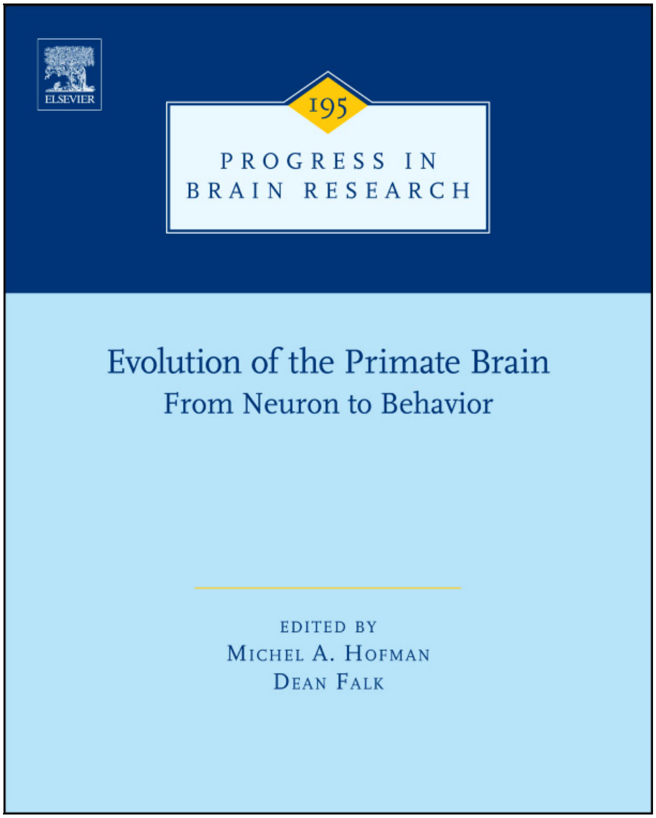

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CHAPTER 17

Neural wiring optimization

Christopher Cherniak*

Committee for Philosophy and the Sciences, Department of Philosophy, University of Maryland, College Park, MD, USA

Abstract: Combinatorial network optimization theory concerns minimization of connection costs among interconnected components in systems such as electronic circuits. As an organization principle, similar wiring minimization can be observed at various levels of nervous systems, invertebrate and vertebrate, including primate, from placement of the entire brain in the body down to the subcellular level of neuron arbor geometry. In some cases, the minimization appears either perfect, or as good as can be detected with current methods. One question such best-of-all-possible-brains results raise is, what is the map of such optimization, does it have a distinct neural domain?

Keywords: Adjacency Rule; *Caenorhabditis elegans*; cerebral cortex; component placement optimization; Size Law; Steiner tree; volume minimization; wirelength minimization.

Introduction

Neuroconnectivity architecture sometimes shows virtually perfect network optimization, rather than just network satisficing. Long-range connections are a critically constrained resource in the brain, hence, there may be great selective pressure to optimize finely their deployment. The formalism of scarcity of interconnections is network optimization theory, which characterizes efficient use of limited connection resources. The field matured decades ago for microcircuit design, typically to minimize the total length of wire needed to make a given set of connections among components. For layout of neural components, such connection minimization has been reported for the nematode nervous system (Cherniak, 1994a), rat amygdala and olfactory cortex (Cherniak and Rodriguez-Esteban, 2010), cat sensory cortex, and macaque visual cortex (Cherniak et al., 2004). Corresponding arbor optimization also applies for some types of dendrites and axons (Cherniak et al., 1999). Results for more primitive nervous systems help fill in some of the evolutionary trajectory of neural optimization phenomena.

Such optimality contrasts with the familiar picture for biological design, of only moderately good engineering: for example, the first chapter

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*Corresponding author.
Tel.: +1-301-405-5689; Fax: +301-405-5690
E-mail: cherniak@umd.edu

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of *Descent of Man* (Darwin, 1871) enumerated many instances of rudimentary structures in humans that are no longer in use (although the neural examples are in fact functional). Instead, it is almost as if neural connections had an unbounded cost. When this simple "save wire" idea is treated as a generative principle for nervous system organization, it turns out to have some applicability: To an extent, across evolutionary levels, wire-minimization yields brain structure.

A caveat is that, in general, network optimization problems are easy to state, but vastly computationally costly to solve exactly. These connection cost-minimization problems are a major hurdle of microcircuit design and are known to be NP-complete (nondeterministic polynomial time complete), that is, *de facto* intractable (Garey and Johnson, 1979). Computation costs of solving problems of comparatively small size typically grow exponentially, to cosmic scale: exactly solving some could consume more space and/or time than exists in the known Universe. The archetypal example of an NP-complete problem is Traveling Salesman: For a given set of points on a map, simply find the shortest roundtrip tour.

Neuron arbor optimization

The basic concept of an optimal tree is as follows: Given a set of loci in 3D space, find the minimum-cost tree that interconnects them, for instance, the set of interconnections of least total volume. If branches are allowed to join at points other than the given terminal loci (the "leaves" and "root"), the minimum tree is of the most economical type, a Steiner tree. If the synapse sites and origin of a dendrite or axon are treated in this way, optimization of the dendrite or axon can be evaluated. Approximately planar arbors in 2D space are simpler to analyze. The most important feature of naturally occurring arbors—neuronal, vascular, plant, water drainage networks, etc.—is that, unlike much manufactured circuitry, for each internodal junction, trunk cost (e.g., diameter) is higher than branch costs.

Local trees

When such Y-junctions are examined in isolation, positioning of the junction sites shows minimization of total volume cost (vs. surface area or length) to within about 5% of optimal (Cherniak, 1990, 1992; 7 of 25 datasets were from primates). In turn, the relation of branch diameters to trunk diameter fits a simple fluid-dynamical model for minimization of walldrag of internal laminar flow in a tree of tubes: Dendrites and axons act like flowing water.

Global trees

This Y-tree cost-minimization constitutes local optimization. Only one interconnection pattern or topology is involved. Such small-scale optimization does not entail larger-scale optimization, where local trade-offs are often required. When more complex portions of a total arbor are analyzed, optimization becomes a global problem, with an exponentially exploding number of alternative possible interconnection topologies. For example, a nine-terminal tree already has 135,135 alternative topologies, each of which must be generated and costed to verify the best solution (see Fig. 1). Neuron arbor samples, each with three internodal Y-junctions and a distribution of different topologies, minimize their volume to within about 5% of optimal (Cherniak et al., 1996, 1999). This optimality performance is consistent for dendrites (rabbit retina ganglion and amacrine cells, and cat retina ganglion cells) and also for some types of axons (intrinsic and extrinsic mouse thalamus). One of eight datasets was from primates.

Topology

The pattern for natural arbors, living and nonliving, is that more costly topologies are more common, cheapest ones are rarest. However, the

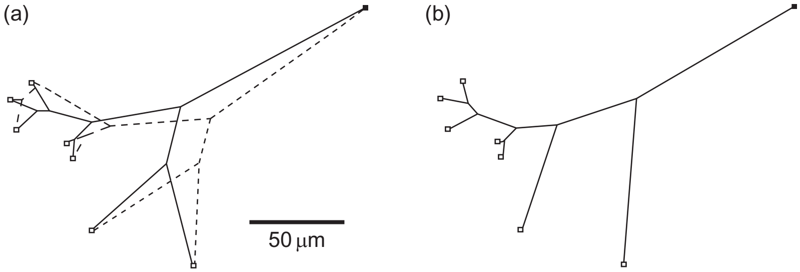


Fig. 1. Actual versus optimal neuron arbors, mouse thalamus extrinsic axon, ascending reticular formation. The arbor best fits a minimized-volume model. (a) Wireframe representation of eight-terminal subtree of observed arbor. Actual tree, with actual topology in its actual embedding, appears in broken lines. Optimal embedding with respect to volume minimization of the actual topology is superimposed in solid lines. The cost in volume of the actual arbor exceeds that of the optimized embedding of its topology by 2.20%. (b) "Best of all possible topologies" connecting the given terminal loci: the optimal topology with respect to volume, optimally embedded. The volume cost of the actual arbor exceeds that of the optimal topology by 2.47%. Only 10 of the 10,395 possible alternative topologies here have lower total volume costs, when optimally embedded, than the actual topology (reprinted with permission from Cherniak et al., 1999).

most costly optimally embedded "pessimal" topologies have relatively little higher cost than the cheapest ones. In this sense, to a first approximation, "topology does not matter". Consequently, neuron arbor anatomy behaves like flowing water, and waterflow in turn acts like a tree composed of weights and pulleys (rather than springs). Fluid dynamics drives fluid statics, that is, vector mechanics. Hence, "instant arbors, just add water," that is, neuroanatomy from physics.

Component placement optimization

Another key problem in microcircuit design is component placement optimization (also characterized as a quadratic assignment problem). Given a set of interconnected components, find the location of the components on a 2D surface that minimizes total cost of connections (e.g., wirelength). A familiar example is siting of computer chips on a motherboard. Again, this concept seems to account for aspects of neuroanatomy at multiple hierarchical levels.

Why the brain is in the head is a one-component placement problem. That is, given the fixed loci of receptors and muscles, positioning the brain as far forward in the body axis as possible minimizes total nerve connection costs to and from the brain, because more sensory and motor connections go to the anterior than to the posterior of the body. This seems to hold for the vertebrate series (e.g., humans) and also for invertebrates with sufficient cephalization to possess a main nervous system concentration (e.g., nematodes).

Caenorhabditis elegans

As for arbors, multiple-component problems again generally require exponentially exploding costs for exact solutions; for an n-component system, $n!$ alternative layouts must be searched. A typical neural wiring optimization result is for placement of the 11 ganglionic components of the nervous system of the roundworm *C. elegans*, with ~1000 interconnections. This nervous system is the first to be completely mapped (Wood, 1988), which enables fair approximation of connection wirelengths. When all 39,916,800 alternative possible ganglion layouts are generated, the actual layout turns out in fact to be the one with minimum total wirelength (Cherniak, 1991, 1994a, 2003a).

Some optimization mechanisms provide convergent support for this finding: A simple genetic algorithm, with wirecost as fitness measure so that shorter wirelength worm layouts are more likely to survive, will rapidly and robustly converge upon the actual optimal layout (Cherniak et al., 2002; see Fig. 2). Also, a force-directed placement algorithm, with each connection approximated as a weights-and-pulleys mechanism (non-Hooke's law, i.e., not a spring) acting between ganglion components, attains the actual layout as a minimum-energy state, with little local-minima trapping (Cherniak et al., 2002; see Fig. 3). Each of these wire-minimization mechanisms operates top-down: that is, each proceeds from nervous system connections to positioning of neural components; vice versa is not necessary.

There is statistical evidence that this brain-as-microchip framework also extends in the worm down to the level of clustering of individual neurons into ganglionic groups, and to soma positioning within ganglia to reduce connection costs (Cherniak, 1994a).

Cortex

The wiring-minimization approach can be applied to placement of functional areas of the vastly more complex mammalian cerebral cortex. In contrast to the fixed character of neural development in invertebrates such as nematodes, it is striking that optimization also holds for malleable mammal brains. Since wirelengths and branch patterns of corticocortical connections are difficult to estimate, one strategy is instead to explore a simpler measure of connection cost, conformance of a layout to a wire-conserving Adjacency Rule:

> If components *a* & *b* are connected,
> then *a* & *b* are adjacent.

Exhaustive search of all possible layouts is still required to identify the cheapest one(s). A promising calibration is that the actual minimum-wire layouts of the nematode ganglia are among the top layouts with fewest violations of the Adjacency Rule. One primate cortex example is that, for 17 core visual areas of macaque cortex,

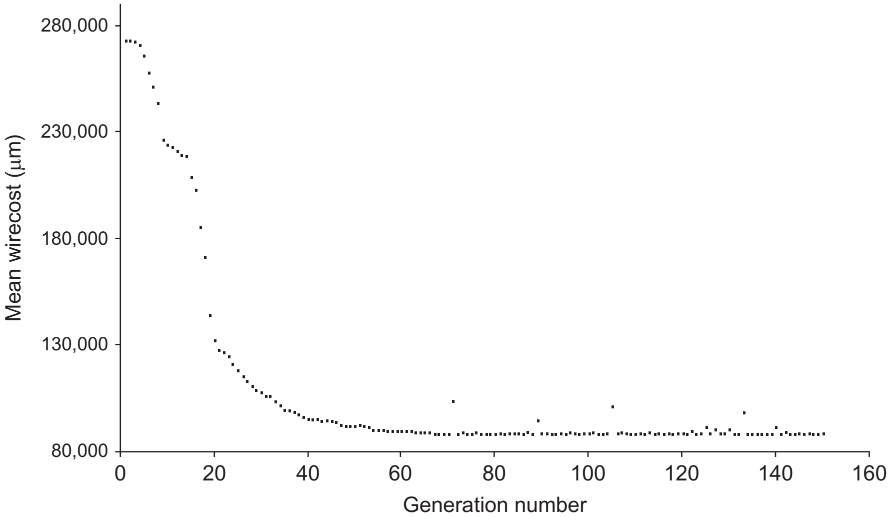
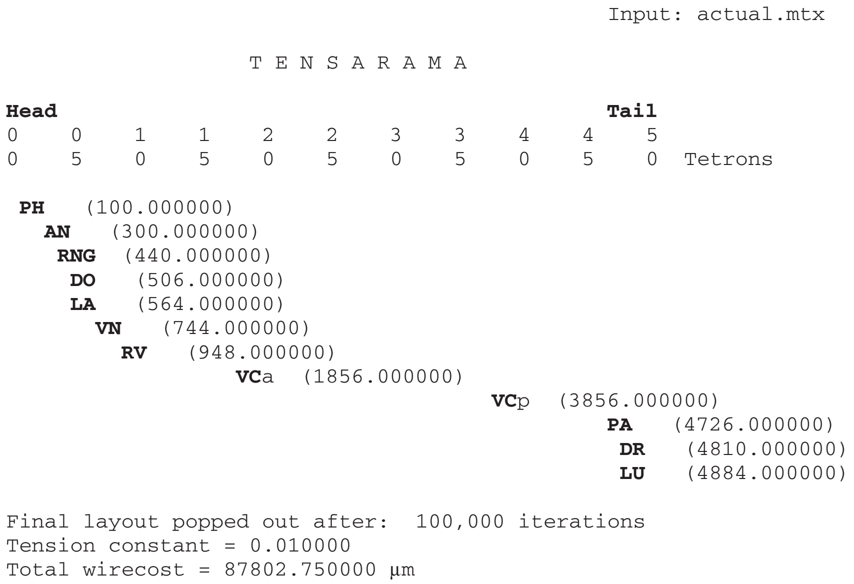


Fig. 2. A simple genetic algorithm, GenAlg, rapidly and reliably finds the optimal layout of *C. elegans* ganglia among 11! alternatives. Fitness measure for survival is total wirelength of individual nervous system. The initial population of this run was only 10 individuals, all with reverse of actual ordering of ganglia (reprinted with permission from Cherniak, 2005).



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                                               Input: actual.mtx

                   T E N S A R A M A

Head                                           Tail
0    0    1    1    2    2    3    3    4    4    5
0    5    0    5    0    5    0    5    0    5    0  Tetrons

 PH   (100.000000)
   AN   (300.000000)
    RNG  (440.000000)
     DO   (506.000000)
     LA   (564.000000)
       VN   (744.000000)
         RV   (948.000000)
                  VCa  (1856.000000)
                                      VCp  (3856.000000)
                                               PA   (4726.000000)
                                                DR   (4810.000000)
                                                LU   (4884.000000)

Final layout popped out after:  100,000 iterations
Tension constant = 0.010000
Total wirecost = 87802.750000 μm
```

Fig. 3. Runscreen for a force-directed placement algorithm, Tensarama, for optimizing layout of ganglia of the nematode *C. elegans*, that is, minimizing total length of interconnections. This vector-mechanical simulation represents each of the roundworm's ∼1000 interconnections as a weights-and-pulleys mechanism (as opposed to a spring) acting upon the horizontally movable ganglia "PH," "AN," etc. Connections themselves do not appear on runscreen nor fixed components such as sensors and muscles. The screendump here shows the final configuration of the system after 100,000 iterations (reupdate cycles for forces and locations). The system has terminated with the global minimum-cost positioning of the ganglia (using about 8.7cm total of wire), which is also the actual layout. In this way, physics suffices to generate this neuroanatomical structure, out of ∼40 million alternative possible configurations (reprinted with permission from Cherniak et al., 2002).

the actual layout of this subsystem ranks in the top 10^{-7} layouts best fitting this adjacency costing. For 15 visual areas of cat cortex, the actual layout ranks in the top 10^{-6} of all layouts (Cherniak, 2003b; Cherniak et al., 2003, 2004; see also Cherniak, 1991, 2003a; Young, 1992). Other examples include rat olfactory cortex and amygdala (Cherniak and Rodriguez-Esteban, 2010; see Fig. 4).

Size Law

In general, a Size Law seems to apply to cases with such local–global trade-offs. If a complete system is in fact perfectly optimized, then the smaller the portion of it considered by itself, the poorer the optimization appears. Or, to reverse the reasoning:

> The larger the proportion of a total optimal
> system that the evaluated subsystem is,
> the better its optimization.

A Size Law applies to each of the above cortex systems (see Fig. 5). For the largest systems studied (visual, auditory, and somatosensory areas of cat cortex), there is evidence along these lines of optimization approaching limits of current detectability by brute-force sampling techniques. A similar Size Law pattern also appears to hold for Steiner tree optimization of neuron arbor topologies (cf. Fig. 1). The overall picture then is of limited connections deployed very well, a predictive success story. The significance of ultra-fine

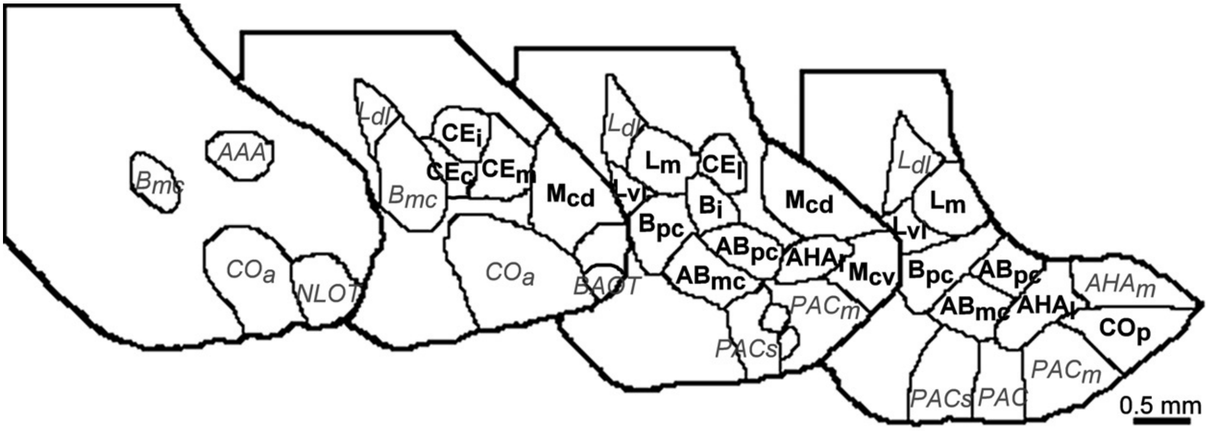

Fig. 4. Rat amygdala represented as a stack of slices: 3D topological interrelations among its nuclei. Fourteen contiguous core components for optimization analysis of their layout are shown with **boldface** labels; immediately surrounding edge areas are in *italic*. For interconnections, and successive subset sizes 1–14, see Table 2, Cherniak and Rodriguez-Esteban (2010).

neural optimization remains an open question. Levels of connection optimization in the nervous system seem unlike levels of optimization elsewhere in organisms.

Related optimization results

Some other recently reported instances of biological network optimization provide perspective on the above neural optimization cases. For example, an amoeboid organism, the plasmodium of the slime mold *Physarum polycephalum*, is capable of solving a maze, that is, not just finding some path across a labyrinth, but a shortest path through it to food sources (Nakagaki et al., 2000). Generating such a minimum-length solution is a network optimization feat for any simple creature. However, it should be noted that this shortest path problem is not computationally intractable; in particular, it is not NP-complete (Garey and Johnson, 1979). "Greedy algorithms" can solve it and also can be implemented as simple vector-mechanical "tug of war" processes. Nonetheless, that a slime mold can optimize a path through a network converges with observations of network optimization in nervous system anatomy. The latter results entail solution of computationally complex (i.e., NP-complete) problems. Such consilience lends support to the neuroanatomical findings.

Path optimization by social insects has also been reported. For example, wood ants (*Formica aquilonia*) form complex tree structures as foraging paths; however, their length by itself is not minimized (Buhl et al., 2009). Bumblebees (*Bombus terrestris*) satisfactorily solve similar Traveling Salesman foraging problems among food sources (Lihoreau et al., 2010), and Argentine ants (*Linepithima humile*) can find efficient tree structures interconnecting their nests (Latty et al., 2011). However, the networks involved have only five or less nodes.

Some critiques have appeared related to the main wiring optimization result reported here for *C. elegans*, that the actual layout of its ganglia has the minimum total wirelength of all 11! alternative possible configurations. Since primate cortex optimization results depend upon the soundness of the nematode results, we review the critiques of the latter. For the exhaustive searches of worm layouts, we employed the

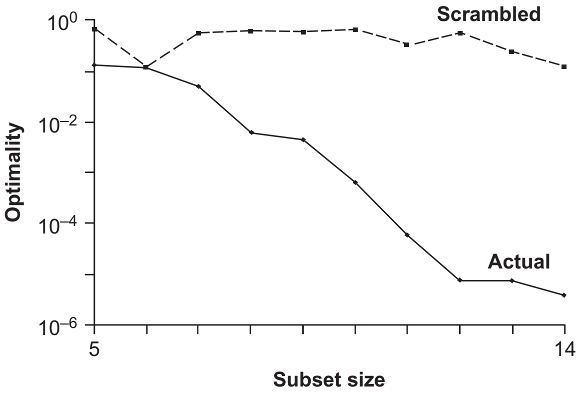

Fig. 5. Rat amygdala layout optimization analysis. Plot of optimality rankings for a series of nested subsets of the 14-area core (see Fig. 4) shown by solid line. For comparison, a randomly generated layout with areas' relative positions scrambled and their interconnections preserved is similarly analyzed for a succession of progressively larger subsets (dashed line). A layout is scored in terms of its violations of the Adjacency Rule. Each nested compact subset is compared with all possible alternative layouts of that subset for Adjacency Rule optimality. A Size Law trend—increasing optimality with increased subsystem size—is apparent for the actual layout, but not for its scrambled control version. For the best-fit line for optimality of the subset series of the actual layout, $r^2=0.96$, $p<0.0001$. Layout optimality rank for the complete amygdala system analyzed is in top 3.9×10^{-6} of all possible layouts of the full 14 areas, comparable to cat and macaque visual cortex (Cherniak et al., 2004) (reprinted with permission from Cherniak and Rodriguez-Esteban, 2010).

simplest cost metric, a linear function of total wirelength; this cost measure also performs well for a force-directed placement simulation, and as fitness measure for a genetic algorithm (Cherniak et al., 2002; see also Figs. 2 and 3 above).

Chklovskii (2004) proposes that wiring cost scales instead as sum of squares of wirelengths, and offers a quadratic minimization analysis of ganglion position. However, among perturbation analyses we had also performed to explore the optimization landscape was an exhaustive search of all 11! layouts with connection cost instead as wirelength squared. The worm's actual layout then drops in rank, from optimal # 1 to # 404,959; the actual layout costs 21% more than the cheapest. So, compared to wirecost=wirelength, a wirelength squared model does not do well in terms of goodness of fit. And, in fact, Chklovskii concludes that this model does not predict actual order of all ganglia, in particular, for the dorsorectal (DR) ganglion. (For comparison, see, e.g., DR position in Fig. 3 above.)

Chen et al. (2006) extend the Chklovskii (2004) connection-minimization model from ganglia down to the level of individual neuron positioning in *C. elegans*. Again, a wirelength squared measure for connection cost is employed. At this finer scale of anatomy, for our analyses of neuron arbors (Cherniak et al., 1999), we had found that such a Hooke's Law model, where connections behave like springs, similarly did not perform well compared to a simple linear cost model. In addition, Chen et al. principally employ a "dedicated-wire" model, where a neuron cell body must have a separate connection to each of its synapses, rather than a more realistic "shared-wire" model. One germane calibration is that we had performed another series of exhaustive searches of all 11! layouts without any actual shared connections at the ganglion level. The actual ganglion layout then drops in rank, from # 1 to # 2,948,807; with the redundancy of these dedicated connections, the actual layout now costs 38% more than the least costly one. Further, the more shared connections allowed—the more permitted branchings—the better the actual layout performs.

Chen et al. (2006) calculated neuron positions that minimize their quadratic cost function. A caveat for such analytic solutions (see also Chklovskii, 2004) is that, as mentioned, this optimization problem is in fact NP-complete, that is, generally not exactly solvable without exhaustive search. (For examples of local-minimum trapping for ganglion layouts, see Fig. 6 of Cherniak et al., 2002 and Fig. 8.5 of Cherniak, 2009.). Chen et al. do not address the NP-complete character of the wiring problem. Chen et al. conclude that some neurons show strong deviation from the "optimal" placement model; total wiring cost of the actual configuration is nearly four times greater than that of their optimized layout. Compared to the linear minimization account for the ganglia, performance of this quadratic minimization model for neurons turns attention back to how connections were costed.

Contemporaneous with Chen et al. (2006), Kaiser and Hilgetag (2006) also argued that the actual layouts of macaque cortex areas and of *C. elegans* neurons were not in fact minimum-wirelength configurations. We focus on similar questions that arise for this analysis of the worm nervous system. To reiterate, in combinatorial network optimization theory, the component placement optimization problem is, given a set of components and their interconnections, find a siting of components that yields minimum total cost; length of particular individual connections is not an issue. Kaiser and Hilgetag report that rearranging positions of 277 of the worm's 302 neurons can yield an alternative network with total wiring cost reduced by 48%. However, as for Chen et al. (2006) above, how multiple synapses from a neuron fiber are dealt with in alternate placements again needs examining. As an instance, Kaiser and Hilgetag raise the question of accurate representation of sensory and motor connection costs in their alternative neuron layouts. We had performed another search of all 11! alternative ganglion layouts, with only muscle connections deleted. The actual layout's rank then dropped from # 1 to # 63,161, with 10% greater wirecost than the optimal. Again, interpretation of alternate layout connection-costing would benefit from clarification.

Thus, similar questions seem to remain about meaningfulness of both the Chen et al. and Kaiser–Hilgetag neuron placement optimization results. Also relevant here is the observed neuron wiring-minimization pattern mentioned earlier, that if two *C. elegans* neurons are connected, they tend strongly to be clustered in the same ganglion. Further, within ganglia, antero-posterior siting of somata conforms significantly to a connection-length minimization model (Cherniak, 1994a, 1995). In addition, at a yet finer scale, we reported volume minimization of dendrite and axon arbors (Cherniak et al., 1999).

Finally, Klyachko and Stevens (2003) have reported that layout of functional areas of macaque prefrontal cortex is optimal, in that the actual placement of the 11 areas minimizes total wirelength of their known interconnections. Along lines of Cherniak (2003b) and Cherniak et al. (2003, 2004), we reanalyzed the Carmichael and Price (1996) prefrontal neuroanatomy used here, employing instead simple conformance to the Adjacency Rule as a connection cost measure, as discussed above for cat and macaque visual cortex, etc. An exhaustive search of alternative placements showed that the actual layout of the prefrontal areas then ranked in the best 2×10^{-5} of all possible alternative layouts. In our earlier adjacency-cost analysis of macaque visual cortex, the actual layout of a core subset of 11 areas had ranked in the top 1.07×10^{-5} of all layouts. So, connection optimization of prefrontal cortex areas seems to agree with our results for visual cortex.

Mapping neural optimization

Mechanisms of neural optimization are best understood against the background that the key problems of network optimization theory are NP-complete; hence, exact solutions in general are computationally intractable. For example, blind trial and error exhaustive search for the minimum-wiring layout of a 50-component system (such as all areas of a mammalian cerebral cortex hemisphere), even at a physically unrealistic rate of one layout per picosecond, would still require more than the age of the Universe (Cherniak, 1994b). Instead, even evolution must exploit "quick and dirty" approximation/probabilistic heuristics.

One such possible strategy discernible above is optimization for free, directly from physics. That is, as some structures develop, physical principles cause them automatically to be optimized. Evidence was reviewed above for arbor optimization via fluid dynamics, and for roundworm ganglion layout optimization via force-directed placement. The worm layout is among the most complex biological structures known to be derivable in this way for free, directly from simple physical processes, without intervention by DNA mechanisms.

For processes of component placement optimization, a chicken–egg question arises of whether components begin in particular loci and make connections, or instead start with their interconnections and then adjust their positions, or some mix of both causal directions. However, it is worth noting that both a force-directed placement algorithm for ganglion layout and genetic algorithms for layout of ganglia and of cortex areas suggest that simple "connections→placement" optimization processes can suffice.

Wiring optimization is of course subject to many basic constraints and so cannot be ubiquitous in the nervous system or elsewhere; the question is where it does in fact occur, and how good it is. Trade-offs of local optimality for better global cost minimization of a total system (as Fig. 2, Cherniak et al. (2004) illustrates) are one way in which global optimization can be obscured.

The very fact of neural resource limitations appears to drive "save wire" fine-grained minimization of connections. Another part of the functional role of such optimization may be the picture here of the prebiotic pervading the biotic: "physics→optimization→neuroanatomy." Perhaps, such an economical means of self-organizing complex structure generation eases transmissibility through the "genomic bottleneck," that is, the limited information carrying capacity of DNA. This constitutes a thesis of "Non-Genomic Nativism," that significant complex biological structure is not encoded in DNA, but instead derives from basic physical principles (Cherniak, 2005).

Such an account is an innateness hypothesis: There is inborn structure—not only at the abstract cognitive level (e.g., of linguistic competence) but also at the brain hardware level. The harmony of physics and neuroanatomy yielding optimization is an instance of self-organizing biological structure. For such an account, the blank slate of the nervous system is in fact instead preformatted—however, not via the genome, but by the underlying physical and mathematical order of the Universe (see Chomsky, 2005). A division of labor holds between the genome and this underlying order.

The "connective tissue" minimization findings suggest optimization of neural layouts to a level at least in the best one millionth of all layouts. And this across much of the evolutionary trajectory, from nematode to macaque—another dimension of convergent confirmation of neural optimization.

In addition, the Size Law raises the possibility of extrapolation, that larger neural systems that take into account more connected components may in fact be attaining even better cost minimization. And, in fact, Cherniak (2003b) and Cherniak et al. (2004) include results for the 39-component cat sensory cortex system (visual, auditory, and somatosensory), where optimization falls in the top one billionth of all layout possibilities. This begins to approach some of the most precise confirmed predictions known in science, such as those of quantum electrodynamics (e.g., Peskin and Schroeder, 1995). Such a best-in-a-billion optimization model seems a predictive success story.

Yet, against the familiar background of biological satisficing, this neural minimizing may appear gratuitous. There are many other competing design desiderata besides "save wire." Extreme connection minimization itself in turn stands in need of further explanation. In his discussion of neural wiring economy, Sporns (2010) concludes that brain connectivity optimization to minimize wirecost is unlikely; instead, brain wiring is a compromise of many factors. Such views, of course, are familiar; Gould (1980), along Darwinian lines, is a contemporary *locus classicus* for the idea that evolution yields improvised *ad hoc* tinkering, not ideal design.

However, none of Gould's examples are neural. Optimization to physical limits has long been reported also for stimulus amplitude sensitivity of sensory systems for vision, hearing, olfaction, etc. (e.g., Cherniak et al., 2002). So, an emerging picture might suggest exploring the conjecture of a neural/nonneural divide for the scope of optimization prevalence. Sensors would fall just on the neural side of such a boundary. Next questions include, what are other domains of optimality, and why would neural systems tend more to be organized in this different way from many other biological systems?

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