Visualization in the Neurosciences:
Addressing Problems in Research, Teaching and Clinical Practice

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This paper will discuss the use of visualization in five neuroscience projects. The paper addresses a central issue: How can structural models be best manipulated to gain insight into nervous system function? Current visualization projects that take up this issue from three different user perspectives (researcher, student, and clinician) will be described. Several conceptual and technical issues these projects (and others like them) pose will also be taken up here.

Introduction

Understanding the links between structure and function of the Central Nervous System (CNS) can be immensely difficult. In a system as complex as the CNS, different perspectives on visualization are required by the particular needs of researchers, clinicians, and educators. We will describe here five representative CNS visualization projects that reflect these perspectives. The first two projects focus on the molecular level, particularly mechanisms of process and control within neuronal systems. The next two relate functional subsystems to gross morphology and neuroanatomical pathways in educational applications. The final project describes a long-term effort underway to develop a national resource of images related by function. These projects, when taken together, exemplify current trends and approaches in this area.

Several technical and conceptual issues that extend beyond these projects will also be discussed. These include delivery platforms, integration paths, the development of standards for image acquisition and representation, and use in routine medical practice.

Project Descriptions

Mapping of specific neuronal populations in the human brain: *University of Massachusetts Medical Center*

Microscopic systems coupled with small computers can be used to generate high resolution panoramic maps and 3-dimensional (3D) reconstructions of human brain tissue. The human brain is the biggest and most complex of all mammalians. Mapping the human brain requires scaling 5 orders of magnitude, from 1 um (thickness of an axon) to 6 inches (length of a complete section). The study of antibody stained populations in the human brain, therefore, provides a good benchmark for judging the capabilities of brain mapping systems.

We have recent experience with 2 small-computer based mapping systems which use a computer-controlled motorized microscope stage. These systems superimpose computer graphics over live microscopic images [1]. These computer resources coupled with innovative antibody staining techniques enable us to overcome limitations of scale, and will aid researchers in formulating hypotheses regarding structure-activity relationships within the CNS.

Specific neuronal populations can be collected and analyzed in a rigorous and meaningful way. In addition, computer-aided techniques that allow for the comparison of normal and pathological human brain tissue may lead to important insights into mechanisms underlying human neurological disease [2,3].

An ideal mapping system must fully integrate database management facilities with the data acquisition described. This is a prerequisite for the widespread acceptance of mapping systems by the neuroscience research community.

The Visualization of Neuronal Cell Sub-Populations in the Rat: *Tufts University School of Medicine*

A major effort in our laboratory has been devoted to quantifying parameters of a peptidergic neuronal system, i.e., one that contains luteinizing hormone releasing hormone [LHRH] in rats.

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TH0311-1/90/0000/0322/$01.00 © IEEE

To study this system of neurons (diffusely distributed in 3 dimensions) specialized 2D and 3D visualization methodologies have been developed.

"Scepter", a custom written mapping program, is used to identify the x,y,z coordinates of each immunocytochemically labelled neuronal cell. Specific subpopulations of LHRH+ neurons are then reconstructed in 3D with a modified version of MOVIE.BYU on a MicroVax 3500. These subpopulations can be visualized with a reference model containing major anatomical landmarks, enabling us to selectively compare experimental data sets. For instance, male vs. female, gonadectomized vs. intact, effect of antiserum, and phase of endocrine estrous cycle [4]. Without these visualization techniques, it would have been impossible to identify a nonvariant medial "core" group of LHRH + cells, and a variant peripheral "stripe" group [5].

2D techniques are employed to study further ultrastructural characteristics of these neurons at the electron microscope level [6]. Image enhancement and feature extraction techniques are performed on digitized images [512 x 512 with 256 gray levels]. Enhancement techniques include standard transformations and filtering. Image segments are extracted using artificial intelligence algorithms for boundary tracing and scene segmentation. "IMMOVE", a custom developed kernel, integrates automated measurement capabilities with the enhancement and analysis routines. Insights gained by the application of the visualization techniques described have led us to develop new research questions.

A Responsive Learning Environment: *Tufts University School of Medicine*

To understand the functioning human nervous system requires a comprehension of the basic organization of the Central Nervous System (CNS). To achieve this, students must develop viable mental models of a 3D CNS, typically from 2D section views (ie. tissue sections, photomicrographs, atlas figures, MRI scans). Imaginative reconstruction of this kind is a prerequisite to differentiating dysfunction in a clinical context.

A student is typically under severe time pressure to internalize these concepts, and if they do not, basic concepts of clinical neurology will prove to be incomprehensible. These concepts are among the most difficult and frustrating medical students must develop.

Non-interactive linear video sequences of color-coded, animated models can provide powerful aids for the visualization of CNS structure. Our efforts are centered on developing interactive paradigms for the integration of these 3D models with various forms of functional knowledge. It is believed that, in this way, systems can be developed that will greatly raise the student's ability to relate structure and function. Of the large corpus of knowledge the neuroscience student must learn, we have been concerned with basic functional information, namely Conscious Sensory and Voluntary Movement Systems. The modules we are developing give students "guided tours" of particular functional subsystems. Students can freely explore individual structures, their physical relationship to each other, and the pathways interconnecting them. This includes the free placement of lesions and prediction of resulting losses in function [7].

The 3D computer reference models we have developed are polygonal surface representations, reconstructed from serial section data. This data was obtained from photographs of freshly cut surfaces of a frozen brain following removal of consecutive 50 micron sections through the coronal plane [8]. The tissue sections were digitized and manually contoured by an anatomist. Model views are then developed and animated sequences are rendered on a high-powered graphics workstation. The resulting NTSC images are recorded on analog videodisc. We have chosen, as our initial delivery platform, the IBM InfoWindow system; consisting of an IBM PC, videodisc player, EGA overlay hardware, and touch screen monitor.

Developing A Comprehensive 3D Database of CNS Structure: *University of Washington School of Medicine*

To construct a manipulable neuroanatomical 3D data base, major brain sections have been digitized using tracings of 35 mm slide projections of images of fixed, unstained specimens. We are able to resolve structures as small as the fornix system of fibers. The digitized contours of each image were realigned using fixed fiducials. Objects such as the cerebral cortex, underlying white matter, striatal components, thalamus, hypothalamus, septal and basal regions, amygdala, hippocampus, cerebellum, brain stem and ventricles were digitized individually. 3D reconstructions were made of nuclear subdivisions of the thalamic, hypothalamic, septal, basal and amygdaloid regions.

We are also reconstructing the human brain stem from 40 um serial sections of Weil and Nissl material. The larger structures seen in the Weil sections (such as the surface of the medulla, pons and midbrain, peduncles, lemnisci, spinal trigeminal and solitary tracts, and ventricle system) have been digitized.

Currently we edit display files interactively and render objects with surface, color and variable light sources, using custom developed software [9], on Silicon Graphics 4D series workstations. Data is saved in standard sets so the same object can be viewed from different angles or different objects visually compared. Our long range goal is to prepare "generic" 3D graphic neuroanatomical models of the brain that can be viewed in frontal, horizontal and sagittal sections, and cognate models from MR and CAT scan data [10]. We envision that such structural models can be used in different levels of teaching and problem solving in the neurosciences.

The Visible Human Couple: *National Library of Medicine*

The National Library of Medicine Long Range Planning effort of 1985-6 foresaw that National Library's bibliographic and factual database services would be complemented by libraries of digital images, distributed over high speed computer networks and by high capacity physical media. The issue for NLM was how to best support the development of such image libraries.

A NLM Planning Panel on Digital Image Libraries in Biology and Medicine was set up, met during 1989 and recommended that NLM should undertake, as a first project, building a digital image male and female cadaver [11]. This "Visible Human Couple Project" would include digital images derived from computerized tomography, magnetic resonance imaging and cryosection photography. To achieve this, standards for acquisition and representation of the image data would have to be established. The "Visible Human Couple Project" would serve as a foundation for future sets of related image libraries and as a test platform for developing imaging methods and standards.

A follow-on research effort would develop tools, methods and standards to extract, manipulate and display Project image subsets such as organs, tissue and functional body systems. In addition the Planning Panel argued that this initial "normal" image library should over time be expanded to encompass specialized image sets.

Development, Delivery and Integration Paths

Technological advances in rendering hardware continue to be swift. Within the next 10 years, we should reach a critical price/performance milestone for graphic workstations. When this time comes, dynamic (real-time) manipulation of photorealistic CNS models by users will become commonplace [12].

In the development of more powerful visualization environments, issues of implementation must be carefully examined. Some of those issues discussed here include competing reconstruction methodologies, knowledge representation, and integration.

Currently, much effort is being devoted to development of volume-based modelling and rendering techniques [13]. Automated segmentation of neural tissue, however, remains particularly problematic. Fuchs, et. al. have developed techniques for rendering mixtures of volume data and polygonally defined objects [14]. This hybrid approach may prove particularly fruitful in the neurosciences. Volumetric models can be generated quickly from non-invasive sources. They could then be interfaced with robust comprehensive anatomical reference models of polygonal surfaces painstakingly created by brute force manual contouring and refined over a period of time. In this way, the strengths of each modality can be used to complement the other.

Regardless of the particular reconstruction technique, 3D structural models need to be better linked to other knowledge forms. While the hypertext community has done research in the flexible linking of disparate information, these research efforts have largely concentrated on text and text linkages [15]. The integration of images (let alone 3D structural models) with textual knowledge remains an unsolved problem, and should become an important area for research. At the very least, for visualization environments to be accepted in the biomedical community, they must effectively link 3D models to 2D images as well as to text.

Major emphasis has thus far been placed on the creation of tools for extracting and building of 3D data sets. As these data sets begin to accumulate, increasing effort should be placed on the development of novel user interfaces to address visualization needs in specific domains of neuroscience research, teaching, and clinical practice. These platforms should provide an integration path to new rendering power as it becomes available. One important element is the development of libraries of precomputed images stored on optical media according to a standardized scheme. Standards need to be developed for the systematic variation of animation parameters, eg. viewpoint, color-coding and transparency in the creation of these libraries. Delivery platforms can then be developed which make use of these stored libraries of images while providing seamless integration to the real-time manipulation of the 3D data sets.

As this field matures, for visualization resources to be utilized in any significant way, the knowledge requirements and work forms of particular users have to be taken into account. To achieve this, will require an interdisciplinary approach.

Visualization: A Cognitive Asset for Routine Practice

Although 3D modeling tools have only recently gained widespread application in the medical sciences, it is widely believed that these resources can significantly contribute to research, education and clinical practice [12]. More importantly, all the projects discussed here foreground a routine dimension of medical knowledge and practice -- visual or kinesthetic reasoning. In other words, either this has been taken-for-granted or the implication is it has not been systematically pursued. With one exception [7], this has been the case with these projects. The same can be said, it seems, for much of the literature on 3D modeling.

Kinesthetic, particularly visual, modes of understanding inform all medical thinking about the dynamic relationship between structures (traditionally analyzed out-of-time and in isolation) and functions (conceptualized in real time and implicating multiple structures). For example, empirical studies of clinical practice in neurology suggest there are two fundamental principles of medical reasoning [16]. First, adequate interpretation depends on the practitioner's ability to deduce histories and real-time processes from static series of synchronic descriptions. Given this, it is not surprising that a mode of visualization, the ability to accurately translate information from two to three dimensions, underlies much of their work. Second, a great deal of this type of reasoning is implicit. While it is embedded in, and characteristic of, neurological practice, it is seldom reflected upon apart from discussions of particular clinical cases [16].

For the most part, such modes of understanding have not been explicitly formulated or explored analytically. In short, there is a need to make this type of reasoning an explicit object of inquiry. When this issue has been raised, it has taken a very pragmatic turn and becomes an issue of what kinds of visual information are the most significant or useful [17]. Again, this is largely because these modes of understanding are embedded in the routine practices of medicine and science and consequently have not been critically examined in their own right.

There is a promise and a peril that these new computer resources pose. On the one hand, to be successful, the development of these resources has to lead to a more adequate knowledge of this kinesthetic mode of understanding. This is because to develop these resources requires that models be constructed that can specify the essential features of this mode of understanding. The construction of these models would contribute greatly to our understanding of routine practice and thought in medicine. This, in turn, would enable developers to create resources and environments that would more effectively support routine practice throughout the biomedical community.

On the other hand, there is a peril that the development and implementation of these resources will proceed in the absence of any clear, well-defined understanding of routine medical practice and reasoning. The failure of "strong" artificial intelligence in medicine illustrates what can happen when the design and implementation of new technological resources do not proceed hand-in-hand with detailed analyses of work, practice and thought in medicine [18]. When this occurs, resources will be implemented that do not directly support routines and perspectives central to, and characteristic of, particular end users.

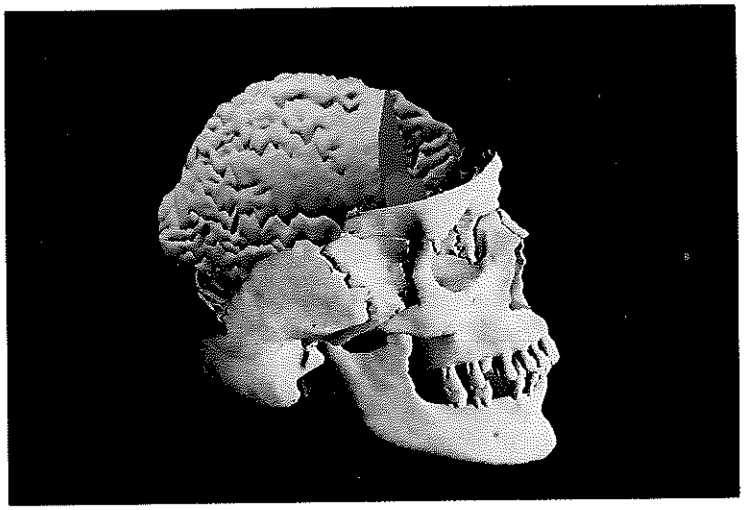
The development of integrated visualization systems now stands at the crucial juncture. The technological resources and basic developmental principles have demonstrated their potential. Increasingly, time, money and resources are being committed to these systems and environments. However much less attention and support has been given to descriptions and analyses of routine practices upon which the ultimate success of these technologies depends.

In order to achieve this success, two interpretive strategies need to be in place throughout the design and implementation cycle. The first will identify and describe forms of reasoning and practice that are important to the technological modeling of visualization. The second is to translate practitioner understandings (clinician and researcher), routines and practices into idioms developers can both understand and utilize. For these interpretive strategies to be most effective, what is needed is an interdisciplinary, collaborative development effort that involves medical practitioners and researchers, technical designers and social scientists.

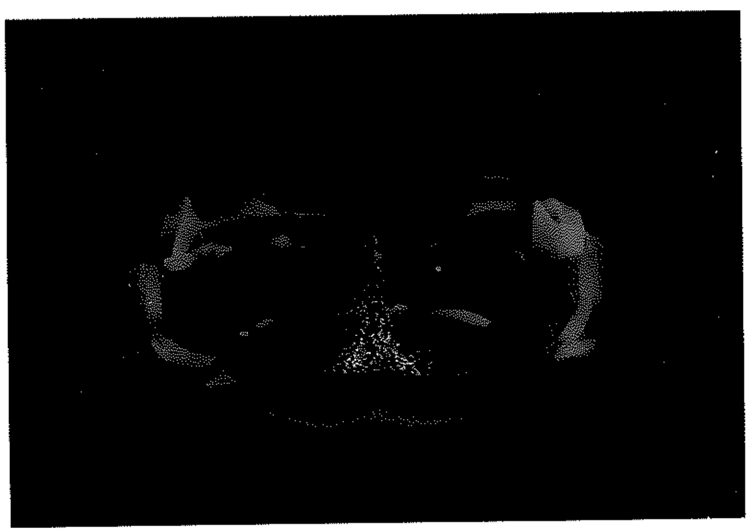
The task here is to establish a development path for computer resources that rests on something other than arbitrary models and fixed categories of data [19]. In this development path, designers would, when given a problem, mediate what is technically and cost feasible. Medical staff, clinicians and researchers, would help define a particular visualization problem or issue as a project area. The contribution social scientists would make is to translate routine practice and meanings embedded in both the problem and project area into idioms and terms all members of the development community could understand, agree with and use.

Conclusion

Understanding the links between CNS structure and function can be immensely difficult. Five visualization projects that attempt this on a variety of levels have been described in this paper. Each of the projects manipulates structural models and the insight each provides into CNS function has been discussed. As well some technical and conceptual issues that cut across these projects have been taken up. These issues include delivery platforms, integration paths, the development of standards for image acquisition and representation, and additionally the need to arrive at definitions of visualization that drive both higher order work and support specific sets of routine practice in medicine.



This image synthesizes data from MRI and CT sources. The brain contains a right frontal lobe tumor. The surface of the cortex is smooth due to the underlying edema. The brain model, obtained from MRI scans has been scaled to fit the skull model, obtained from CT scan data. Image computed and rendered using the Skandha system on a Silicon Graphics 4D/GT70. Image by J.W. Sundsten, Computer Graphics Group, Dept. of Biological Structure, University of Washington. Scans courtesy of G. Stimac.



This image shows populations of neurons in the rat brain. The color-coded pyramids represent LHRH containing perikarya from females in different endocrine states: intact, and 3 different times following ovariectomy. The landmarks visible in the reference model include the ventricular system [red], the anterior commissure [blue] and the optic chiasm and optic tracts [green]. This image was computed on a VAX 11/780 running MOVIE.BYU and rendered on a Gould/Deanza display system. Image by J.C. King, Dept. of Anatomy and Cellular Biology, Tufts University School of Medicine, and Image Analysis Laboratory, Tufts-New England Medical Center.

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