Visualization in the Neurosciences:
Utility in Research, Teaching, and Clinical Practice

Stuart A. Tobet¹, Joan C. King², Steven L. Wertheim³, Frank H. Duffy⁴

¹E.K. Shriver Center, Harvard Program in Neuroscience, Boston, MA; ²Tufts University School of Medicine, Boston, MA; ³Harvard Medical School, New England Regional Primate Center, Southborough, MA; ⁴Children’s Hospital, Boston, MA

Introduction

Increasingly, visualization techniques are becoming necessary for the analysis and presentation of data in the biomedical sciences. This has become particularly evident with data in the neurosciences. Data must be presented in perspectives that range from basic to clinical research, and from instructional to diagnostic purposes. This panel will address a sampling of this spectrum of uses for visualization in the Neurosciences. Panelists will:

1) Present particular research and teaching usages of image analysis techniques

2) Discuss how the use of visualization is essential for data interpretation

3) Suggest directions for future developments

Panelists Statements

Stuart A. Tobet - Image analysis for basic neurobiological problems.

In our Imaging Facility we have tackled a wide range of morphological analysis problems by using independent workstations which take advantage of complementary visualization solutions. One workstation utilizes the x,y,z coordinates of points at any magnification, and is comprised of a PC-based computer, drawing tube, monitor, joystick, and motorized stage (Neuron Trace System; Eutectics Electronics, Inc.). This has been particularly useful for vector display reconstruction and quantitative analysis of individual neurons (e.g., Golgi-stained cells). Additionally, we utilize the x,y,z accuracy to register cell locations in a broader context, and port coordinates to a serial section reconstruction system. Consecutive sections are reconstructed in 3D so that the coordinates of rotated images can be used for quantitative analysis.

We have utilized this approach to map different types of Purkinje cells in the murine cerebellum or the distribution of estrogen receptor containing cells in the developing and adult ferret hypothalamus. By adapting specific color icon representations for different estrogen receptor cell types we were able to visualize striking sex differences in the distribution of estrogen receptor containing cell types in the adult ferret hypothalamus.

While visual reconstructions from microscope input has been helpful for mapping and cell reconstruction, we utilize grey level image processing to analyze a wide range of additional problems (IBAS Image Analysis System; Zeiss/Kontron). Thus, we have measured such things as cortical areas, cell density along morphologically relevant boundaries, multiple characteristics of autoradiographically labelled cells, numbers of immunoreactive dendritic and glial profiles, and characteristics of cells grown in vitro. Basic contrast enhancement and segmentation algorithms are utilized to isolate morphological features of interest and then derive quantitative values to compare samples from different experimental groups.

Finally, we find that with the increasing number of visualization based solutions that we work with, image archiving is an issue on several levels. On a simple level, getting a specific image for presentation is a function of "useful" image storage, and proper output devices (e.g., analog film recorders). On a more complex level, it is becoming more important to be able to compare results over time (e.g., how does today's result relate to a result from several years ago?): Dr. King's 3D reference model system allows the
overlay of any two groups regardless of when the data was collected. Dr. Duffy's data analysis and compression techniques allow the comparison of EEG data in the same patient over time. Finally, it will become more important from the visualization standpoint to ask how results differ among laboratories. These comparisons will become more obvious with increasing use of databases similar to the one Dr. Wertheim will discuss.

Joan C. King - Image analysis from basic to applied neurobiological problems.

In our basic research we have developed protocols to analyze data collected from multiple levels that range from electron microscopy to low magnification light microscopy. Our research interests focus on the regulation of synthesis and release of the neuropeptide, luteinizing hormone-releasing hormone (LHRH). At the electron microscopic level we have employed 2D image processing, including image specific subcellular enhancement and feature extraction techniques, to determine the relative amounts of peptide that reside in compartments in relation to physiological conditions. Using light microscopy at high magnification we have adapted similar 2D imaging techniques to analyze the distribution and density of fibers that contain LHRH. In addition, we have adapted a 3D approach using light microscopy data at low magnification as our input. The x,y,z coordinates of each LHRH containing neuron of a brain (rat, guinea pig, or human) are registered in reference model sections containing major anatomical landmarks. The models with cells in register are reconstructed in 3D using a modified version of MOVIE.BYU and comparisons can be made between groups using color-coded icon overlays. Such overlays have made possible the determination of distinctive subgroups of LHRH neurons that differ in detectability in response to physiological conditions.

Based on the importance and utility of visualization approaches in our data analysis problems we extrapolated this experience to a teaching environment. Visualizing the interrelationships of human brain structures and how those relationships relate to clinical problems poses one of the most taxing challenges that health science students and clinicians address. We developed interactive paradigms which integrate 3D models, 2D slices, and conceptual questions. The programs are designed to allow students to freely explore different structures, their interrelationships (proximity and pathway connections), and test clinical consequences of specific lesions. The integration of these levels is made possible through the use of NTSC video images stored on video disc, interfaced through host software to an IBM PC platform with a touch sensitive screen (InfoWindow system, IBM) or a mouse with the M-Motion card.

Steven L. Wertheim - NeuroDatabase: Managing images and graphics from anatomical experiments.

NeuroDatabase is an information tool for neuroscience that is being developed to aid research and teaching. It focuses on the acquisition, analysis, and presentation of two and three-dimensional anatomical and biochemical data sets. It is distinguished from most other computer-based neuroscience tools by the presence of a flexible underlying database. This design enables a neuroscientist to handle the data of both current and future experiments and teaching exercises as well as engage in collaborative efforts. Each laboratory can have its own, private copy of the database to which local data can be added. The vocabulary, data storage structures and analysis tools are shared. It will be relatively simple to extract experimental data from one's own database and send it to a distant colleague.

The demands of the subject matter have given NeuroDatabase two principal characteristics: a heavy emphasis on imaging and a provisional knowledge representation for neuroscience. Images, the primary data in anatomically-based branches of neuroscience, are increasingly being captured and analyzed electronically. Basic analyses include definitions and measurements of objects in images followed by 3D reconstruction and visualization. A rudimentary knowledge representation is necessary because the user and the system must navigate through the large (and sometimes confusing) terminology of the nervous system, and also through the relationships between terms. Our knowledge base is the minimum needed to aid creation and parsing of queries. The flexibility of its design will allow additions and modifications by others with expertise in specialized areas.

NeuroDatabase is available under a low-cost academic license to interested laboratories who have the appropriate hardware and software. Data collection and 2D analysis is done on a Macintosh II with 8Mb RAM, hard disk and 19" 8-bit color display. 3D reconstruction (optional) will be done on Silicon Graphics, Iris workstations.
This talk will emphasize the research applications of NeuroDatabase including: laboratory notebook functions, computer-assisted video microscopy, management of image series of varying resolution, quantitative morphology, and 3D reconstruction.

Frank H. Duffy - Visualization and analysis of multivariate electrophysiological data sets: basis for the new field of Quantified Electroencephalography.

The clinical practice of electroencephalography (EEG) has changed very little since the 1940s. Classic analysis of multichannel EEG polygraphic recordings typically involves estimation, by unaided visual inspection, of (1) each channel’s spectral content, (2) the distribution of each classic EEG spectral band (delta, theta, alpha and beta) across the scalp, (3) consistency of the findings over time, and (4) degree of abnormality on the basis of "clinical experience". Attempts to supplant visual spectral estimates with computerized calculations (FFT) failed to gain acceptance since physicians found a stack of XY spectral plots difficult to interpret. Our initial solution was to enhance the visualization of spectral data by creating two dimensional pseudo-color maps each representing the topographic distribution across the scalp of one of the EEG spectral bands, calculated as the average spectral content over several minutes. Spaces between real electrode locations were filled by interpolation. Thus, in one operation the clinician was relieved of the necessity of performing spectral analysis and visualizing the results across the scalp in his own mind. No sooner was this done than it became clear that the spatial distribution of EEG was not as symmetrical and even as had been previously believed. When was a certain amount of asymmetry out of normal bounds? To address this issue we developed the process of Significance Probability Mapping (SPM) where a patient’s data are remapped and displayed in standard deviation units from the mean value for a data base of normal subjects. This relieves the clinician from having to memorize normal values and patterns. Moreover the Z-statistic process, being sensitive to coefficient of variation, even out a bias of visual impression induced by spatial differences in mean spectral values.

A similar approach was taken to the display of long latency sensory evoked potentials (EP). Such low amplitude scalp derived EPs are created by signal averaging the response to several hundred stimulations. Analysis of multichannel EP data involves appreciating variation not only across time but also space (scalp). By mapping the instantaneous distribution of voltage, and serially viewing or "cartooning" the result, complex spatio-temporal relationships could be recognized for the first time. Data are made clinically useful by applying the Z-statistic SPM to the EP data and cartooning the result.

A potential problem with large data sets, such as those that are gathered in neurophysiology, is that if variables are relatively uncorrelated then there is a high probability for type I statistical error, or false positives. For example the flash EP results in 2944 variables (128 data points per channel times 23 channels). To search for the intrinsic dimensionality of such data we employed the technique of principle components analysis (PCA). Results demonstrated that no more than 20 factors described 70-85% of the variance, a relatively low intrinsic dimensionality. To understand the meaning of each factor we employed the traditional technique of investigating the "factor loading scores" or correlations of the given factor with all 2944 input variables. As might be expected, making sense of such a large set of loading scores required mapping the result on the spatio-temporal framework of the initial variables. When so visualized the many factors took on obvious meaning.

We will discuss the great value of such image graphics techniques better comprehending and utilizing large neurophysiological data sets in clinical practice.

Panel Participants

Stuart A. Tobet is an Assistant Professor of Neuroscience at Harvard Medical School. He is currently the director of the EK Shriver Center Image Analysis Facilities. His research interests include the biochemical bases of sex differences in neural organization, mechanisms of hormone action during brain development, image analysis solutions to morphological and biochemical problems, and biochemical correlates of immunocytochemical results.

Joan C. King is a Professor and Chairman of the Department of Anatomy and Cellular Biology at Tufts University School of Medicine. She is also the director of the Center for Reproductive Research at Tufts and the co-director of its Imaging Core. Her research interests include the neuroendocrine regulation of lutinizing hormone-releasing hormone synthesizing neurons, and image analysis applications for data analysis and teaching applications. She was the

382
originator of the Tufts Learning Environment for Medical Neurosciences teaching program. jking@OPAL.tufts.edu

Steven L. Wertheim is an Instructor in Neurology at Harvard Medical School. He received his Ph.D. in neuroanatomy from MIT in 1984 where he worked with W.J.H. Nauta. Subsequently he was a Research Associate in the Department of Brain and Cognitive Sciences at MIT where he developed educational software using the resources of MIT's Project Athena. The product of that work, the Neuroanatomy Learning Environment, was an early demonstration of interactive video in medical education. Since 1989 he has been developing NeuroDatabase in the laboratory of Dr. Richard L. Sidman, head of the Division of Neurogenetics, New England Regional Primate Research Center. stevew@athena.mit.edu

Frank H. Duffy is an Associate Professor of Neurology at Harvard Medical School and Director of the BEAM (quantified EEG) Laboratory and the Developmental Neurophysiology Laboratory at Children's Hospital. He holds undergraduate degrees in electrical engineering and applied mathematics and obtained his medical degree from Harvard Medical School. His clinical training encompassed neurosurgery, neurology, and electroencephalography (EEG). His research focuses on numerical analysis of brain electrical activity recorded from the human scalp with an emphasis on the use of statistical and visual imaging techniques to enhance clinical utility. His research has involved the study of premature infants, learning disability, attentional deficit disorder, depression, schizophrenia, normal aging, Alzheimer's disease, and epilepsy.