A VIRTUAL ENVIRONMENT: EXPLORING THE BRAIN FOREST

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ABSTRACT

Exploring the Brain Forest, a virtual environment currently in design, will present hierarchical views of the brain at several levels of scale from a global overview to immersion within its forest of neurons and glial cells. Participants are encouraged to enter, become immersed in, and wander within the most spatially complex structure known in nature. *Exploring the Brain Forest* is being designed as a 3D graphical model onto which will be mapped brain data sets drawn from microscopy of rat, monkey and human brain tissue mapped at the limit of optical resolution. In the cortex, for example, pyramidal neurons scaled up 50,000 times resemble giant Sitka spruce trees, while other neurons mimic hardwoods of tropical rain forests. This volumetric brain model will provide both an initial orientation and a portal into the virtual microscopy of brain structure.

Methods for constructing the environment include creating a finite element model of the human cortex and implanting this solid model with synthetically-generated morphological models of neurons. Stochastic L-system models are used for this purpose. The imagery is sufficiently complex that its presentation in a virtual reality simulation requires several entwined display strategies to be successful. Two such strategies exploiting the limitations of the human visual system, gaze-contingent and scale-dependent geometric modeling, are employed to reduce the graphical complexity of the environment.

*Support for the virtual environment, *Exploring the Brain Forest,* has been provided by a Texas Advanced Technology, Program grant 999903-124 from the Texas Higher Education Coordinating Board.

1. THE VIRTUAL ENVIRONMENT

Exploring the Brain Forest * is being developed to present hierarchical views of the brain at several levels of scale from a global overview to immersion within its forests of neurons and glial cells. Participants are encouraged to enter, become immersed in, and wander within the most spatially complex structure known in nature. *Exploring the Brain Forest* is being designed as a 3D graphical model onto which will be mapped brain data sets drawn from microscopy of rat, monkey and human brain tissue scanned at the limit of optical resolution. This volumetric brain model will provide both an initial orientation and a portal into the virtual microscopy of brain structure.

Exploring the Brain Forest will also serve public education. Predominantly the public views the brain as impenetrable and unfathomable, and therefore premature for voyages of discovery and mapping. This demonstration will show that modeling brain structures is not unlike exploring and mapping an Amazonian rain forest. We will also use distribution by VRML 2.0 over the Web and CD-ROMs for this educacional purpose.

1.1. ATTENTIVE GRAPHICAL DISPLAY OF COMPLEX VIRTUAL ENVIRONMENTS

Graphical display of complex virtual environments today lacks realism. Real-time display of virtual environments of the computational complexity of *Exploring the Brain Forest* is currently unmanageable without the displaytime compression promised by attentive graphical display techniques describes below.

The first scale-dependent strategy is contingent upon displaying model neurons at multiple levels of geometric detail.

The second gaze-contingent strategy tracks the viewer's eye and matches the imagery to the gaze-contingent perceptual limitations of the human visual system.

1.2. Scale-dependent geometric modeling

The first strategy evokes different geometric models at different ranges (scales) from the viewer (Figure l). For extreme close-ups we use implicit function surface models, so that neuronal spines can be visualized. At midrange, we use cylindrical models (typically 7-9 polygons for dendritic and axonal segments, where a neuron typically may have 1000 segments. At greater distances we employ wireframe models (with varying integer thickness of wire). And beyond the range of stereo discrimination we fall back upon texture mapping -largely a precomputed backdrop of the neuronal forest. The hierarchical model we have described above requires solving one of the basic computational problems in computer graphics: making smooth transitions between different geometric primitives. We must smoothly change from geometry to texture maps in real time.

1.3. Gaze-contingent geometric modeling

The second strategy, guided by parallel on-going research in our laboratory on gaze-contingent visual telecommunication,[4] would deliver to the eye only that minimal level of information which maintains foveal vision while preserving scene integration. This strategy, perhaps surprisingly, is closely related to the first strategy: range dependent geometric modeling. Specifically, a midrange neuron, viewed with the fovea, requires cylindrical modeling of its segments; the same neuron viewed in the periphery might be modeled with a wireframe model: and the far periphery, as texture map.

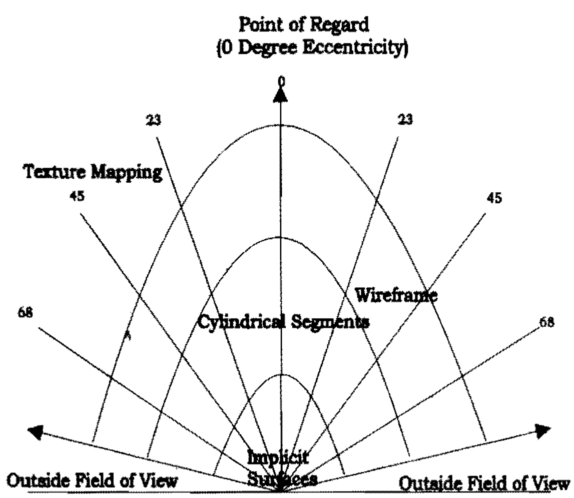


Figure 1. Gaze-contingent segmented stage

For this gaze-contingent strategy, an eye tracker, acquired in a recent NSF (USA) instrumentation grant is being used. Initially we are using the stereo display on our SGI Onyx machine and plan to migrate later to a head-mounted display (HMD) with helmet-mounted eye tracking.

2. Modeling neuron development and morphology

A representational framework for modeling neuron development and morphology is being developed that is adequate for both the quantitative description and the stochastic generation of neuron populations. The neuron morphology modeler, N++ is being tested by analyzing a sparse array of 300 manually traced pyramidal cells from the rat visual cortex. All models are limited to modeling neuron morphology as viewed at the limit of optical resolution. N++ will also be interfaced with the compartmental neuronal modeling programs, Neuron and Genesys, to facilitate functional modeling.

At the data level, a quantitative description of cells (their dendritic and axonal arbors, soma, and spines) is transferred to a neuron morphology *data repository*. The morphological data can be from either optically traced biological neurons or from synthetically generated neurons. A *neuron visualizer* allows a three-dimensional interactive display of neurons in the data repository, either singly or in juxtaposition. The data level of N++ is currently operational.

At the knowledge level, the population of cells in the database is transferred to the *statistical analyzer*, where distribution functions governing the stochastic generation of neurons are extracted from the data and stored in the *knowledge base* as components of stochastic Lsystem models of neuron morphology. The *neuron generator*, then completes the cycle by generating a synthetic population of neurons. The neuron generator is fully operational, but statistical analysis currently employs only primitive *ad hoc* procedures.

Our goal for N++ is two-fold: (1) that stochastically generated neurons should be statistically indistinguishability in their morphology from a random sample of the original optically traced neurons, and (2) that the growth of these neurons is accurately modeled.

2.1. Terminology for neuron morphology

The constituents of a neuron are its soma, one or more dendritic arbors, and its axon or axonal arbor[8] (Figure 2).

Given a dendritic tree, three types of nodes are identified:

(1) the *soma node* representing the point of attachment of the dendritic tree to the soma; (2)*branch points* at which the dendrite branches; and (3) *terminal nodes*, the end-points of the dendritic arbor. Starting at the soma node a unique path exists to any other node of the dendritic arbor.

A *dendritic segment* is the portion between two consecutive nodes in the dendritic arbor. The *stem segment* has its origin at the soma node and is counted as the first-order segment. Daughter segments arising from the first-order branch point are called second-order segments, and so on. A segment ending in a terminal node is called a *terminal segment*; all others are called *nonterminal segments*.[7,8]

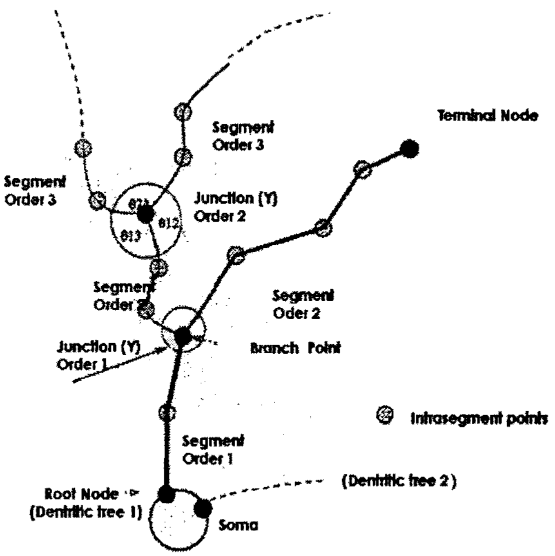


Figure 2. Dentritic arbor representation[8]

The *junction* at a branch point is called a *bifurcation* if the parent segment branches into two daughter segments, and a *multifurcation* if the junction gives rise to more than two daughter segments.[7,8]

Axonal processes, including axonal arbors if present, are describes by nodes, segments, and junctions in like manner.

2.2. The role of stochastic L-system modeling

Today L-systems are an accepted tool in plant modeling.[9,10] Neurons, when scaled up by 10,[5] show a strong resemblance to trees. This similarity led us to harness the power of L-systems to produce geometric models of neurons. A formal representation of neuron morphology, adequate for the geometric modeling of manually traced neurons, is presented in Mulchandani's thesis[8] and in the computational neuroscience literature.[5,7] The concept of a stochastic L-system is then introduced, and the critical distribution functions are defined that govern the stochastic generation of dendritic and axonal trees. Mulchandani's experiments with various stochastic L-system models for pyramidal, motor-neuron, and Purkinje cells are reported (Figures 3, 4, 5). These models generate synthetic neurons with promising proximity to neurons described in the neurobiology literatura. A prototype neuron morphology modeler, N++, has been designed and its stochastic L-system neuron generator and data-level facilities for data acquisition, transactions with the data repository, and neuron visualization have been implemented, as described below.

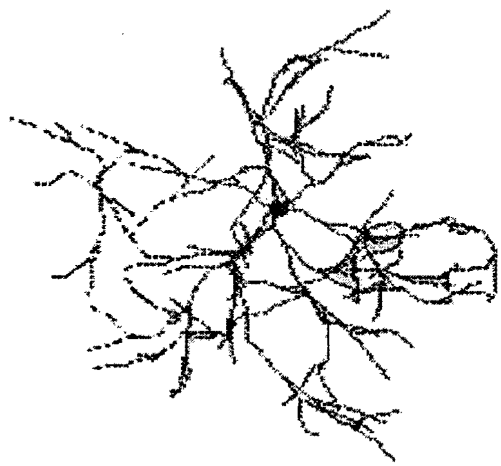


Figura 3. Synthetic L-System motorneuron

The use of stochastic-systems is mandated by the nondeterministic nature of neuron morphology. No two neurons, even of the same type, are identical; yet they are sufficiently similar to be classified as being members of the same cell type. This property points to the existence of a common family of rules, or grammar, where the rules are chosen stochastically to generate instances of the neuron type. These rules presumably mirror the genotype of the neuron. The neuron generation process dynamically mimics the parallel growth of the dendritic and axonal arbors.

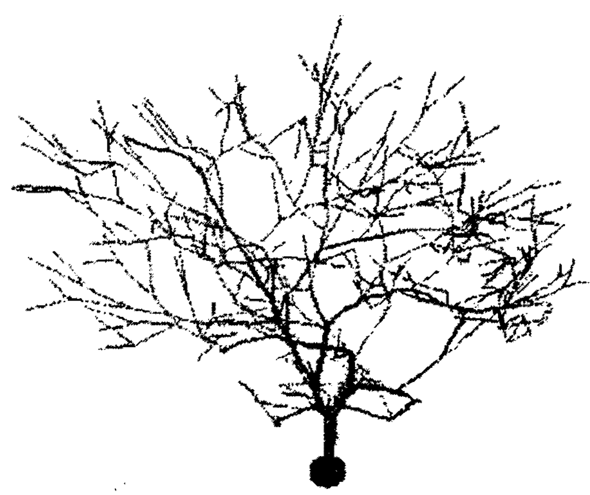


Figure 4. Synthetic L-System purkinje cell

The advantages of these stochastic L-system models are several. The L-system models bring coherence to existing neuron databases; and they allow us to estimate the new information contributed by additional measurements of neuron morphology. In summary, L-system models provide the appropriate methodology for describing the development and morphology of neuron populations.

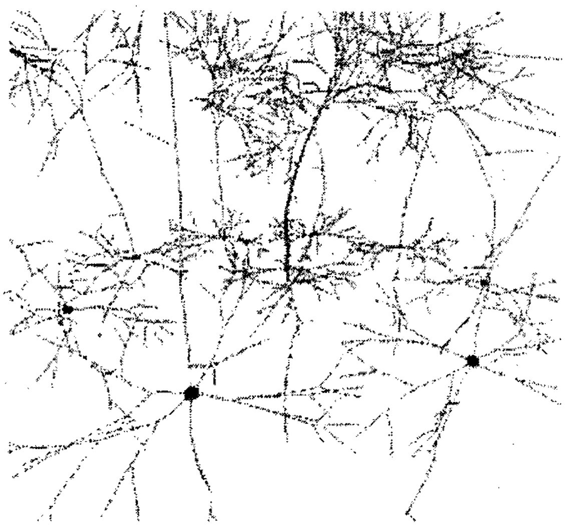


Figure 5. Forest of synthetic pyramidal cells

2.3. N++, A PARAMETRIC STOCHASTIC L-SYSTEM MODELER

N++ provides a representational framework for the description of neuron development and morphology. N++ has been designed with three key features in mind:[7,8]

1. Accurate growth modeling. The system should accurately model the growth and development of neurons within the confines of neural tissue.

2. Accurate structural representation. The syntax of the representation should reflect the morphology of neurons.

3. Ease of statistical modeling. The syntax should lend itself to the types of statistical analysis likely to be needed for stochastic modeling.

These requirements led to the development of a parametric bracketed string notation with a parallel rewriting grammar -a classical Lindenmayer system- for the developmental modeling and structural representation of neurons.

N++ was created to address four issues in neuronal development and morphology:

- What structurally defines cell typology?
- What constitutes the pattern of growth of a cell type?
- What defines normal/abnormal morphology of a cell type?
- When can the morphology of two cell populations be statistically differentiated?

In N ++, cell typology is defined by the representational syntax; cell growth is handled through the application of a parallel rewriting grammar: the normal morphology of a cell type is described through stochastic modeling; and the N++ string representation of cells allows for statistical analysis and differentiation.

2.4. MODELING NEURON DEVELOPMENT AND STRUCTURE WITH A STOCHASTIC L-SYSTEM

Experiments with various stochastic L-system models of neuron morphology have given us neurons with promising proximity in shape to neurons illustrated in the neurobiology literature.[8] While our group is working to improve this degree of proximity, a more important goal is to validate the L-system neuron models against databases of traced neurons. To this end the neuron morphology modeler, N++, described below, has been devised and largely implemented to provide for iterative refinement of L-system models[7,8] (Figure 6).

Data level of the modeler Central to the neuron morphology modeler, N++, at the data level is the *neuron morphology data repository* (Figure 6), a relational database system hosted on a SQL-compatible database server. This database management system stores for each neuron a representation of its soma and for cach dendritic or axonal arbor a representation of its segments and junctions. A graphical user interface to the data repository (designed in Optima++, PowerSoft Corporation) is provided for PCs running Windows NT/Windows 95.

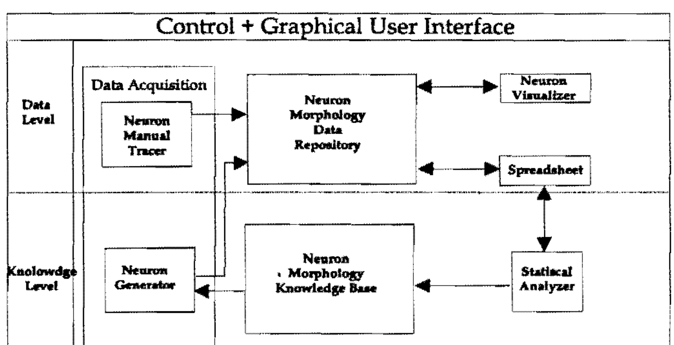


Figure 6. N++ Neuron Morphology Modeler[8]

The neuron morphology data repository can receive input (at the data level) from the neuron tracer (Neuron tracing System, Eutectic Electronics, Inc., Raleigh, NC) or (at the knowledge level) for the stochastic L-system *neuron generator* (built upon public-domain software for L-system modeling, known as *lsys,* copyright (c) 1990, 1991 by Jonathan Leech, University of North Carolina). In this sense the data repository is indifferent as to whether it is storing data from real traced neurons or synthetic neurons.

Upon command, through the graphical user interface, the data repository, can prepare database files for the spreadsheet program (Excel, Version 7.0, Microsoft Corporation). The spreadsheet program allows data editing and graphical summarization and provides the natural input to the next stage of analysis, the knowledge level of the neuron morphology modeler, N++, as described below.

Knowledge level of the modeler. We now enter the knowledge level (Figure 6), where spreadsheets generated from the neuron morphology data repository provide the convencional input to the *statistical analyzer*, (Systat, Version 5.03, Systeat Inc, Evanston, IL). In particular the statistical analyzer estimates the distribution functions for segment nontermination, segment trajectory and length, and the rotations characterizing bifurcations. At present only primitive *ad hoc* techniques that our group has developed are available for this purpose. The parametric distribution functions ascertained by the statistical analyzer are used to refine the L-system models of the neuron populations.

Next, paralleling the neuron morphology data repository, we have at the knowledge level the *neuron morphology knowledge base,* which stores the L-system grammars and their associated distribution functions for stochastic generation of synthetic neurons. And finally, closing the loop, we return to the *neuron generator*, described above.

With experience we anticipate the system components at the knowledge level will evolve into a knowledge system for L-system modeling of neurons.

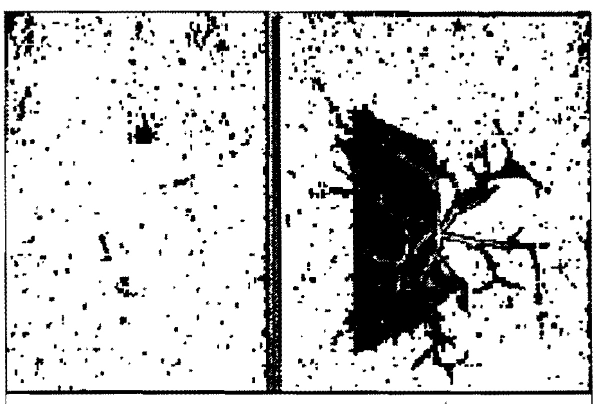
2.5. Neuron visualization

A Neuron Visualizer, developed by Mulchandani[8] and extended by Tewari[2] Burton, and DeVaul, can read the object-model format of a neuron's morphology and display the neuron in 3D. The neuron visualizer is written in OpenGL and C++. Some salient features of the visualizer are listed below:

- *Display mode* - The neuron morphology is recreated from the input files and displayed in 3D (Figure 7). Three modes of display are available: the stick model, the cylindrical model, and the implicit surface, model.

In the stick model, all segments are displayed as lines with integral thickness. The stick model gives a nearly instantaneous response when using the navigation or editing features described below. In the cylindrical model, segments are drawn as colored, lighted cylinders with dimensions proportional to the segment diameters. The implicit surface model is used for viewing space-filling neuronal structures, where typically the growth cone of neurites are explicitly modeled.

- *Navigation* - The camera view of the scene is under the user's control. Any of the camera controls, namely, the field of view, the eye position, or the gaze direction, may be altered interactively.
- *Segment query* - A segment can be selected using point-and-click interaction. On a successful selection, the selected segment and the dendritic or axonal subarbor rooted at that segment are highlighted. All the basic information about the segment and its daughter segments, if any, are accessed from memory and displayed to the user.
- *Plane of intersection* - A translucent plane can be moved along the Z-axis. and intersections of this plane with the neuronal processes are displayed simultaneously in a separate window. This is equivalent to taking a section of the neural tissue parallel to the plane. This paradigm is similar to viewing serial sections of neural tissue containing a stained neuron or forest of stained neurons.



Segment ID is SEG0032
Primary Daughter is SEG0032
Secundary Daughter is SEG0048
Junction for which its a base JUNC0015

Figure 7. 3D Neron Vusualizer [8]

3. The finite element brain

Our group at Texas **A&7M** University has developed techniques to construct a finite element model of human cortex and populate selected finite elements with synthetically generated neurosis. These procedures are describes below.

3.1. 3D reconstruction of human neocortex

Contouring - Consecutive human brain sections (512 x 512 pixels) where provided by Arthur Toga (http://www.loni.ucla.edu) (Figure 8). Contours were generated using *Elastic* Reality from Avid Technology. *Elastic Reality*, a special effects tool for 2D and 3D animation, allows contour construction using piecewise cubic bezier curves and facilitates comparison of consecutive contours. Contours were generated for the outer and inner cortical boundaries. The contours are resampled and the resulting points used for 3D reconstruction.

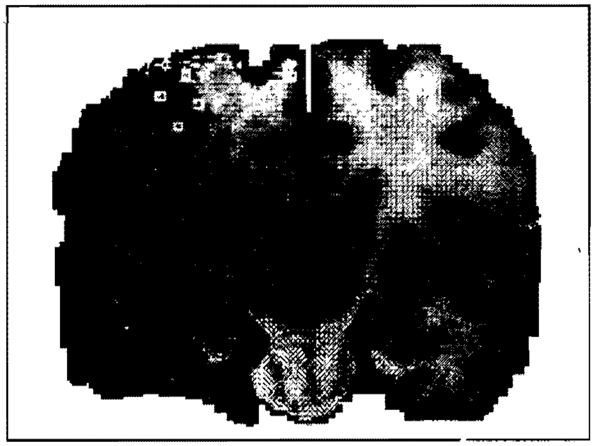


Figure 8. Contour construction with bezier curves

3.2. Biologically-consistent finite element decomposition

The reconstructed tissue must be partitioned into three dimensional finite elements prior to numerical grid generation.

Biological consistency - The finite elements are chosen to follow the natural symmetries of the tissue, as defined by its primary native neuron type and thinking how a neuroanatomist would cut tissue locally to make successive sections look as alike as possible.

Cortical FE decomposition - Each finite element has four vertices on both the outer and inner cortical surfaces. From each vertex (u, v) on the outer surface, a vertically oriented w-curve is dropped which follows the estimated axis of a pyramidal cell at this location. The intersection of this dropped w-curve with the inner cortical surface defines the curvilinear coordinate (u, v) on the inner surface. The inner cortical surface is then reparameterized to match that of the outer cortical surface.

Then v-isosurfaces are chosen perpendicular to crest lines (defined by the gyri). Finite element modeling terminates at valley lines (defined by the sulci). The curvilinear coordinates u, v, and w, chosen this way, maximize symmetry -making successive sections look as similar as possible. Figures 9 and 10 show two views of the same reconstructed human neocortex.

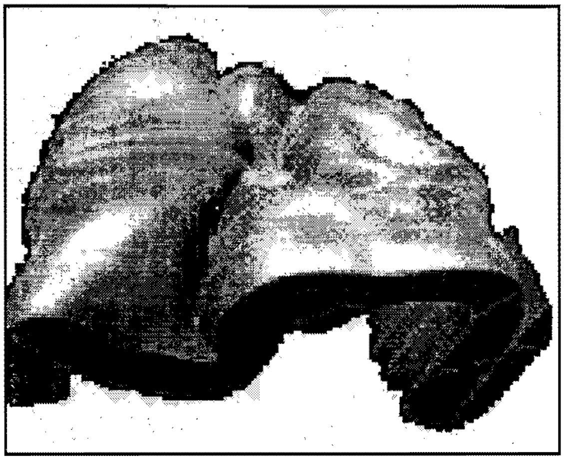


Figure 9. Finite Element model of human cortex (viewed from the outer surface)

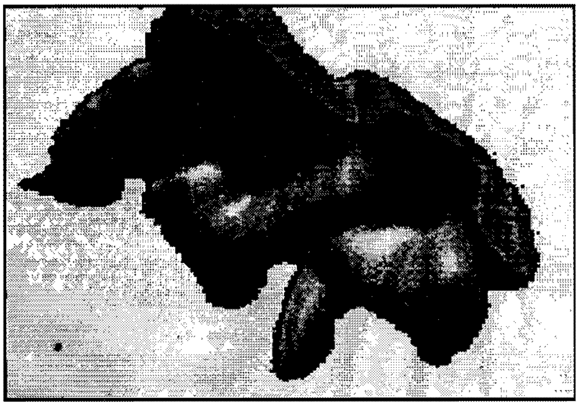


Figure 10. Finite element model of human cortex (viewed form the inner surface)

4. Numerical irid generation within neocortical finite elements

A curvilinear coordinate system, consistent at its boundaries with that of the bounding finite element, must be imposed to provide a lattice for the generation of synthetic neurons. Numerical grid generation, as this problem is called, is well described in Knupp and Steinberg.[1] These 3D grids provide a basis for morphing transformations which compensate for the specimen-specific environment in which neurons develop in life, which can idiosyncratically distort their dendritic and axonal arbors.

Three-dimensional grid generation techniques have been developed by us to impose curvilinear coordinate systems upon biologically-consistent finite element models of cortical areas, and to provide spatial normalization and registration. [3] 3D numerical grid generation methods define mappings between a logical domain (unit cube) and a physical domain (finite element of reconstructed tissue). The finite element of reconstructed tissue serves in turn as a solid model with six parameterized surfaces. 3D numerical grid generation embeds a curvilinear coordinate system within the reconstructed tissue. At the boundaries of each finite element the curvilinear coordinate system matches the original surface parameterization.

We have used algebraic grid generation, using tricubic interpolation, to good effect[3] (Figure 11). Alternative techniques for grid generation are described in Batte's thesis.[3]

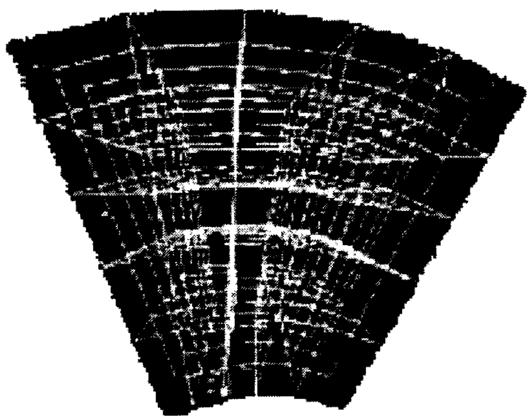


Figure 11. Gridded human cortex finite element

4.1. Neuron implantation within the finite element

0.25-1 million neurons are typically housed in a finite element (nominal volume = $1mm^3$). From seed points within the finite element the stochastic L-system neuron generator can grow synthetic neurons. And of course optically-traced biological neurons can also be placed within the tissue. Figure 12 shows a finite element of human cortex populated with synthetically generated neurons.

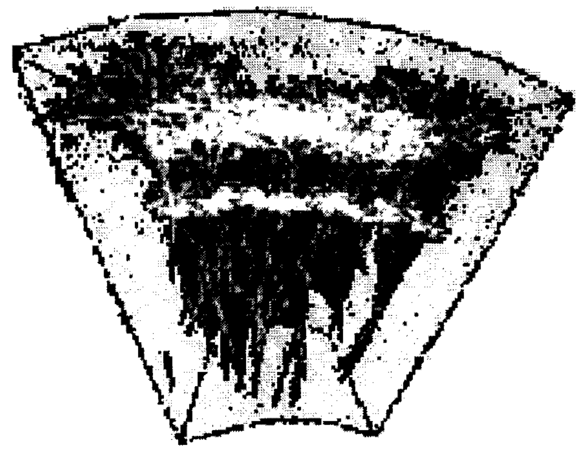


Figure 12. Finite element populated with synthetic neurons

5. Significance and summary

The research discussed above provides three general insights:

- graphics display-time compression techniques based on a visuotropic model of the human visual system,
- smooth transitions within a hierarchy of geometric primitives depending on the viewer's point of gaze and range (and hence, scale) of the object, and
- demonstration of these graphical techniques in a complex virtual environment: *Exploring the Brain Forest.*

Attentive graphical display of complex environments can be expected to benefit disciplines such as (1) virtual reality, where encoding of imagery at the viewer's point of gaze imiproves realism: (2) computer animation, where intended regions of interest are scripted into the imagery; and (3) computer-supported collaborative work, where attentive display enhances telecommunication. More generally, the identification of visual information that must be delivered «just-in-time» to the viewer should inaugurate an era of viewer-adaptive visual communication.

The emergence of form in the development of biological objects is one of the most fundamental problems in biology. Modeling brain morphology at the cellular and tissue level brings a richness to our understanding of brain organization that both complements and transcends knowledge derived exclusively from neurophysiology and brain atlases. Our studies deal with the fundamental neuronal and glial structures that underline nervous function in the brain.

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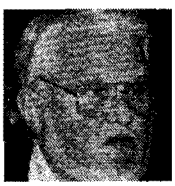

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PÁG. 44 **Juan Luis Díaz de León Santiago**. Nacionalidad mexicana, obtuvo el doctorado en el CINVESTAV del I.P.N, México con especialidad con ingeniería eléctrica. Profesor titular en el Centro de Investigación en el I.P.N.	PÁG. 44 **Juan Luis Díaz de León Santiago**. Nacionalidad mexicana, obtuvo el doctorado en el CINVESTAV del I.P.N, México con especialidad en ingeniería eléctrica. Profesor titular en el Centro de Investigación en Computación en el I.P.N.
PÁG. 52 Línea 33 [7]...	 Línea 33 [7] A. Rosenfeld. Digital Topology. *Amer.Math. Montly, 86 :621-630, 1979.* [7] G. Matheron. *Random Sets and Integral Geometry.* John Wile and Sons, New York, 1995. [7] B.Vazquez, J.H. Sossa and J.L. Díaz de León Autoguided Vehicle Control using Expended Time B-splines. In *IEEE International Conference on Systems, Man and Cybernetics*, pages 2786 -2791, San Antonio Texas, October, 1994. [7] P. Perner, P. Wang and A. Rosefeld (Eds). Advances in Structural and Syntactical Pattern Recognition, Springer 1996.
PÁG. 53 Línea 14 Loa artículos deben ajustarse a las siguientes especificaciones :	 Línea 14 Los artículos deben ajustarse a las siguientes especificaciones :