyses below. Because of incomplete information, the macaque visual cortex edgering has a gap at PS, 29, and 30.

the cortex. In fact, the nematode layouts that perform best for the above simple adjacency rule also perform very well in terms of wire cost. This type of comparison can be generalized: Fig. 1 is a dispersion diagram for 100,000 randomly sampled worm ganglion layouts (see Fig. 7, which is published as supporting information on the PNAS web site). The amorphous cloud of points indicates that, generally, adjacency rule conformance is

not an efficient means to good wire cost. However, the narrow trail of points at the far lower left of Fig. 1 suggests a special case: extremely good, near-optimal adjacency rule performance does correlate well with very good wire cost (see also Fig. 6).

It should be noted that Fig. 1 shows that merely connecting components to their neighbors will not optimize wire cost; only a layout that is optimized in turn for adjacency rule conformance will do that. Hence, a regress: optimal wire cost can be approximated via optimal adjacency rule conformance, but now the wire cost minimization problem has been replaced by another combinatorial optimization problem of the same NP level of computational complexity (21). [The 2D adjacency-rule placement problem is NP-complete. It can be efficiently reduced to Hamiltonian Path (see ref. 10, problem GT39) (T. Schaefer, personal communication).] [In turn, adjacency optimization itself can be achieved via an evolutionary process such as a genetic algorithm, e.g., we have so implemented our GenAlg (22).] That the worm's connection matrix should be just such that the best adjacency rule layouts match the very cheapest wire cost ones, although the set of all others does not, may be an instance of the type of connection matrix fine-tuning we reported (22) for a force-directed placement algorithm, i.e., that the worm's set of connections appears to be just such that it has relatively few local minima traps.

Size Law

So, the first provisional conclusion is that very good adjacency performance is indeed worth examining as a feasible, surrogate index of connection-optimization for layout of cortical areas.

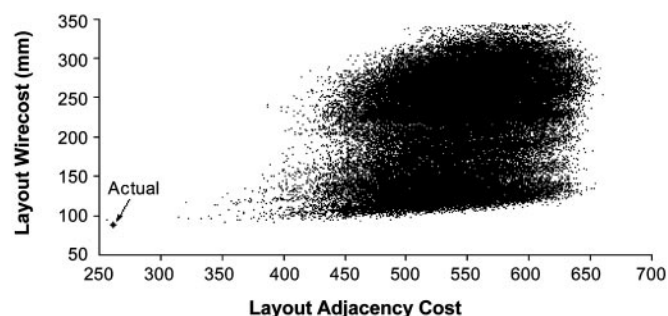


Fig. 1. Adjacency rule conformance, vs. total wire cost, of 100,000 *C. elegans* ganglion layouts randomly sampled from the set of all 11! possible layouts (2). Correlation between adjacency rule performance and wire cost is not strong ($r^2 = 0.051$); in general, the adjacency rule is not an effective means to good wire cost. However, the small set of layouts best fitting the adjacency rule (the points at the far left) behave markedly differently: they correspond closely to the best wire cost layouts. The larger point at the far left represents the actual, minimum wire cost layout. Thus, good adjacency rule scores seem worth exploring as a surrogate for layout wire cost (see Fig. 7).

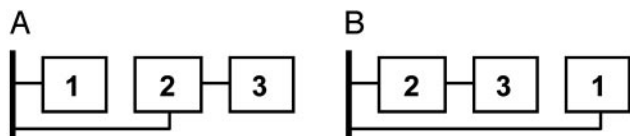


Fig. 2. Global vs. local optimization. A simple illustration shows that connection-minimization of a total system does not entail connection-minimization of its subsets. The total system here consists of a 1D array of movable components, 1–3, with fixed edge-terminal (vertical bar) at left. All connections are of equal cost per unit length (horizontal only). Besides internal connection 2–3, 1 and 2 go to the left edge. (A) A globally optimal layout (cost: 4). However, if the system-subset is restricted only to components 2 and 3 with their outgoing connection to the left edge, then the 2 and 3 layout is (locally) suboptimal (cost: 3) compared with a layout with positions of 1, 2, and 3 swapped (cost: 2), as in B. In contrast, the complete layout (B) is locally optimal for subsystem 2 and 3, but at the expense of a higher cost for the total layout (cost: 5).

Another difficulty is that cortical connection and adjacency information is not complete: For macaque (15) and cat (16), the anatomy is satisfactory for the visual areas, usable also for auditory and somatosensory areas, but only partial for frontal-limbic areas. Therefore, any near-term optimization analysis of the cortex will not include the entire system, but only large subsets. On the working hypothesis that the total system was perfectly optimized, what level of optimization would be expected for such a subset? To begin with, the following size law can be conjectured:

If a set of connected components is optimally placed, then, the smaller a subset of the total layout, the less optimal it will tend to be.

The idea of a proof begins with the familiar observation, that global optimality need not yield local subsystem optimality; local means-ends sacrifices are often required for the best overall solution. Furthermore, as an isolated subset of the total optimized system gets smaller, its own constraints (e.g., local-global tradeoffs) will be likely to depart more and more from those of the total layout, and so the subset by itself is less likely to be as well optimized. However, not all types of optimized networks obey such a size law: For instance, a uniform fabric mesh with just a regular, repeating pattern of connections between adjacent nodes, such as among wire intersections in chain-link fencing, will show perfect adjacency-rule optimization for all sizes of subsets (see Fig. 2).

Typical connection costs to be minimized are total wire length, or violations of an adjacency rule. For an n -component layout, there are $n!$ possible layouts. Optimality of a given layout can be expressed in terms of the percentile rank of its cost relative to all other alternative layouts, i.e., the proportion of all layouts that have a lower cost.

How do neural systems behave? The size law can first be evaluated for the 11-component worm ganglion system, with total layout wire length as the cost measure. A nested chain of ganglion subsets was generated, each composed of contiguous elements, proceeding from head to tail, from 4 to the full 11 components. The cost of each subset of the actual layout was compared with all possible alternative layouts of that subset of components. (Components external, but immediately contiguous, to a subset are included in the analysis as fixed “edge” constraints.) For the smallest set, 8.33% of all layouts are better than the actual layout; this performance monotonically improves, up to the full 11-component set, for which (as reported in refs. 2 and 23) no layout is better than the actual one. In addition, when optimality (proportion of layouts better than actual) is plotted logarithmically against subset size, the descending curve closely approximates a straight line ($r^2 > 0.99$, $P <$

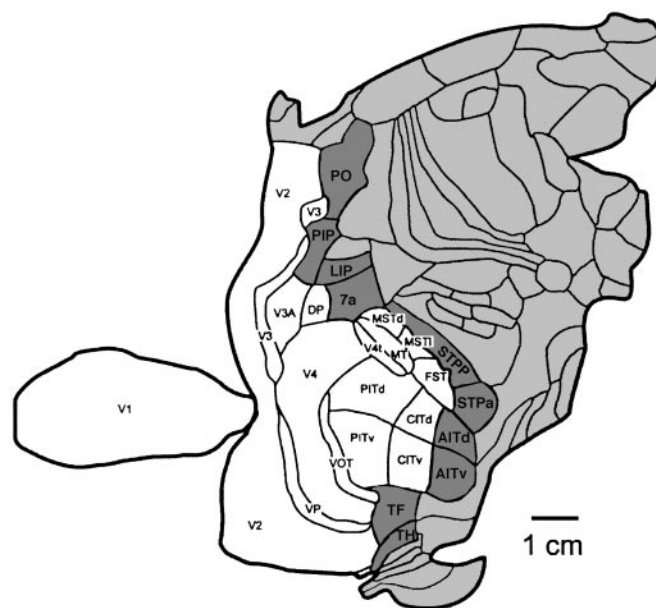


Fig. 3. Parcellation of macaque cerebral cortex. Connection-cost optimization analysis of layout of 17 core areas of the visual cortex (white), along with 10 immediately contiguous “edge” areas (dark gray). Placement of the inter-connected functional areas is evaluated for how well total interconnection costs are minimized. A total of 120 connections are reported among the core areas and with the edge areas. Core and edge areas are listed in Table 1. Rostral is to right. Figure is after Felleman and Van Essen (figure 2 in ref. 15 and figure 6 in ref. 24); areas MIP and MDP have been included in PO.

0.001), suggesting the growth function is in fact a simple exponential one.

Mammalian cortex optimization is of at least as much interest as worm ganglion optimization. Yet, as explained, connection length data are not in general available, and even in the best cases (macaque and cat), adequate information on connections and adjacencies exists mainly for sensory areas. In addition, there is the double-bind that, according to the size law, component sets that are large enough to be well optimized will tend to be too large for feasible search of all layouts. We first evaluated the size law for 17 contiguous core visual areas of macaque cortex (see Fig. 3), with conformance to the adjacency rule as optimality measure. For the macaque visual cortex areas, we constructed a matrix of ipsilateral intracortical connections and a topological database of adjacencies among the areas (15, 25). Areas outside of the core set, but along the immediate periphery of the group, were treated again as fixed edge components (see Table 1). A nested series of compact subsets was generated, each composed of contiguous elements. Although actual cortical areas form a jigsaw puzzle of widely differing sizes and shapes, they are approximated here as uniformly interchangeable: For example, when V1 and V2 are swapped, V1 adjacencies are assigned to V2, and vice versa, whereas V1 and V2 each retain their original connections. (Thus, as also to a lesser extent for the worm ganglion problem, actual cortical layouts are in fact even being tested against some topologically impossible alternative layouts.)

Fig. 4A shows that the size law seems to apply well to the actual cortex layout and does not hold for a corresponding scrambled calibration set. The logarithmic scale of the y axis should be noted: the size law curve fits a straight line well ($r^2 > 0.91$, $P < 0.001$), suggesting, as for the much more complete worm ganglia subset series, a simple exponential growth function. It should be emphasized that the “total set” here consists of only 17 components of the entire ≈ 73 area macaque cortical system and does not include extracortical efferent and afferent connections. The

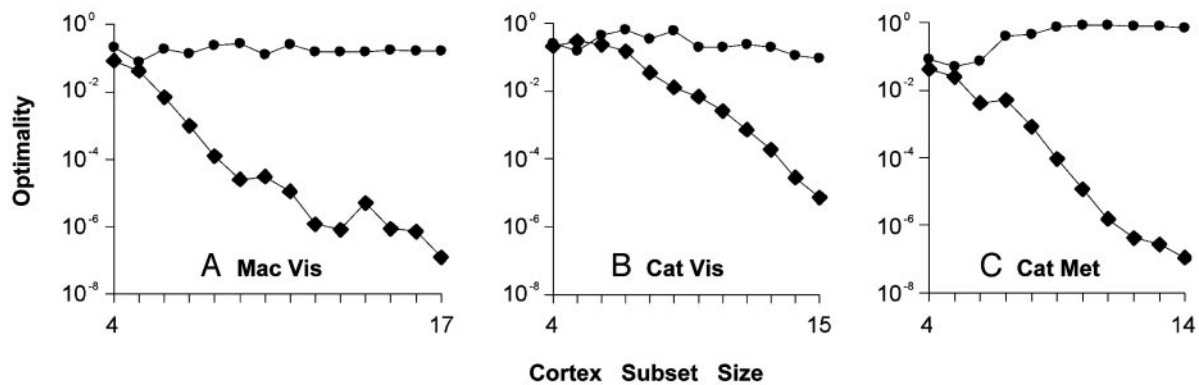


Fig. 4. Size law for cortex areas. In each case, a series of nested compact subsets of the set of cortical areas was generated, each consisting of from four to the full set of areas. Each subset of the actual layout was compared with all possible alternative layouts of that subset for optimality; optimality-measure is conformance of the system to the adjacency rule (2). Sixteen- and 17-element sets were each compared only with random samples of 10^9 alternative layouts. (A) The system of components is 17 contiguous macaque visual cortex areas as in Fig. 3, with connections and adjacencies as in Table 1, and order of successive elements added as in Table 1. (B) Similar analysis for 15 cat visual cortex areas. (C) Fourteen cat cortex metamodules composed from 40 Brodmann areas of visual, auditory, and somatosensory regions (see Figs. 8, 10, and 11, which are published as supporting information on the PNAS web site). In each case, the actual layout curve (diamonds) shows that smaller subsets rank approximately in the middle of their group of alternative layouts. But, as subset size increases, optimality-ranking of the actual layout consistently improves (with one or two exceptions in each series, $P < 0.02$). E.g., for macaque, fewer than one in a million of all alternative layouts conform to the adjacency rule better than the actual layout of the complete macaque set. For comparison, each scrambled layout curve (circles) shows the corresponding analysis for layouts of the areas with their adjacencies randomly shuffled; no size law trend toward improving optimality is now evident.

size law provides an account of how such an incomplete system would attain only an optimality ranking in the top 10^{-7} of all possible layouts, even if the complete system were in fact perfectly optimal.

We similarly analyzed placement optimization for all 15 contiguous visual areas of cat cortex (along with a fixed edge zone of immediately surrounding areas) (Fig. 9, which is published as supporting information on the PNAS web site). From published anatomy (ref. 16, Fig. 1 with corrections, and ref. 27), we constructed a matrix of cat ipsilateral intracortical connections and a topological database of adjacencies among the Brodmann areas. (Area SVA is included in 17, ALG in 19; DP in EPP and AI, V in VP and AII, SSF in EPP; some boundary indeterminacies remain unresolved; see Table 3, which is published as supporting information on the PNAS web site.) The results (Figs. 4B and 10) confirm the picture for macaque visual cortex: again, there is a significant size law effect, with smaller subsets of the actual layout ranking only in the midrange among all possible layouts, but larger subsets performing progressively better in their relative ranking for adjacency rule optimality. Optimality improves exponentially with subset size.

Naturally, these two visual cortex series raise the question of how much finer optimality even larger subsets of the actual layout attain, for instance, as observed via simple random samples of the extremely large total sets of all alternative possible layouts (28, 29). For cat sensory cortex (visual, auditory, and somatosensory), anatomical data for 39 contiguous Brodmann areas was adequate for such an analysis. When the subset was extended from the above 15 visual areas to 20 areas, a sample of a billion of all possible 10^{18} layouts showed a rise of actual layout rank from 10^{-5} into the top 10^{-8} of all layouts. (That is, only three layouts of a billion sampled were better than the actual layout.) For a 25-area subset, a billion-layout random sample yielded no placements cheaper than the actual one, suggesting the actual layout's ranking may be too high to be detectable at this sample size. Similarly no layouts cheaper than the actual one were found for 30 areas, and also up to 39. Although this is, of course, the most striking finding reported here, it should be interpreted with some care; to begin with, larger sample sizes are warranted. For the 39-area cat cortex layout, we performed three separate random samplings, each of 100 billion layouts from the 10^{46} alternative possible layouts: we found no layouts with better

adjacency-rule optimization than the actual one. However, with only 39 of the total 57 areas included in this analysis, the size law would suggest the 39 areas need not be perfectly optimally laid out, even if the total 57-component system was. (In addition, of course, the neuroanatomical database inevitably still includes errors.) We therefore constructed a simple genetic algorithm, along the lines of one we had developed for the worm ganglion placement problem (22); it quickly finds layouts of the 39 areas cheaper than the actual one.

Metamodule Grouping

Of course, exhaustive search of all $57!$ alternative layouts of the 57 Brodmann areas of cat cortex ($= 4 \times 10^{76}$ layouts) would be cosmically unfeasible (2, 23). Another sampling strategy is instead to unite and conquer: Cluster the Brodmann areas of the actual layout into groups of topologically contiguous components, then search the smaller set of alternative placements of these locked-down "metamodules" (see Table 4, which is published as supporting information on the PNAS web site). This strategy is based on a metamodule conjecture:

If a set of connected components is optimally placed, then a set of metamodules, each consisting of a subset of those components in the same positions, is also optimally placed.

Figs. 4C and 11 show size law optimization performance of a series of nested layouts of 14 metamodules composed of 40 cat cortical areas. Each metamodule was grouped from adjacent Brodmann areas, all of the same modality (visual, auditory, then somatosensory); metamodules were assembled to have approximately equal numbers of areas, to be of approximately equal area, and to be as compact as possible. The main observation is that the full 14-metamodule layout now approaches the top ten-millionth level of optimization, comparable to that found for the worm ganglion system. The size law curve again fits a straight line well ($r^2 > 0.97$, $P < 0.001$). The consistency of the entire size law trend here constitutes further convergent support for the basic cortical optimality conclusion.

Nonneural Networks

As a further calibration of the methods here, we analyzed connection optimization of two types of nonneural systems: a computer microchip and macroeconomic commodity-flow networks. The chip was AMI49, the largest of the set of MCNC

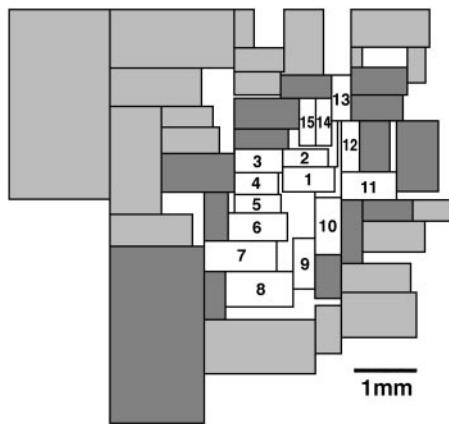


Fig. 5. Integrated circuit network for calibration of optimality analysis: AMI49 microchip, the largest of the MCNC set of benchmark circuits, with 49 modules,⁵ Lin and Chang layout. Cost to be minimized is total wire length.¹¹ The central 15 blocks (white), along with the surrounding edge-zone of immediately contiguous blocks (dark gray), were analyzed. Again, placement of the interconnected areas is evaluated for how well total interconnection costs, adjacency rule violations, are minimized (see Figs. 12 and 13 and Table 5).

microcircuit benchmarks,⁸ which contains 49 blocks or modules, comparable to the number of functional areas in one cortex hemisphere. We studied three AMI49 layouts of fully automatic design, with costs to be minimized: (i) a function of layout area and maximum path delay (30); (ii) a “blended” function of area and total wire length (31); and (iii) total wire length¹¹ (see Fig. 5 and Fig. 12, which is published as supporting information on the PNAS web site). In each case, the central 15 blocks of the chip, along with the surrounding edge-zone of immediately contiguous blocks, was analyzed (see Table 5, which is published as supporting information on the PNAS web site). Again, placement of the interconnected areas was evaluated for how well total interconnection costs (adjacency rule violations) are minimized, with the actual layout compared with alternative possible layouts. The size law curve for the minimum wire length layout (iii) showed the same pattern as for the cortex networks, although somewhat weaker; the full 15-component subset attains an optimality rank of 10^{-3} (see Fig. 6 and Fig. 13, which is published as supporting information on the PNAS web site). Neither of the other AMI49 layouts showed a size law pattern, nor did either attain significant optimality. (In comparisons with the cortex, it should be recalled that, unlike for chips, information on cortex wiring is still not complete.) So, for these calibration networks, adjacency rule conformance seems capable of distinguishing a target of wire length minimization from some other related cost measures. And again, as for the scrambled layouts earlier, adjacency costing does not seem to inflate optimality rankings (see also Figs. 1 and 2).

The macroeconomic system studied was U.S. states (see Fig. 14, which is published as supporting information on the PNAS web site). The “connection” cost to be minimized was combined “export + import” commodity flow (in American dollars) between nonadjacent units. (Because nearly all cells in the matrices have non-0 values, economic transactions above a threshold were analyzed, with cutoff set here to yield approximately the same connectivity density as for macaque and cat cortex above; see Table 2.) Optimality measure was conform-

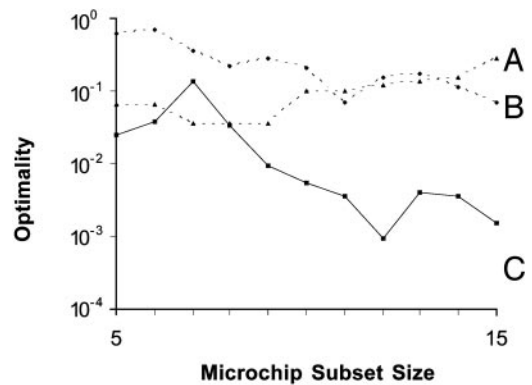


Fig. 6. Size law for three layouts of the AMI49 chip. In each case, the system of components is 15 contiguous central blocks, as in Fig. 5 (connections and adjacencies for Lin and Chang are as in Table 5). Optimality measure is conformance of the system to the adjacency rule, with a layout scored in terms of its number of all-or-nothing violations. A series of nested compact subsets of the set of blocks was generated, each consisting of from 5 to the full 15 areas. Each subset of the actual layout was compared with all possible alternative layouts of that subset for adjacency-rule optimality (14- and 15-element sets were each compared only with random samples of 10^9 alternative layouts). The curve for the Lin and Chang¹¹ layout (C) shows a similar but weaker size law trend as the cortex networks earlier; the full 15-component subset only attains an optimality rank of 1.5×10^{-3} . Both the Esbensen and Kuh (30) layout (A) and the Hong *et al.* (31) layout (B) show no size law pattern.

ance of the system to the simple “all or nothing” adjacency rule, with each layout scored in terms of its number of violations of the rule. For U.S. interstate commodity flow, a core of 15 central contiguous states, along with a surrounding edge-zone of immediately contiguous states, was analyzed (32) (see Table 6, which is published as supporting information on the PNAS web site). We similarly analyzed as pilot data European international commodity flow among eight countries (33). The total U.S. system attains perfect connection-optimization. The smaller European nation set shows a similar pattern. (See Fig. 15, which is published as supporting information on the PNAS web site.) As calibration, a scrambled layout of the U.S. system shows no optimization. This powerful performance of the optimization model (rather than a mere satisficing model) may appear to vindicate the wisdom of the hive, the “invisible hand” of laissez-faire economics. Indeed, very fine component placement optimization may thereby seem a rather pervasive phenomenon. However, each macroeconomic series completely departs from the size law pattern; in particular, smaller subsets already attain perfect optimality, with no alternative layouts better than the actual one. So, optimality does not necessarily entail conformance to the size law. This breakdown suggests the macroeconomic networks are optimized only via local processes, unlike the cortex (and some chip) networks. In contrast, conformance of the cortex systems to the size law suggests they are instead “high-tradeoff” networks requiring long-range micro/macro exchanges of local optimality for global optimality.

Conclusion

For each cortical network above, the population distribution of costs of alternative possible layouts conforms well to a normal distribution. For each neural system, when connections to/from surrounding edges are excluded from the analysis, optimality of the actual layout decreases. Conversely, when weighting information on connection strength is included in the adjacency-rule costing, actual layout optimality improves over simple all-or-nothing costing. Similarly for r^2 fit to the size law. On an assumption that the more realistic the modeling, the more

⁵International Workshop on Layout Synthesis, May, 1992, Research Triangle Park, NC.

¹¹Lin, J.-M. & Chang, Y.-W., Proceedings of the ACM/IEEE Design Automation Conference, June 18–22, 2001, Las Vegas, NV.

optimal a network should appear, these trends further confirm the optimality assessment.

The convergent set of “best of all possible brains” results reported here (see Table 7, which is published as supporting information on the PNAS web site) raises the issue: are complete mammal cortex layouts in fact optimal, as the total *C. elegans* ganglion layout appears to be? As for minimum-volume neuron arbors (4), optimal cortex may be just an initial plan that can be modified and elaborated. Natural next questions arise about optimization mechanisms, for instance, direction of causation—from connections to positioning, or vice versa, or both. Although the point should be interpreted with some care, each of the cortex systems analyzed here shows better goodness of fit to an “if connected, then adjacent” hypothesis than to the converse hypothesis. [The test consists of comparing, for each actual layout (see Table 2), its number of counterexamples to “if connected, then adjacent” with the number of counterexamples to the converse hypothesis; the comparison includes a correction for unequal populations of connections and adjacencies. The scrambled calibration layouts show no bias in either direction.] It is also worth noting that, for the *C. elegans* optimization problem, we have demonstrated simple mechanisms that proceed solely from connections to adjacencies, namely, a genetic algorithm, and also a force-directed placement algorithm (22). A

similar genetic algorithm was described above for cat sensory cortex.

This discussion has focused on neuroanatomy, upon minimization of biological connection-structures. However, the above macroeconomic analyses really concerned abstract, functional “connections,” i.e., commercial transactions. We thereby proceed from anatomy to physiology broadly conceived. The adjacency rule then generalizes, If components are connected in the wider sense of causal interrelation, then they are topologically adjacent. (No action at a distance.) For instance, the large-scale optimization landscapes of cortex and genome may be worth comparing: the structure of the genome would be analyzed similarly as above. Two genes might count as connected if they are coactivated, (approximately) contemporaneously expressed. Contiguity would be interpreted as proximity of position in the 3D genome structure. In fact, a first step toward such an approach may be a recent study of clustering of highly expressed genes in chromosomal domains (34).

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