
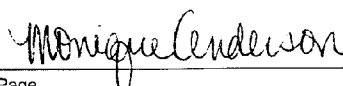


Department of Health and Human Services Public Health Service <b>Grant Application</b> <i>Follow instructions carefully.          Do not exceed character length restrictions indicated on sample.</i>		<b>LEAVE BLANK—FOR PHS USE ONLY.</b> Type      Activity      Number Review Group      Formerly Council/Board (Month, Year)      Date Received	
1. TITLE OF PROJECT (Do not exceed 56 characters, including spaces and punctuation.) <b>Network Optimization in the Brain</b>			
2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES (If "Yes," state number and title) Number:      Title:			
3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR		New Investigator <input type="checkbox"/> YES	
3a. NAME (Last, first, middle) <b>Cherniak, Christopher G.</b>		3b. DEGREE(S) <b>PhD, MA BA</b>	
3d. POSITION TITLE <b>Professor</b>		3c. SOCIAL SECURITY NO. <i>Provide on Form Page KK.</i>	
3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT <b>Department of Philosophy</b>		3e. MAILING ADDRESS (Street, city, state, zip code) <b>Department of Philosophy          Skinner Bldg          University of Maryland          College Park, MD 20742</b>	
3g. MAJOR SUBDIVISION <b>College of Arts &amp; Humanities</b>		E-MAIL ADDRESS: <b>cc27@umail.umd.edu</b>	
3h. TELEPHONE AND FAX (Area code, number and extension) TEL: <b>(301)405-5704</b> FAX: <b>(301)405-5690</b>			
4. HUMAN SUBJECTS <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes 4a. If "Yes," Exemption no. IRB approval date { <input type="checkbox"/> Full IRB or Expedited Review		4b. Assurance of compliance no. <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes 5. VERTEBRATE ANIMALS 5a. If "Yes," IACUC approval date 5b. Animal welfare assurance no.	
6. DATES OF PROPOSED PERIOD OF SUPPORT (month, day, year—MM/DD/YY) From <b>12/01/00</b> Through <b>12/01/05</b>		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD 7a. Direct Costs (\$)      7b. Total Costs (\$)	
9. APPLICANT ORGANIZATION Name <b>University of Maryland College Park</b> Address <b>Office of Research Administration and Advancement          2100 Lee Building          College Park, MD 20742-5141</b>		10. TYPE OF ORGANIZATION Public: <input type="checkbox"/> Federal <input checked="" type="checkbox"/> State <input type="checkbox"/> Local Private: <input type="checkbox"/> Private Nonprofit Forprofit: <input type="checkbox"/> General <input type="checkbox"/> Small Business	
		11. ORGANIZATIONAL COMPONENT CODE <b>20</b>	
		12. ENTITY IDENTIFICATION NUMBER <b>1520710851-A1</b> DUNS NO. (if available) <b>79-093-4285</b>	
13. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE Name <b>Antoinette Lawson</b> Title <b>Assistant Director</b> Address <b>Office of Research Administration and Advancement          2100 Lee Building          University of Maryland          College Park, MD 20742-5141</b> Telephone <b>301-405-6269</b> Fax <b>301-314-9569</b> E-mail <b>oraa@deans.umd.edu</b>		14. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION Name <b>Monique Anderson</b> Title <b>Contract Manager</b> Address <b>Office of Research Administration and Advancement          2100 Lee Building          University of Maryland          College Park, MD 20742-5141</b> Telephone <b>301-405-6269</b> Fax <b>301-314-9569</b> E-mail <b>oraa@deans.umd.edu</b>	
15. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.		SIGNATURE OF PI / PD NAMED IN 3a. (In ink. "Per" signature not acceptable.) 	
		DATE <b>02/20/00</b>	
16. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.		SIGNATURE OF OFFICIAL NAMED IN 14. (In ink. "Per" signature not acceptable.) 	
		DATE <b>2/24/00</b>	

DESCRIPTION. State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This description is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

This computational neuroanatomy project is a continuation of studies of how well a set of formalisms derived from combinatorial network optimization theory fit as models for brain structure. The basic hypothesis is that long-range connections in the brain are a critically constrained resource, hence there is strong selective pressure to optimize finely their deployment, to "minimize wire". One formalism may govern component placement in the nervous system: Prior work of the project indicates that the actual layout of *C. elegans* ganglia in fact requires less total wirelength for all of the worm's ~1,000 connections than any of the tens of millions of other possible placements. The new phase of the work involves compiling neuroanatomical databases (principally from published data), with focus on Brodmann areas of cerebral cortex of macaque, cat, and rat. The experiments will then evaluate the connection-optimality of the neuroanatomy. Good optimization findings immediately raise questions about possible mechanisms--the next focus of the proposed research: Network optimization problems are among the most computationally costly known; in general, only exhaustive search of all possible layouts can guarantee exact solutions. However, some probabilistic/approximation procedures developed for microcircuit design have yielded promising pilot results as starting-point models for "quick but dirty" self-organizing biological mechanisms in neuroanatomy optimization. A grasp of such very general "Save wire" generative rules governing development of the human nervous system would constitute a step in understanding how embryology can be disrupted, and in turn can be protected from birth defects; such basic structural principles would also be valuable in research on therapeutic regeneration of the nervous system, especially use of tissue transplants.

PERFORMANCE SITE(S) (organization, city, state)

Department of Philosophy  
University of Maryland  
College Park, MD

KEY PERSONNEL. See instructions on Page 11. Use continuation pages as needed to provide the required information in the format shown below.

Name	Organization	Role on Project
Christopher Cherniak	Department of Philosophy University of Maryland	P.I.

**RESEARCH PLAN****Specific Aims**

The broad objective of the proposed research is to examine how well a set of general principles drawn from combinatorial network optimization theory predict actual neuroanatomical structure of vertebrate and invertebrate nervous systems. The working hypothesis is that connections in the brain, particularly long-range ones, are a singularly limited resource, both in volume and in signal-propagation times; therefore, minimizing costs of required connections strongly drives nervous system anatomy. Network optimization theory is the field in computer science that has developed formalisms of scarcity, for expressing and solving problems of "saving wire". The primary question here is, How well do such concepts in fact apply to the brain?

As an example, a key problem in large-scale integrated circuit design is "component placement optimization": Given the interconnections among a set of components, what is the physical arrangement of the components that minimizes total length of connections? In fact, our computer search of all 40 million possible layouts of the ganglia of the nematode C. elegans has indicated that the actual layout is the unique first-place winner requiring the minimum wirecost for the worm's over 1,000 connections (Cherniak, 1991, 1994a [= Appendix 1]).

The main technique of these studies is computational experiments, and the main hurdle is the exponentially-exploding computational requirements of the optimization searches. Specific goals of the proposed research:

1. Extension of our prior studies of component placement optimization in the nematode nervous system to layout of Brodmann areas of the mammalian cerebral cortex. We have now developed techniques that enable us to go significantly beyond our earlier statistical optimality tests of macaque and cat visual cortex, and of rat olfactory cortex: we can now implement large-scale searches of sets of alternative possible cortex layouts. Our pilot results for cat and macaque cortex well exceed the above worm results, suggesting optimization to at least one part in a billion, down to current limits of detectability.
2. Such striking optimality observations immediately raise questions about the biological mechanisms. Combinatorial optimization problems typically are highly computationally intractable. However, some "quick but dirty" practical procedures developed for microcircuit layout suggest candidate-models worth exploring for neuroanatomy optimization. In particular, our preliminary studies are encouraging for neural optimization via (a) genetic algorithms, and (b) vector-mechanical "mesh of springs" simulations. -- In fact, the latter models constitute an instance of self-organizing morphogenesis of highly complex biological structure directly from simple physical processes.

### Background & Significance

The theoretical framework of this work grew out of methodological studies of prevailing models of the agent in microeconomic, game, and decision theory (Cherniak, 1986). The basic finding was that these models typically presupposed agents with unlimited computational capacities, and more realistic bounded-resource models were then developed. Subsequently, the same approach was applied in computer science, to connectionist models of massively parallel and interconnected computation that were intended to be more neurally realistic than conventional von Neumann computational architecture (cf. Cherniak, 1988); again, the models tended to drastically overestimate available resources--here, actual connectivity in the brain. At least initial connectionist models often tacitly assumed neural connections were virtually infinitely thin wires. In assembling the quantitative neuroanatomy necessary for evaluating neural feasibility of connectionist models, it became evident that a weaker but still discernible trend toward overestimation of resources then pervaded even some neuroanatomy (Cherniak, 1990).

Thus, a bounded-resource philosophical critique of mind-brain science ("We do not have God's brain") focussed attention on neural connections as a critically constrained neurocomputational resource. The formalism of scarcity of connections in computer science is combinatorial network optimization theory, and so a positive research program emerged: If actual brain connections are in severely short supply, is their anatomy correspondingly optimized? The investigation thus falls in a Pythagorean tradition of seeking simple mathematical patterns in observed natural forms (e.g., Thompson, 1917/1961). In fact, minimum-wiring interpretations of neuroanatomy can be traced back at least as far as Cajal's qualitative "laws of protoplasmic economy" (Cajal, 1909/1995; Cherniak, 1995), and have continued to receive attention (e.g., Mitchison, 1991).

The human brain is commonly regarded as the most complex physical structure known in the universe. In the face of such overwhelming intricacy, neuroanatomy traditionally tended toward "descriptive geography" of the nervous system, i.e., relatively low-level ad hoc characterization of individual neural structures. The abstractive power of concepts from computation theory would aid in coping with the unparalleled complexity of the brain. In particular, network optimization theory may provide a source for a "generative grammar" of the nervous system, some general principles that compactly characterize aspects of neuroanatomy. (Of course, connection-minimization is unlikely to be ubiquitous in the nervous system; indeed, the striking observation is that it should hold in even some conditions, given the many other competing desiderata driving design of a brain. The question then is characterizing where "Save wire" does, and does not, apply.)

For example, in the *C. elegans* ganglia case sketched above, we reduced approximately a thousand pages of published anatomy diagrams (Albertson and Thomson, 1976; White, et al, 1976; White, et al, 1986; Wood, 1988; see also Achacoso and Yamamoto, 1992) to a hundred-page

database, which in turn was represented as a ten-page connectivity matrix (see Figure 3), which we then computationally verified to conform to component placement optimization better than any of the nearly 40 million alternative possible layouts (see Figure 4). If this type of result is confirmed, it constitutes one of the predictive success stories of recent quantitative anatomy.

The proposed research would be relevant to programs such as the Neural Circuitry Database initiative, the Human Brain Project, and the Visible Human Project: It explores a class of formalisms that may provide a useful organizing framework for quantitative neuroanatomy. (Cf. the unique compendium of Blinkov and Glezer (1968)--now out of print for two decades.) Biomedical implications of this "brain as ultimate microchip" approach may include improvements in understanding how normal brain development can be disrupted and safeguarded, and also may be useful in research on therapeutic techniques for regeneration of the brain. In addition, such precise generative models of neuroanatomy might eventually mesh with future development of computer-aided micro-neurosurgery (cf. Satava, 1999).

#### Network Optimization Theory

Combinatorial network optimization theory came of age around 1972 with the emergence of the theory of NP-completeness (Garey and Johnson, 1979). (The best nontechnical introduction to the field remains Lewis and Papadimitriou (1978), with Stockmeyer and Chandra (1979).) The key formal concept of a computational problem being NP-complete ("non-deterministic polynomial-time complete") need not be defined here; it is strongly conjectured to be linked with a problem being intrinsically computationally intractable--that is, not generally solvable without exhaustive search of all possible solutions. Because the number of possibilities combinatorially explodes as the size of a problem-instance grows, such brute-force searches are extremely computationally costly. (For example, a 50 component system, such as set of Brodmann areas of the human cerebral cortex, would have  $50!$  possible alternative layouts, far more than the number of picoseconds since the Big Bang 20 billion years ago.) Many of the most important real-world network optimization problems (e.g., the best-known, Travelling Salesman) have been proven to be NP-complete or worse in computational complexity. Component placement optimization and Steiner tree, problems examined by the present research, are of this type, having been proven to be "NP-hard."

Component placement optimization, the main focus of the projected research here, has received the most attention in computer science recently in connection with design of large scale integrated circuits (Kuh and Ohtsuki, 1990; Sherwani, 1995). As mentioned earlier, The problem can be defined as: Given the connections among a set of components, find the spatial layout of components that minimizes total connection costs. The simplest cost-measure is length of connections (often represented as the sum of squares of the lengths); usually the possible positions for components are restricted to a matrix of "legal slots." As a simple example, Figures 1a and 1b diagram two of six possible configurations of components 1, 2, and 3 in slots A, B, and

C; for the connections among the components, placement 1a requires the most total connection length, and 1b the least.



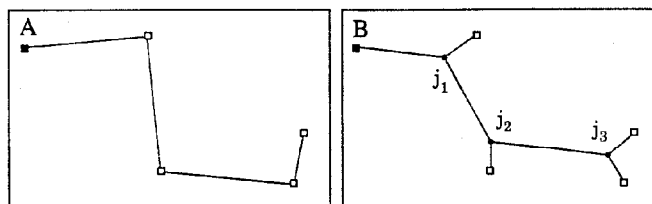
**Figure 1.** Component placement optimization: Two alternative placements of elements 1, 2, and 3 in positions A, B, and C. For the given interconnections, placement (a) has greater total connection length than placement (b). (From Cherniak, 1995.)

Computation costs for exact solution of component placement optimization problems are of a magnitude not encountered in most bioscience computing, and constitute one of the main technical hurdles of this research. For  $n$  components, the number of alternative possible placements is  $n!$  (Size of this search space generally is unaffected by whether permissible component positions are located in 3, 2 or 1 dimensions.) Heuristic procedures that yield approximately optimal solutions can be much more feasible, but their performance (e.g., how close to optimality are they likely to come) is not well understood. (For an experimental study of human use of a heuristic in deductive inference, see Cherniak, 1984).

Steiner tree, the focus of some of our just-completed research, has been studied in its simplest form at least as early as the Renaissance (Courant and Robbins, 1941/1969; Hwang, Richards, and Winter, 1992). The most relevant version of the problem is: Given a set of fixed node loci, find the set of arcs (or branch segments) between those loci that interconnects all loci and has shortest total length. The resulting network will always constitute a tree. When it is permitted to have branch junctions only at node sites, it is a minimal spanning tree; when branch junctions may also occur at sites that are not nodes, it constitutes a Steiner tree. The total length of the Steiner tree for a set of nodes is equal to or less than the length of the minimal spanning tree for the nodes. For example, Figures 2 A and 2 B show, respectively, a minimal spanning tree and a Steiner tree for five nodes on a plane. The Steiner tree is about 4% shorter than the minimal spanning tree.

Since Steiner tree, like component placement optimization, is a member of the class of NP-hard problems, it is not surprising that the largest unconstrained Steiner tree problems that can currently be solved have only ~100 nodes (cf. Bern and Graham, 1989). However, while minimal spanning trees are equal to or longer than corresponding

Steiner trees, they are not at all computationally intractable; exact algorithms for the former problem today perform well for quarter-million node sets. The basic question of goodness of fit of the Steiner tree concept to actual neuroanatomy is, do the dendritic and/or axonic arbors of a neuron form optimized Steiner trees interconnecting the cell body with a set of synaptic loci? The key idea needed for such applicability is that for real-world trees, living and non-living, not all segments are equal: the concept of an optimal tree had to be extended to include variably-weighted branches (Cherniak, 1992).

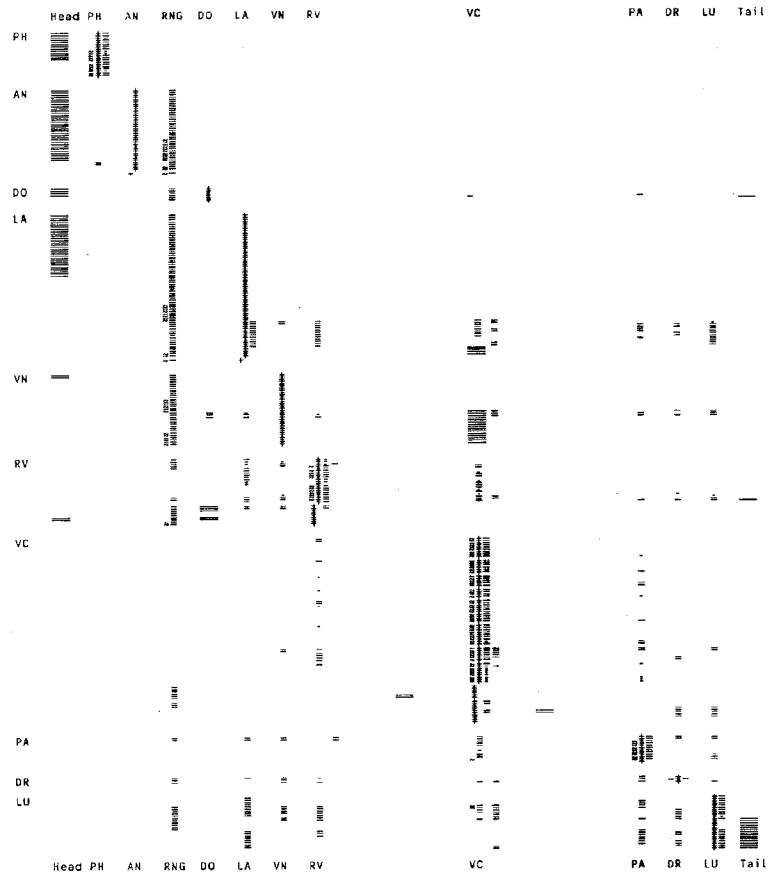


**Figure 2.** Minimal spanning tree, A, and Steiner tree, B, for five nodes on a plane surface. The Steiner tree is shorter, but much more computationally costly to construct. (From Cherniak, Changizi, and Kang, 1999.)

Perhaps the most salient, and daunting, feature of nontrivial global optimization problems is the presence of local minima traps on the optimization landscape--that is, parameter values that yield least costs within a subregion of the search space, but not across the total space. For example, with regard to vector-mechanical force-minimization treatments of the above two problems: (1) The tree of Figure 5 (C) below is suboptimal because of its topology, while Figure 5 (D) shows the minimum-cost topology; no vector-mechanical tug of war re-embedding of the suboptimal topology can transform it into the best topology. (2) Similarly, Figure 6 shows a vector-mechanical local minimum trap for the ganglion component placement problem. The extensive and impressive modelling of cellular structures and processes in terms of compression-tension "tensegrity" by Ingber (e.g., 1993, 1998) does not deal with local minima, and therefore cannot account for such global optimization problems of evading such traps. Correspondingly, Van Essen's tension-based model of cortical folding in terms of white-matter tensegrity ((1997); but see Armstrong et al, 1991, 1995) also does not deal with local minimum traps, and so will not work for global optimization problems of wiring-minimization.

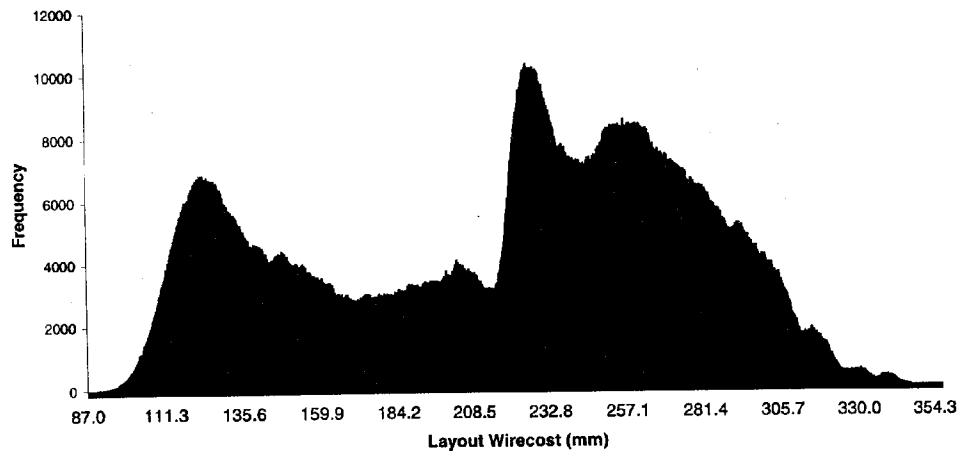
### Progress Report

The period covered since this project was last reviewed competitively is January 1, 1993 - December 31, 1999. Chief specific



**Figure 3.** Total ganglion-level connectivity map for *C. elegans* nervous system. Each horizontal micro-line represents one of the 302 neurons: +, soma; -, asymmetrical synapse; ~, symmetrical synapse; ~, muscle connection; —, sensor. "PH", "AN", etc. are codes for the ganglia. (All non-ganglionic neurons also included.) Compiled from the published anatomy, this appears to be a candidate for the first complete depiction in a single image of a nervous system at the individual neuron level. A connectivity diagram of this type is required to represent connection-branching; a conventional connectivity matrix cannot. (From Cherniak, 1994a [= Appendix 1].)





**Figure 4.** Distribution of wirecosts of all possible layouts of ganglia of Caenorhabditis elegans. 10,000-bin histogram compiled from exhaustive search of all 39,916,800 alternative orderings of the 11 ganglia. Least-costly and most-costly layouts are rarest. In effect, the search approximates a simulation of the maximal possible history of the evolution of this aspect of the nervous system. The worm's actual layout (Figure 3 above) is in fact the optimal one, requiring 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 connection fiber as the optimal one. (See Cherniak, 1995 [= Appendix 3].)

aims of the project were: (a) evaluation how well neural structures conform to minimum-wiring principles of economical use of connections, and (b) seeking biological mechanisms of the observed extremely fine network optimization. Importance of the project findings includes: some "Save wire" neuroanatomy results that begin to approach the most precise confirmed predictions in science; and neuroanatomical candidates for some of the most complex biological structures shown to be derivable purely from simple physical processes (cf. Kauffman, 1995). This research constitutes a step in developing an understanding of generative rules that yield the highly complex anatomy of the nervous system.

Table 1 lists all relevant publications that have resulted from this project since it was last reviewed competitively; see also Appendices 1 - 6.

## I. Large-Scale Optimization of Dendrites and Axons

Some complex neuroanatomical structure seems to be self-organizing. The key underlying pattern is network optimization, "Save wire." The particular hypothesis in this case is, Neuron arbor morphogenesis behaves like flowing water. (See Cherniak, Changizi, and Kang, 1999 [= Appendix 4].) The major methodological enterprise of the project centered on developing STRETCH (Kang, Huang, Kahng, and Cherniak, 1996; Changizi and Cherniak, 1997), a package of algorithms for the computationally intractable ("NP-hard") task of generating optimal trees (Hwang, Richards, and Winter, 1992) against which to compare observed neuroanatomical trees.

(a) "Neural fluid mechanics": a simple fluid-dynamical model--for minimized walldrag of pumped flow through a system of pipes--will predict the geometry of some types of dendrites (e.g., of mammalian retinal ganglion cells) and axons (e.g., in rodent thalamus) almost as well as it predicts configuration of non-living structures such as river drainage networks. For neurons, the fluid dynamics falls in the laminar-flow, vs. turbulent, regime.

(b) Waterflow in branching networks in turn acts like a tree composed of weights and pulleys, that is, vector-mechanically; so also do the neuron arbors. As a result, they globally minimize their total volume to about 5% of optimum for interconnecting their terminals. (See Figure 5.) One unanticipated moral that emerged is that in a sense, "Topology does not matter"--that is, the "pessimal" connection-pattern typically costs only relatively little more than the optimal pattern, compared to the corresponding possible range of costs for embedding a given topology. The conclusion here is only that the minimum-volume configuration is the default neuron arbor structure, probably often modified in many complex ways (for example, cf. Purves and Lichtman, 1985).

## II. C. elegans Ganglion Placement Optimization

We have extended our above results on large-scale optimization of individual neuron arbors to the entire C. elegans nervous system. The

**Table 1.** Project Publications (and Unpublished Reports and Software):  
1/93 - 12/99. [MH49867]

Publications

C. Cherniak, Component placement optimization in the brain, J. Neuroscience **14**, 2418-2427 (1994). [= Appendix 1]

C. Cherniak, Philosophy and computational neuroanatomy, Philosophical Studies **73**, 89-107 (1994). [= Appendix 2]

C. Cherniak, Neural component placement, Trends in Neurosciences **18**, 522-527 (1995). [= Appendix 3]

C. Cherniak, Reply to Letter to Editor, Trends in Neurosciences **19**, 414-415 (1996). [ [www.wam.umd.edu/~cherniak/](http://www.wam.umd.edu/~cherniak/) ]

C. Cherniak, M. A. Changizi, and D. Kang, University of Maryland Institute for Advanced Computer Studies Technical Report No. 96-78 (1996); C. Cherniak, M. Changizi, and D. Kang, Large-scale optimization of neuron arbors, Physical Review E **59**, 6001-6009 (1999). [= Appendix 4]

Unpublished Reports

Changizi, M. A., and Cherniak, C. (1997) Research manual for "Large-scale optimization of neuron arbors" (University of Maryland, College Park).

Changizi, K. S., and Cherniak, C. (1997) Research manual for costing software for C. elegans (University of Maryland, College Park).

Changizi, M. A., and Cherniak, C. (1998) Modelling large-scale geometry of human coronary arteries with principles of global volume and power minimization (University of Maryland, College Park).

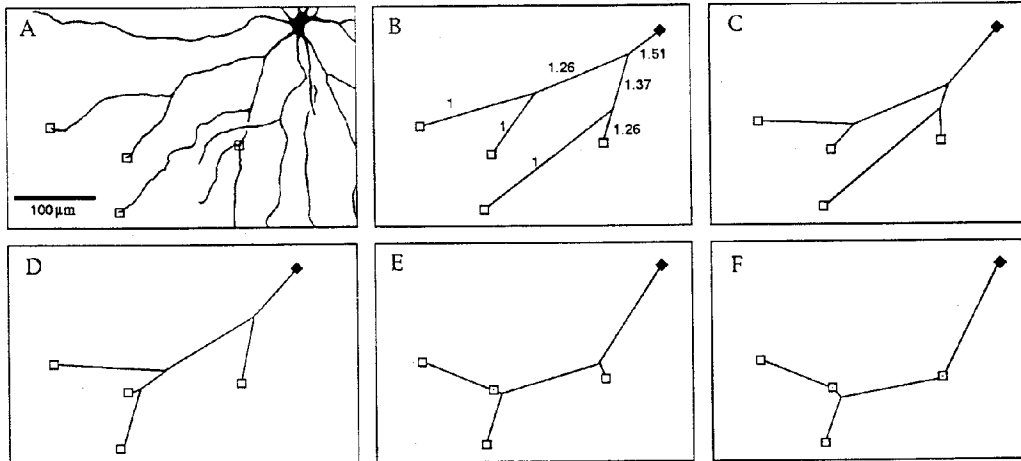
Software

Kang, D. W., Huang, J.-H., Kahng, A., and Cherniak, C. (1996) STRETCH Embedder / Topology-Generator / Coster Package for Steiner-Tree Optimization (University of Maryland, College Park).

Changizi, K. S., and Cherniak, C. (1997) Costing the worm: A software library for variant adjacency and branching rules for C. elegans (University of Maryland, College Park).

Nodelman, U., and Cherniak, C. (1997) TENSARAMA Force-directed placement algorithm for optimization of C. elegans ganglia (University of Maryland, College Park). [cf. Appendix 5]

Mokhtarzada, Z., and Cherniak, C. (1998) GENALG Genetic algorithm for placement optimization of C. elegans ganglia (University of Maryland, College Park). [cf. Appendix 6]



**Figure 5.** Optimization analysis of a 5-terminal sub-tree from dendritic arbor of an alpha ganglion cell in rabbit retina. (A) A quadrant of the original camera lucida drawing containing the sub-tree (after Peichl, Buhl, and Boycott, 1987); soma is in upper right corner. "Leaf-terminals" of the analysis are boxed (note that one of them is not a branch-termination); "root-terminal" is at soma. (B) Wireframe representation of actual tree, with branch segments straightened between loci of terminals and internodal junctions. The labels give diameters assigned to the branch segments via the power law of the laminar-flow model. (C) Optimal (re)embedding of the topology of the actual tree, with respect to total volume-cost, via the STRETCH algorithm; this minimum-volume embedding of the actual topology is 1.06% cheaper than the volume of the actual tree in (B). (D) Optimal embedding of the optimal topology for the given terminal loci, with respect to volume-cost. It can be seen to differ from the actual topology of (A) - (C); it is only 2.64% cheaper in volume than the actual topology in its actual embedding, in (B). (E) Optimal embedding of the optimal topology, with respect instead to total tree surface area; actual vs optimal error is now 27.22%, much greater. (F) Optimal embedding of the optimal topology, with respect to total tree length; actual vs optimal error is now 60.58%, even greater. Thus, this dendritic arbor best fits a minimum-volume model. (From Cherniak, Changizi, and Kang, 1999 [= Appendix 4].)

basic picture is indeed that vector mechanics suffices for optimization of placement of the ganglia of C. elegans. As mentioned earlier, our prior research had found that the actual placement of the ganglia in the worm was optimal, in that it required the least total length for the animal's (~1,000) interconnections, out of roughly 40 million alternative possible ganglion orderings. As noted, if this 1-in-10-million type of result is replicated, it begins to approach some of the most precise confirmed scientific predictions (see Brush, 1995; Kinoshita, 1995); hence, we sought convergent support by finding feasible mechanisms for such fine-grained optimization.

We have constructed TENSARAMA [cf. Appendix 5], a force-directed placement simulator (cf. Quinn, 1975), where each of the worm's connections behaves like a micro weight-and-pulley system (see Figure 6). Analog-hardware devices of this type have been used to solve simple (non-combinatorial) placement optimization problems for over a century (Francis, McGinnis, and White, 1992). Over a wide range of input configurations of the ganglia, our vector-mechanical net outputs the actual layout via tug-of-war, converging on equilibrium at the actual, minimum-wirecost positioning of the ganglia--without major susceptibility to local-minima traps. We have also constructed GENALG [cf. Appendix 6], a genetic algorithm (cf. Mitchell, 1996) package that stably outputs the actual, minimum-wirecost placement (see Figure 7); it is, in effect, a demonstration that evolutionary processes can suffice for worm wiring optimality. (A caveat on interpretation of the vector-mechanical models: While actual physical forces appear to drive arbor optimization, it is likely in the case of nematode ganglion layout that the forces involved should instead be viewed more abstractly as governing natural selection processes; neuron somata need not in fact move during development of the individual organism. We have argued similarly (Cherniak, 1995) concerning the simplest neural component placement problem, of brain positioning, that the brain's sensory-motor connections of course do not behave literally vector-mechanically over evolutionary history.)

But the bottom line here once more seems to be that, in a sense, "Physics suffices": Since no genome is required for this self-organization, some interesting limits might thereby emerge on the central dogma of genetics. A discrete-state process like a genetic algorithm is not needed to generate some highly complex types of biological structure. One rationale for such non-genomic anatomy-generating processes--as well as for such simple generative rules as "Save wire"--is apparent in a dilemma Nature confronts: Human brain wiring is among the most complex structures known in the universe, yet its layout information must pass through the "genomic bottleneck" of very limited DNA information-representation capacity (Cherniak, 1988). The harmony of neuroanatomy and physics suggested here would lower this hereditary information load by accomplishing network optimization without required participation of the genome.

Another observation worth further study (see below) is that, for both the global arbor and ganglion neural optimization problems--unlike typical network optimization--random noise-injection (e.g., as in simulated annealing; Kirkpatrick, et al, 1983) generally was not

Input: actual.mtx

## T E N S A R A M A

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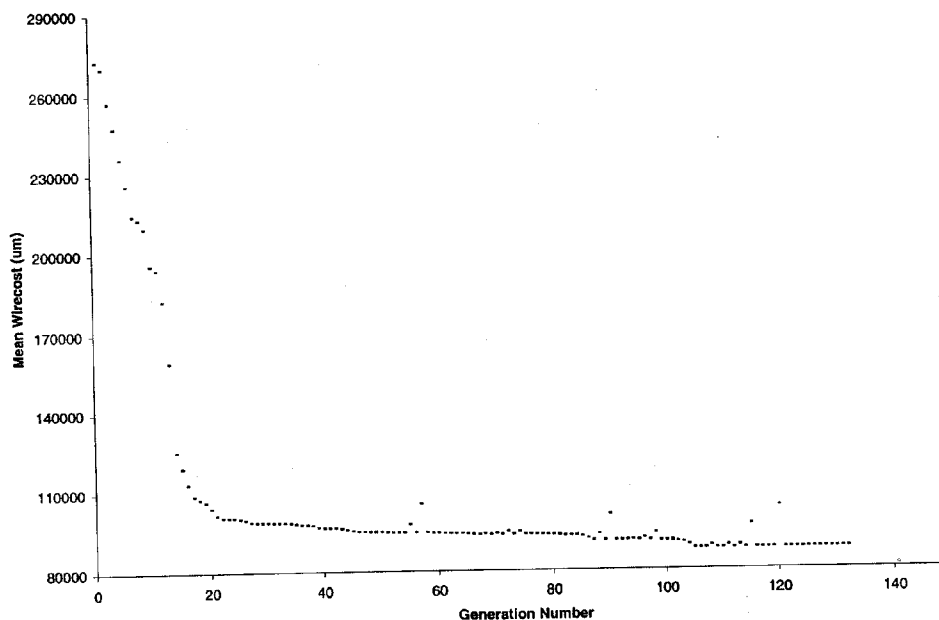
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VCa (2004.000000)
VCp (4004.000000)
PA (4874.000000)
DR (854.000000)
LU (928.000000)

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Final layout popped out after: 1,000,000 iterations  
Tension Constant: 0.001000  
Total Wirecost: 88485.250000 um

**Figure 6.** Runscreen for "Tensarama", a force-directed placement (FDP) algorithm for optimizing layout (minimizing total wirecost) of C. elegans ganglia. This vector-mechanical simulation represents each of the worm's ~1,000 connections (cf. Figure 3 above) as a weight-and-pulley (non-Hooke's Law) element acting upon the movable ganglia. At each iteration, the program computes net horizontal force on each ganglion, and correspondingly updates its position; the cycle is repeated a given number of times. (Ganglion locations are in "tetrons", or quarter-microns, to decrease round-off errors.) The most striking feature of Tensarama performance for the actual worm's connectivity matrix is its general unsusceptibility to local minima traps--unlike Tensarama performance for minor modifications of the actual connectivity matrix, and unlike FDP algorithms in general for circuit design. However, the above runscreen shows the final configuration of the system for one of the few types of identified "killer layout" inputs of the actual matrix: Tensarama has frozen in a local minimum with ganglia in positions (notably, DR and LU in head, rather than tail) that yield a final layout wirecost of 88,485.25 um, about 0.8% more than the actual layout. The fatal initial layout here (ganglion left edges at 0 tetrons) differs only slightly from a quite innocuous initial layout (ganglion centers at 0). (See Nodelman and Cherniak, 1997 [cf. Appendix 5].)



**Figure 7.** "GenAlg", a simple genetic algorithm, rapidly and reliably finds the optimal (minimum-wirecost) layout of *C. elegans* ganglia. The initial population in this run is small, 10 individuals, each here with a reverse ganglion ordering of that found in the actual worm; the algorithm converges upon the minimum total wirecost layout (87,803 um) in only 130 generations. The evolution of wirecost shows the usual pattern: a very rapid initial improvement of fitness (about 90% during the first 20 generations), followed by a much longer, slower finetuning phase to optimality. Some of the random mutations cause the half-dozen brief "blips" of increased mean wirecost of the population during the later phase. The robust performance of this genetic algorithm, and also of our force-directed placement algorithm, is further converging support for the hypothesis that the actual layout of *C. elegans* is in fact perfectly optimized. (See Mokhtarzada and Cherniak, 1998 [cf. Appendix 6].)

needed to evade local-minima traps.

### III. Other Neural Network Optimization Results

We have also examined interrelations between optimization of branching in C. elegans neuron arbors and optimization of ganglion placement (Changizi and Cherniak, 1997 ). The worm's nervous system approximates a 1-dimensional array, with its arbors forming "1-dimensional trees". We have now run a series of exhaustive searches of all worm ganglion layouts, with non-local connection branchings replaced by more costly separate direct connections: When all branchings are removed, the actual layout ranking drops sharply, from first place to about 3,000,000 place. In this way, component placement optimization seems intimately meshed with the connection branching so ubiquitous in nervous systems.

Another group of results in this series turns out to be especially relevant for the planned research sketched below (cf. Figure 8). We studied wirecost performance of a family of variants of the adjacency rule. The basic quick and dirty heuristic for minimizing wire is: If two components are connected, place them adjacent to each other. It is not difficult to devise *prima facie* more fine-grained adjacency rules that take into account weightings for length and/or density of connections, etc. The surprising finding is that, when all 40 million alternative worm ganglion layouts are searched, none of these potentially more sensitive wiring rules does better at finding the minimum wirelength layout than the above simplest adjacency rule (indeed, some do markedly worse). An idea thus emerges for further study that the simple adjacency rule might in fact have some type of physiological reality.

Finally, as explained below, on the model of the above worm ganglion searches, we seem to have worked out successful methodologies for optimality searches of layouts of the Brodmann areas of cat cerebral cortex. While these are preliminary and confidential pilot results, a picture similar to nematode ganglion placement emerges: the cortical areas appear optimally placed, down to the limits of our current computing resources. Consequently, this will be the chief focus of our future research.

## Research Design & Methods

### I. Cortex Area Placement

The main objective of this stage of the investigation is to evaluate placement optimization of mammalian cortical areas: Is there evidence of optimal positioning to minimize connection costs, as found for C. elegans ganglia? Of course, a mammal cerebral cortex is vastly more complex than the 300-neuron nervous system of the worm; it is also molded by experience much more extensively. (i) Furthermore, even when connections have been reported between two Brodmann areas, connection-lengths (and densities) usually are not available. (ii) In addition, the two-dimensional cortical sheet is intricately folded, so that measuring distance between two areas becomes a three-dimensional



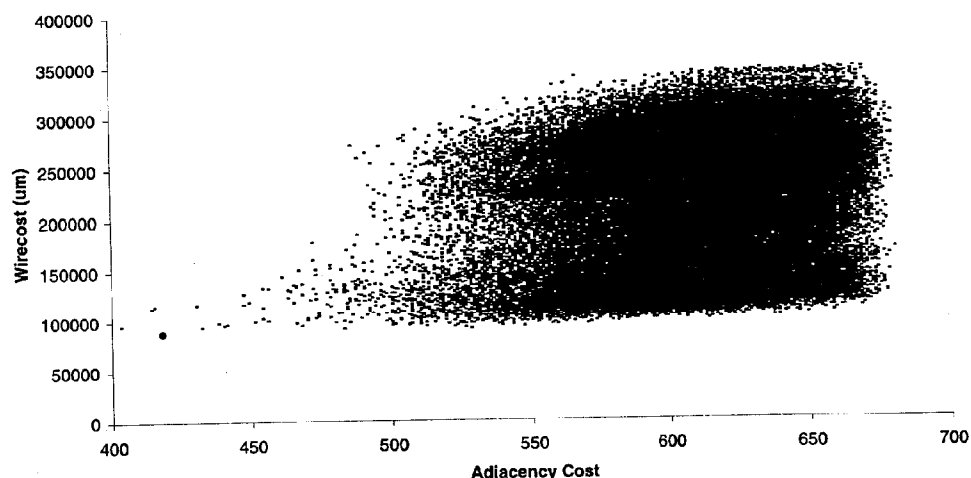
problem. (iii) Observing the actual course of an axon bundle in the white matter is yet another layer of difficulty. (iv) Finally, Widespread axonal bifurcation of corticocortical connections in cat and monkey visual systems has been reported (Bullier & Kennedy, 1987), with estimates of branching ranging above 30% for some populations of projecting neurons. Such a bifurcation can save around 10% of the corresponding length of two separate connections (Hwang, Richards, and Winters, 1992). However, cerebral connection compendia such as Felleman & Van Essen (1991) only describe links between pairs of areas, therefore cannot systematically represent these branchings, and so remain inaccurate as a basis for computing wirecosts. Is optimization still observable through so many barriers?

(a) Adjacency Rule Costing

If connection costs of cortex layouts are to be compared as were worm ganglion layouts, this obstacle maze must be navigated. However, conformance of a layout to the adjacency rule would be much more feasible to compute than its total wirelength: just compare connections and contiguities of the layout's components, and score how many violations of "if connected, then adjacent" occur. In fact, such a rule is well-confirmed for macaque and cat visual cortex areas, rat olfactory cortex areas, and *C. elegans* ganglia (Cherniak, 1991, 1994a, 1995; Young, 1992). How useful would such an adjacency costing be? The basic point is that component placement optimization is a computationally intractable, NP-hard problem; hence, a quick and dirty heuristic like the adjacency rule by no means can provide a general solution to such a problem. So the first question would be, How closely correlated here in fact are layout wirecosts and adjacency performance? As just explained, we cannot expect to have useful wirelength data for cerebral cortex. However, another approach is to use our *C. elegans* databases as a pilot testbed for such queries; a positive picture for the worm would motivate exploring a similar working hypothesis for the cortex.

As described earlier, one of our prior worm studies had revealed that in fact the layouts that perform best for the above simplest adjacency rule also perform very well in terms of wirecost. This type of comparison needs to be generalized: Figure 8 is a dispersion diagram for 100,000 randomly sampled worm layouts. The amorphous cloud of points indicates that adjacency rule conformance generally is not an efficient means to good wirecost. (A vertical cross-section through this "point-blob" will be a sampling approximation of the layout-wirecost distribution shown in Figure 4 above.) However, the striking trail of points at the far lower left of the diagram suggests a special case: extremely good--near-optimal--adjacency rule performance does correlate well with very good wirecost.

It should be noted that the scattergram shows that merely connecting components to their neighbors will not optimize wire cost; only a layout that is optimized for adjacency rule conformance will do that. Hence, a regress, from the frying pan into the fire: optimal wirecost can be achieved via optimal adjacency rule conformance, but now the wirecost minimization problem has been replaced by another



**Figure 8.** Adjacency rule conformance, vs total wirecost, of 100,000 worm ganglion layouts randomly sampled from the set of all 11! possible layouts. Correlation between good adjacency rule performance and cheap wirecost is weak ( $r^2 = 0.051$ ); generally, the adjacency rule is not an effective means to good wirecost. However, it can be seen that the small set of layouts best fitting the adjacency rule--the points at the far left--behave strikingly differently: they correspond closely to the best wirecost layouts. (The larger circular point in the far left of the dispersion diagram represents the actual, minimum-wirecost layout.) Thus, the adjacency rule in itself is not enough to achieve the observed low wirecost; an additional mechanism in turn is required, to optimize adjacency scores.

combinatorial optimization problem of the same NP-hard level of computational complexity. (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.) That the worm's matrix of connections should be just such that the best adjacency rule layouts match the very cheapest wirecost ones--while the set of all others does not--appears to be another instance of the type of connectivity matrix finetuning we reported earlier for the force-directed placement algorithm (Figure 6), i.e., that the worm's set of connections appears to be just such that it has relatively few local minima traps.

(b) Size Law

So, the first provisional conclusion is that very good adjacency performance is indeed worth examining as a feasible, surrogate index of layout optimization for cortical areas. A next difficulty is that cortical connection and adjacency information is not complete: for macaque (Felleman & Van Essen, 1991) and cat (e.g., Scannell et al, 1995), the anatomy is most satisfactory for the visual areas, usable also for auditory and somatosensory areas, but only partial for frontal and limbic areas. Therefore, any near-term optimization analysis of the cortex cannot include the entire system, but only large subsets. On the working hypothesis that the total system was perfectly optimized, what sort of optimization would be expected for such a subset?

As a first approximation, optimization of a total system does not entail optimization of its subsets. Furthermore, we propose the following Size Law as an assertion of graph theory:

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

Typical costs to be minimized are total wirelength or conformance to an adjacency rule. A sketch of the idea of a proof begins with the familiar observation, that global optimality need not yield local optimality; local sacrifices are often required for the best overall solution. As a subset of the total optimized system gets smaller, its constraints--e.g., connections to surrounding edges--will be likely to depart more and more from those of the total layout, and so the subset is less likely to be optimized itself.

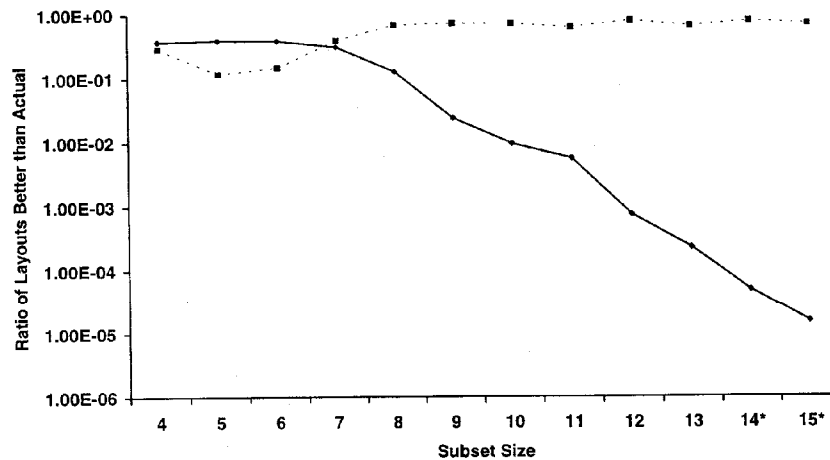
To begin with, the Size Law can be evaluated for the 11-ganglion worm system, with wirecost as the optimality measure. A nested series of ganglion subsets were generated, each composed of contiguous elements, proceeding from head to tail, from 4 to the full 11 components. Cost of each subset of the actual layout is compared with all possible alternative layouts of that component subset. 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 no other layout is better than the actual one. In addition, when optimality is plotted against subset size, with "proportion of layouts better than actual" on a logarithm scale, the

descending curve very closely approximates a straight line ( $\bar{r}^2 > 0.99$ ,  $p < .001$ ), 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 is not available, and even in the best cases (macaque and cat), adequate information on connections and adjacencies only exists for sensory areas. In addition, of course, 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. As a pilot demonstration of the validity of the methods outlined here, we evaluate the Size Law for all 15 contiguous visual areas of cat cortex, with conformance to the simple adjacency rule as optimality measure now. While actual cortical Brodmann areas form a jigsaw puzzle of widely differing sizes and shapes, they are approximated here as uniformly interchangeable (thus, the actual layout is in fact even being tested against some topologically impossible alternative layouts).

From Scannell et al (1995) with corrections, and Rosenquist (1985), we constructed a matrix of cat intracortical connections and a topological database of adjacencies among the Brodmann areas. Figure 9 shows that again the Size Law seems to apply well--and does not hold for a corresponding random calibration set. The logarithmic scale of the y-axis should be noted: the Size Law curve fits a straight line well ( $\bar{r}^2 > 0.94$ ,  $p < .001$ ), suggesting--as for the much more complete worm ganglia subset series--that a simple exponential growth function may be involved. It should be noted that the "total set" here consists of only 15 components of the entire 57 Brodmann area cortical system, and does not include extracortical efferent and afferent connections. The Size Law provides an account of how such an incomplete system would only attain an optimality ranking in the top  $10^{-5}$  of all possible layouts, even if the complete system were in fact perfectly optimal. Naturally, this series immediately raises the question of how much finer optimality even larger subsets of the actual layout attain--e.g., as observed via simple random samples of extremely large total sets of all alternative possible layouts.

Provisional results as of this writing: when the subset is extended to 20 areas, a sample of a billion out of all possible layouts shows a rise of rank into the top  $10^{-8}$  of all layouts (in other words, only 10 layouts out of a billion sampled layouts were better than the actual layout). With a 25-area subset, a billion-layout random sample yields no placements cheaper than the actual one--i.e., the actual layout's ranking is too high to be detectable at this sample size. Similarly for 30 areas, and also for 35. While this is of course the most striking finding reported in this proposal, it should be interpreted with some care; certainly larger sample sizes are warranted. We have also now begun similar placement optimization studies for macaque visual cortex areas (Van Essen, 1985; Pandya and Vetterian, 1985; Felleman and Van Essen, 1991); our earliest, provisional results are consistent with the picture for cat cortex.



**Figure 9.** "Size Law" for cat visual cortex areas. The Size Law: If a set of connected components is optimally placed, then, the smaller a subset of that total layout, the more poorly optimized it will tend to be. The system of components here is 15 of the cat visual cortical areas, with connections and adjacencies represented in a database. The optimality-measure is conformance of the system to the simplest adjacency rule: If two components are connected, then they are adjacent to each other (Cherniak, 1994a). A layout is scored in terms of its number of violations of this adjacency rule. A series of nested compact subsets of the 15 Brodmann area total set was generated, each consisting of from 4 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). As the solid-line curve shows, 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 exception,  $p < 0.02$ ). Only one in a hundred thousand of all alternative layouts conform to the adjacency rule better than the actual layout of the complete 15-component set. For comparison, the broken-line curve shows the corresponding analysis for a layout of the 15 visual areas with their positions randomly shuffled; no Size Law trend toward improving optimality is now evident.

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(c) Metamodule Grouping

Of course, exhaustive search of all 57! alternative layouts of the 57 Brodmann areas ( $= 4.05 \times 10^{76}$  layouts) of cat cortex would be cosmically unfeasible (Cherniak, 1994). Another sampling strategy instead is to cluster the Brodmann areas of the actual layout into groups of topologically contiguous components, then to search the smaller set of alternative placements of these "meta-modules". This strategy is based upon a Meta-module Thesis:

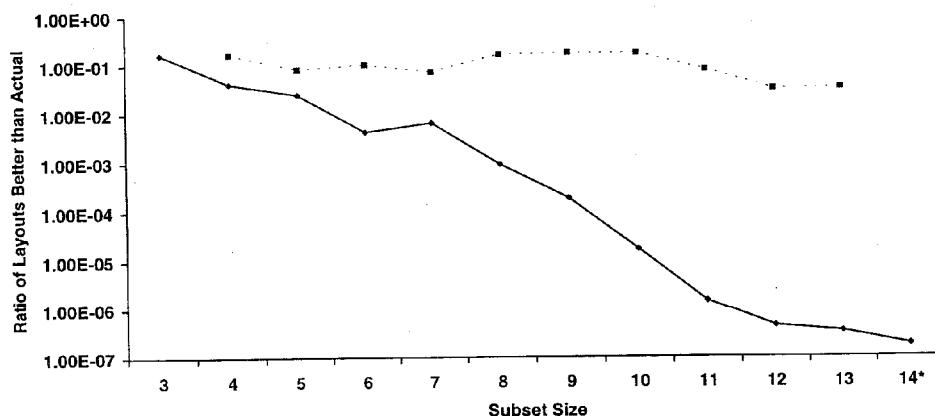
If a set of connected components is optimally placed, then a set of meta-modules, each consisting of a subset of those components in the same positions, is also optimally placed.

Figure 10 shows Size Law optimization performance of a series of nested layouts of 14 meta-modules composed of 40 cat cortical areas. Each meta-module was grouped from adjacent Brodmann areas, all of the same modality (visual, auditory, then somatosensory); meta-modules 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 meta-module layout now attains the top ten-millionth level of optimization--comparable to that found for the worm ganglion system. The Size Law curve fits a straight line well ( $r^2 > 0.97$ ,  $p < .001$ ) again. The consistency of the entire Size Law trend here effectively constitutes a type of further convergent support for the basic cortical optimality conclusion.

(d) Next Steps

These pilot results for mammal cortex raise the question, Are cortical areas in fact optimally positioned, as *C. elegans* ganglia appear to be? A wide range of independent replications are needed to convergently support such a broad conclusion. Indeed, some review of problems and methods for dealing with them like that above is really required to motivate treating this question even as realistically approachable. To begin with, we need to examine a number of variations on the simple adjacency rule (cf. those examined for the worm in the previous section). There are of course natural chicken-egg questions about which way causation runs--from connections to adjacency, or vice versa, or both. Cortices of other mammals ought also to be analyzed in the same way as macaque and cat; Zilles and Wree (1994) may provide a start at the relevant rat cortex neuroanatomy for compiling connectivity and adjacency databases. -- The clearer the picture of the Size Law growth function can be rendered, the more feasible it becomes to use that function in turn to extrapolate out to a predicted optimization rank for entire cortical systems.

And, of course, these striking optimization observations immediately raise a series of questions about mechanisms by which nervous systems could attain this performance: A starting point is to implement and evaluate a genetic algorithm for cortex optimization, along lines of the elementary but robustly-performing GENALG for worm ganglia described earlier (to simplify cortex-genome isomorphism, we



**Figure 10.** Size Law for cat cortex "meta-modules". If a set of connected components is optimally placed, then a set of meta-modules each consisting of a subset of those components in the same positions will also be optimally placed. The 40 Brodmann areas of the visual, auditory, and somatosensory regions of the cat cortex (with connections and adjacencies as described above) were grouped into 14 such meta-modules. A series of nested subsets of those meta-modules was then generated, as in Figure 9. The same Size Law trend of optimality improvement of the actual meta-module layout with increasing subset size is evident as for the actual layout of individual components of the visual cortex: As subset size increases, optimality-ranking of actual layout consistently improves (with one exception,  $p < 0.02$ ). (Exhaustive searches of all alternative layouts were performed, except for the 14 meta-module set, where  $10^3$  layouts were sampled.) However, since 40 individual areas are now included in these 14 meta-modules, the Size Law furthermore implies that such a larger subset of the total 57-area cortical system should show better optimization than the 15-area visual subset. Such improvement is evident here: For example, by a subset size of 10 meta-modules (= 31 cortical areas), the actual layout's top  $10^{-5}$  rank equals the full 15-area visual system's rank; the full 14-meta-module actual layout ranks in the top  $1.76 \times 10^{-7}$  of all  $14!$  possible alternative layouts--about a hundred times better than the full 15-area visual system. Broken-line curve shows corresponding analysis for a randomly shuffled layout of the meta-modules; no Size Law trend is now evident.

will explore a "2-dimensional genome" concept). In general, such surprising results stand in need of multiple, independent confirmation (cf. Tensarama and Genalg in connection with the worm ganglion optimization results): Synopsys Inc. has offered to make available "FlexPlace", their latest microchip circuit placement design software package (Goering, 1999), for us to test on the two-dimensional cortex layouts. It should be noted that, according to the Size Law as explained, with larger layouts, fewer alternative layouts will be expected to be cheaper; yet the search space will be growing exponentially. As a consequence, even an interpretable random sample of alternative layouts will rapidly cease to be feasible. Our only alternative assay of optimality will then be such guided hill-climbing procedures as genetic algorithms or simulated annealing.

## II. Other Neuroanatomical Optimization Agenda

To illustrate the fan-out of lines of inquiry from the main axis of this research program, we will also sketch some longer-range topics.

Mapping "chaotic" optimization landscapes: As reported earlier, we have found that both a genetic algorithm like Genalg and a force-directed placement (FDP) algorithm like Tensarama perform notably well in optimizing ganglion placement for the actual connectivity matrix (Figure 3) of C. elegans. This good performance turns out to be interestingly narrow-tuned: (i) Adding or removing as little as a single connection (of ~1,000 total) in some cases can change the actual matrix into a "killer matrix" input that is highly prone to paralyzing a FDP algorithm in local-minima traps. (ii) Similarly, one can find some "killer layout" initial input positionings of the ganglia of the actual matrix that will paralyze the FDP algorithm (Figure 6). (iii) We have also seen that, for the actual worm matrix, only the very best layouts in terms of adjacency-rule performance correlate well with cheap total wirecost (Figure 8). Each of these instances of discontinuous, very sharply tuned performance *prima facie* suggests "chaotic" structure (e.g., Thompson and Stewart, 1986), and seems worthy of further, systematic exploration. For, each exhibits a Butterfly Effect: some quite small changes of input conditions--but only in a limited range--yield drastic changes in behavior. We need to compare these natural neuroanatomical matrices with some typical benchmark VLSI circuits. [E.g., <http://vlsicad.cs.ucla.edu/~cheese/ispd98.html>]

In addition, if we develop a robustly-performing genetic algorithm for cortex layout optimization, similar sensitivity analyses will be indicated. These studies will entail basic mapping of the optimization terrain--for instance, the "neighborhood" around actual cortical layouts (i.e., the subregion of nearby layouts that differ from the actual one by only a small number of component swaps) appears to be a particularly good one, richer in lower-cost layouts than randomly-sampled zones.

Self-optimizing large-scale neuron arbor anatomy: We will continue to seek other analyzable arbor data sets, particularly ones



that include branch diameter data via electron microscopy. We have identified some of the most complex biological structures to be generatable "for free, directly from physics"--namely, neuron arbors (Cherniak, Changizi, and Kang, 1999), and, in a sense, the layout of worm ganglia via vector mechanics; it is natural to seek along these lines for other examples of neuroanatomical self-organization. Another basic issue worth continuing examination is, does Steiner tree optimization for dendrites and axons mesh in interesting ways with component placement optimization for worm ganglia or cortex areas (cf. the earlier discussion of branching and ganglion placement)? Also, The significant role of fluid flow behavior in our "neural fluid mechanics" account of arbor morphogenesis draws attention to the idea that modulators of the fluid-mechanical milieu of the nervous system may govern aspects of its normal development. Modification of properties such as viscosity and surface tension therefore seem worth investigation--for instance, toward promoting connection regrowth after injury. (Such a study will involve collaboration with a developmental physiology laboratory.) Conversely, complex tree-structures derivable from simple fluid dynamics might provide an enriched milieu for developing "neuromorphs"--artificial neuronlike signal processing elements (Mead, 1989)--that could grow their own networks.

Other network optimization concepts: Almost all of our work thus far has focussed on Steiner tree and component placement optimization. Another concept that seems applicable to neuroanatomy is subgraph partition (Garey and Johnson, 1979; Sherwani, 1995), which is also NP-complete. As an example, are the 302 neurons of *C. elegans* optimally grouped into ganglia; or, are there alternative clusterings that would decrease the total number of long interganglionic connections? Another optimization concept that seems applicable to anatomy and/or physiology is flow maximization in a network (Garey and Johnson, 1979), which requires only polynomial time for solution. (Similarly, linear programming problems (Hillier and Lieberman, 1990), perhaps the most widely encountered optimization tasks in current operations research, seem concepts worth exploring for modelling some types of behavior.) indeed,

Other neuroanatomical connectivity datasets: (i) In *C. elegans*, the circumpharyngeal ring functions as the main crossbar network--one third of all connections in the nervous system occur there (Cherniak, 1994a). The published anatomy of the ring (principally White et al, 1986; see also the study specifically of ring structure by Durbin, 1987) appears to be sufficiently detailed to permit an optimization analysis of the siting of fibers within the ring for making connections. In addition, some information on the developmental trajectory of the *C. elegans* nervous system is available (e.g., positions of nuclei in embryos at several stages, cf. Sulston et al, 1988); this temporal dimension is of course relevant to questions about the mechanisms of optimization. (ii) *Ascaris* is a much larger nematode, the neuroanatomy of which Goldschmidt studied extensively via light microscopy at the beginning of the last century. Goldschmidt's *Ascaris* work is largely ignored today, (perhaps because Goldschmidt was on the losing side of the cellularist-reticularist

debate); he only published some of the worm's neuroanatomy. However, examination of, e.g., Goldschmidt (1909) reveals a surprisingly extensive map of the most complex portion of the most complex structure in the nematode nervous system: the junction of the ring with the ventral cord. Connectivity information is extractable even when neurons are represented as anastomosing, rather than synapsing, with each other. We have located Goldschmidt's unpublished neuroanatomy at the University of California, Berkeley library; it needs to be examined as at least a first step at another possible connectivity database. (iii) Similarly, Krieg (1963) may be a starting point worth exploring for modelling connections of the cerebral white matter (e.g., via simple "stack of slices" imaging software). Given traditional attention instead to cortex anatomy, even such preliminary data might have pilot biomedical significance, for instance, in meshing with the Visible Human project [[www.nlm.nih.gov/research/visible](http://www.nlm.nih.gov/research/visible)].

Finally, a larger question: If one takes seriously the instances of distinctively fine-grained neural optimization we have uncovered already, a larger question emerges: Why is such extreme connectivity minimization occurring? Of course, "Save wire" has obvious fitness value as explained earlier--in reducing volume of a delicate, metabolically costly tissue, and in reducing signal propagation delays in a notably slow transmission medium. However, such optimization nearly to absolute physical limits is rarely encountered in biology (e.g., Cherniak (1994b) cites human visual and auditory system amplitude sensitivities under certain conditions). The usual view (e.g., Gould, 1980) is that Nature cannot afford to optimize, but instead--like any finite-resource engineer--only sacrifices, with a compromise among competing desiderata that is "good enough". Natural selection almost never gets to begin with a clean slate, but instead must design organisms as a prisoner of prior evolutionary history.

Thus, the type of striking neural optimization we are observing in itself needs explanation regarding its functional role: it could be either a clue about basic brain mechanisms that require such extraordinary connectivity minimization, and/or a sign of some unexpectedly feasible means of attaining such optimization. Neuroanatomical cases where such optimization is not present become as diagnostically significant as cases where it is present. "Why" thus becomes as important as "how" here. Attention thereby naturally turns to issues of neural function as well as structure--indeed, in any case, the two really seem to mesh seamlessly. Just as a real brain does not consist of infinitely thin wires, its connections do not have virtually infinite signal propagation velocity. Hence, the methodological approach we started with for brain structure volume, and the stringency of limits upon it, needs in turn to be recapitulated for brain function and its temporal constraints.

### III. Implementation

The above enumeration indicates the range of investigations entailed by this research program; which of the later projects is undertaken will of course depend upon earlier results. The main

technical hurdle of this work is the enormous, exponentially-exploding, computational costs of the optimization searches. We can only asymptotically approach a proven answer to the simple question whether the full set of cortical areas of a brain are in fact optimally placed. And the main technique of the contemplated research is continuing the series of computational experiments, employing a hierarchy of computational resources:

- (a) A small group of ~1 Gflop Windows-based workstations (to be acquired by stages, about 1/year), for our laboratory.
- (b) Time on the IBM SP-2 parallel array at University of Maryland Laboratory for Parallel and Distributed Processing, particularly for optimization of our code.
- (c) Time on the Cray SV1 parallel machines at (i) the NCI-Frederick Advanced Biomedical Computing Center (ABCC), and (ii) the National Partnership for Advanced Computer Infrastructure (NPACI) at the San Diego Supercomputing Center.
- (d) We are also interested in exploring the emerging idea of "worldwide distributed computing," harnessing idle processor time of some of the  $10^8$  computers presently connected to the Internet--on the model of the ongoing SETI analysis of the cosmic electromagnetic spectrum.<sup>1</sup>

Our basic "minimum computational force necessary" strategy in choice of computational environment for a given task entails, in particular, tying up as little funding as possible in acquisition of hardware (which rapidly obsolesces (cf. Moore's Law), requires costly maintenance regimes, etc.). We plan to proceed by phases through the above hierarchy: Our typical billion-layout cortex optimization searches take less than 100 hours on 1/2 Gflop workstations; after code-optimization (our programs have minimal memory requirements, and easily parallelizable structure), we can expect each would require less than an hour on the 100 Gflop parallel machines of ABCC or NPACI. As explained earlier, cortical systems of 20 or more components will require larger searches.

Project schedule: Of course, as the timeline below extends further, timetable uncertainties accumulate, since later project stages depend upon prior outcomes.

#### Tentative timetable

- | Year |  |
|------|--|
| 1    | Cortex optimization searches:              |
| 2    | cat (vis, aud, som), macaque (vis), rat... |
| 3    | Optimization mechanisms:                   |
| 4    | genetic alg, force-directed placement...   |
| 5    | Functional roles of neural optimization.   |

(No hazardous materials, nor human or other vertebrate subjects, are to be used in the proposed research.)

1. Some current "collaborative computing" Websites:

Seti: [www.seti.org/setiathome.html](http://www.seti.org/setiathome.html)  
Code breaking: <http://rc5.distributed.net>  
Pi: [www.exploratorium.edu/learning\\_studio/pi/pi.html](http://www.exploratorium.edu/learning_studio/pi/pi.html)  
Large Primes: [www.utm.edu/research/primes](http://www.utm.edu/research/primes)

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