

ESTABLISHING
IDENTIFIED
NEURON
DATABASES

A Report on Workshops
held at
The National Science
Foundation

Arlington, VA

April 28-30, 1994
and
June 23-24, 1994

ACKNOWLEDGMENTS

This report derives from extensive discussions by workshop participants and written comments they provided on earlier versions of this document. All were enthusiastic contributors.

Session I

April 28-30, 1994

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June 23-25, 1994

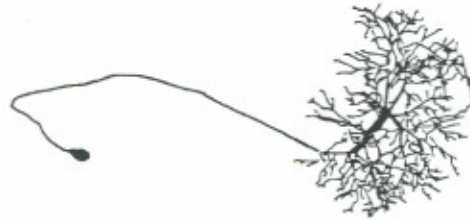
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In addition, a number of NSF staff and program officers participated including Peter Arzberger, Tom Brady, Larry Brandt, Christopher Comer, Charles Keith, Kathie Olsen, Christopher Platt, John Porter, Karen Sigvardt, and Susan Stafford.

Finally, there were many "virtual participants" to the workshop who read drafts and provided feedback over the Internet. We would especially like to thank Doug Baxter, George Boyan, Robert Eaton, John Hildebrand, Ron Hoy, Terry Sejnowski, and Monte Westerfield. Layout and design by Madeleine McCall.

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INTRODUCTION

There currently exists a large body of information gathered by neuroscientists about the structure, function and development of individual nerve cells. This information exists for neurons from a wide variety of organisms, vertebrates and invertebrates, gathered by many laboratories around the world. Access to information about specific neurons, either as individuals or as ensembles, is essential to the coordination and guidance of neuroscience research of all types: molecular and genetic analyses of events occurring within neurons, computational studies of functional circuits, and behavioral studies. Driven by the emergence of many new techniques, information about identified neurons is being acquired at a quickening pace.

The data management problem facing neurobiologists is not unlike the problem that faced molecular biologists in the recent past when many researchers were independently identifying and sequencing proteins and nucleic acids. It became essential to progress in molecular biology and genetics to create a system for the acquisition and storage of information about biologically important molecules and, eventually, entire genomes. This development not only stimulated the pace of molecular biology, it affected all of biology since it made new studies possible in areas ranging from structural biochemistry to evolutionary biology. The progress of neurobiology would also be stimulated greatly if information about individually identifiable neurons were organized and made accessible to researchers.

Under sponsorship of the National Science Foundation, a pair of workshops was recently held to discuss the electronic database needs of scientists whose work concerns identifiable cellular elements of the nervous system. Those in attendance represented several different backgrounds including neurobiology, molecular biology/genetics, and information/computer science.

The main goals of the workshop were to determine: (1) What is the level of interest in electronic database resources to the research communities that work with model systems containing identifiable neurons? (2) Is it feasible to design identified neuron databases that would be freely available over the Internet for purposes of research and teaching? This report is intended to summarize the consensus that emerged from the workshops, and elicit comment from the wider community of neuroscientists and interested computer scientists.

These workshops were supported by NSF grant IBN-9411967. Any opinions, findings, conclusions, or recommendations expressed in this report are those of the panel and do not necessarily reflect the views of the National Science Foundation.

BACKGROUND AND CURRENT NEEDS

In order to produce a complete understanding of how a brain functions, it is essential to bring together the images and datasets generated by the various individual laboratories studying it. This recognition recently led to the human brain mapping initiative (see Institute of Medicine, 1991), and functional atlases of mammalian brains are beginning to be developed in electronic database formats (e.g. Fox et al., 1993).

Historically, some of the most detailed information about nerve cells has come from studies of individually reidentifiable neurons recognized in invertebrate nervous systems (see Arbas et al., 1991). However, there are now examples of uniquely identifiable neurons in vertebrate brains (e.g. Lee et al., 1993). Furthermore, the characterization of gene expression within nervous systems is leading to the recognition of many distinctive neuron classes, even in cases where individual identity is not yet established. Neurons are elements of circuits, and therefore the properties of individuals or discrete classes influence the function of the whole system. Ultimately, the power of neurobiological experiments at both integrative (systems) and molecular levels is significantly enhanced by the ability to conduct multiple experiments on reidentifiable cells.

Despite the fact that databases have become a vital piece of infrastructure for molecular biology, and more recently ecology, there is no registry of any sort in which established identities of neurons are recorded, or in which basic data about identified cells may be deposited (e.g. Rowell, 1988). Therefore when one characterizes a cell (or a distinct group of cells) anatomically, physiologically, chemically, or genetically, it is difficult to determine if the neuron(s) has been previously identified. This makes it unusually difficult to avoid duplication of effort. Furthermore, it makes it impossible to bring together consistent data sets that would allow comparative and evolutionary questions to be addressed.

As part of this effort, twenty seven scientists, and a number of NSF staff (see list of participants above) met on two different occasions, for 2 days each. Some of those in attendance at the second meeting of the workshop were also present at the first meeting to provide for continuity of effort. The charge to the groups: examine the need that neurobiologists currently have for database resources, determine some of the impact that neuron databases could have on neuroscience research and education, and discuss the principles that should guide the design and implementation of these resources.

FINDINGS AND RECOMMENDATIONS

Importance of Electronic Databases

It was widely agreed that there is currently a wealth of anatomical and physiological data on identified neurons which may be lost if not rendered into a usable, electronic form. It was further agreed that the collection of cellular neurobiological data in the future, and the assimilation and interpretation of those data would be facilitated by the availability of databases. In particular, interactive electronic databases will allow great time savings, they will go far beyond the non-interactive printed literature, and they will provide for a distribution of effort. Finally, the involvement of NSF and other federal agencies in assisting with the establishment of these database resources was deemed appropriate and timely (in fact, long overdue).

General Design Principles

In order for databases to be truly useful, they must be designed, from the outset, with a clear recognition of the many uses of neurobiological data, including:

Identification: gathering information sufficient to specify and to refine the uniqueness of individual neurons.

Classification: using information to specify behavior of a class of similar neurons, grouping neurons in a class, or characterizing representatives of a class.

Modeling: deriving the information necessary or useful to model or simulate a cell or network.

Coordination: acquiring information by different experimental techniques and then combining it to characterize the same cell or preparation.

Participants stressed the need for databases to be extensible in design to allow for inclusion of new data types and to take advantage of the rapidly changing resources that will be available on the network and from digital technology. For example, no one wants to have to re-enter data all over again when a new technique comes along. (This is a potentially serious problem with anatomical data, since several initial formats might be allowed such as scanned camera lucida drawings, [for current and historical data], confocal images, or 3D reconstructions.)

One principle that must motivate the design of any database is that the entries must be treated for what they are — scientific observations, not established truth. It should not be possible to change an entry in any covert way. It is essential that there be a clear audit trail of all entries relating to a particular cell or class of cells. For example, if something new were observed about a particular cell, it is entered separately with a new accession number and perhaps a pointer to existing entries that might represent the same cell.

Discussion of all the design and management issues that arise with scientific databases would be extensive. There is good information available from the computer science community about the general issues that need to be considered in establishing databases. So as not to repeat already well defined issues here, we refer readers to a recent report (University of Virginia, 1990) that contains a succinct outline of the relevant issues.

Database Scope

It is clear that there is no need for there to be just ONE database. This is consistent with the development of database resources in molecular biology (Smith, 1990). Current computer technology can easily support the linkage of databases developed within the various distinctive research communities that are now generating data on identifiable neurons. Nonetheless, it seems desirable to arrive at certain consistencies in higher level design features, which would facilitate users moving from one constituent database to another. Some examples of such consistencies will be given below.

The databases that would be most widely useful in support of current and future research are neural databases. By this we mean that the information in the databases should not be referenced only to uniquely identifiable cells, or even particular types of neurons. The frame of reference should be the plan of nervous systems, but with identifiable neurons as an integral part of that plan. For example, an electronic catalogue of neurons found in the nervous system of *Drosophila* would be most usefully displayed with reference to a standard atlas of its nervous system, so that data on regional localization of transmitters, or patterns of gene expression could be correlated with identified classes of neurons as well as uniquely identifiable individuals.

If a multiplicity of databases can be imagined, how would one recognize those development projects which ought to be encouraged and supported, especially right now? It was felt that certain criteria can be suggested by which the most useful database projects could be recognized. (1) Initially, they would probably come from research communities where there are already many examples of identified neurons. (2) They would likely come from communities where other types of databases, or network communication resources are already in use. (3) They should unify individual species [e.g. an insect database would be of greater interest than a locust or cricket database]. (4) They should ultimately be able to handle information at all levels [e.g. nucleic acids, ion channels, cell geometry, physiological processing, network connectivity, regional anatomy].

Ultimately, of course, databases should be developed for a number of organisms, and all should have similar formats. In order to achieve this end, several strategies are possible. One strategy is a large, centralized project with database design experts at the top to coordinate the effort, and biologists as consultants. To avoid the considerable overhead inherent in "top-down" project management, with its inevitable imposition of distance between goals and implementation, the workshop considered methods for distributed yet integrated "bottom-up" design.

There are several variant forms that "bottom-up" initiatives might take. The model considered at the first workshop was a set of organism-specific databases, with each of several groups concentrating upon development of models for data storage and retrieval that would be specialized for the needs of researchers working on one organism or a group of closely-allied organisms. The second workshop spent some time considering the possibility that initial efforts should be centered on "data types" rather than organisms. That is, different groups would concentrate on methods for the storage, retrieval, and display, within areas such as: electrophysiology, single-cell morphology, atlases and the anatomy of multineuronal assemblies, behavior, cell biology (including neurochemistry). There already exist well-defined data types and tools for molecular and genetic analyses.

Either of the two approaches sketched out above, would have some pitfalls. For example, one concern is that various organism-specific database teams might develop incompatible solutions to the same sets of data handling problems. This potential problem may be circumvented if tight coordination of effort were required from the start. One possible advantage to a "data-type" approach is that methods for collecting, classifying, and examining neurobiological data are less likely to be organism-specific than technique-specific. On the other hand, most organisms are studied using combinations of several methods, and the sociology of research communities is such that collaborations built around organisms already exist.

Over all the panelists expressing specific views on this matter, there was somewhat greater support for organism based efforts. However, it must be noted that the two approaches are not mutually exclusive: even in projects that are organism-based, many of the goals would be aimed at developing techniques and strategies for the storage of particular types of data.

No matter which types of projects are proposed by the community, and ultimately supported, they will likely need to have several organizational features. (1) In their initial phases they should consist of small projects by groups of investigators, that would propose goals (working models) achievable within 2-3 years. (2) They should subsequently lead to a data entry and testing period that would permit many investigators to enter their data in the same format and begin to test particular search strategies. This phase is essential before a large effort is launched to implement these new techniques into "production level" software. (3) They should include experts on neuroscience, computer science, and database design. (4) It was strongly suggested that any supported groups meet twice a year, perhaps at one of the NSF funded supercomputer centers, for extensive discussions and progress reports.

The NSF supercomputer centers (see list in appendix I) can provide valuable resources for those wishing to develop databases. They can provide archiving facilities and means of software distribution. For databases installed at a Center, supercomputer time can be granted for conducting intensive searches of the database. Parallel platforms are available for development of parallel database software. The Centers undertake collaborative software development projects with scientists, providing expertise in production software, and leverage from work on similar projects (e.g. databases) in other scientific domains.

Many felt that a low level text and simple graphics catalog would be useful as a first phase effort while more powerful tools (true, integrated databases) are being developed. Many also agreed that already available formats such as Mosaic, with simple browsing pages for different topics and organisms, would be very helpful — and perhaps essential for generating interest in the project. (Mosaic is a display program that provides an interface to World Wide Web [WWW] servers — hence "surfing the web". With display programs like Mosaic one can follow, one at a time, links between data items. Crucially, what a database supplies is a means to search the data for key words, key parameter values, image features etc. WWW servers are really for browsing through data. However, a database with query facilities can be hooked to the Web and used to construct queries and responses in the basic WWW format (Hyper Text Markup Language or HTML) which Mosaic can then display, eliminating the need to write a graphical user interface.)

An excellent example of the power of A Mosaic catalog was presented by Marnie Halpern, who described the efforts of the zebrafish community to interact via WWW. One of the most valuable aspects of this simple "database" is information on the location of stocks of mutant fish, maintained at the University of Oregon. This effort opens the door for other zebrafish groups to also distribute their lists of stocks. Another useful aspect is an interactive discussion group, where workers in the field post questions and receive answers from the community. This catalog also contains all of the references for papers published on zebrafish as well as the names and e-mail addresses of all members of the zebrafish community. This WWW server is largely the work of one individual, Monte Westerfield. It was emphasized that it is relatively easy to set up something like this for any community.

All participants felt strongly that the database effort should include the scientific community in Europe and Asia. Experts from several countries should be involved in planning, execution and oversight of projects to ensure that the databases will be a resource worldwide. Separate and incompatible databases in different countries would defeat a major goal of the project and preclude collaborative efforts between laboratories in the US and abroad.

The Content of Neuron Databases

The information in any database should be organized so that it can be scanned for comparison with new material, and it is essential that a method for adding new information about previously identified cells be worked out. Electronically stored anatomical images in such a database might become equivalent to "type specimens" which are maintained in museums for unambiguous species identification by animal and plant taxonomists.

Must there be universal scheme for naming neurons? Given that searching is likely to be based quite often on particular attributes, there was a feeling that naming does not have to be standardized. However, as in classical taxonomy, it is crucial for a database to preserve synonymy. For example, if three different names have been applied to an individual cell, two do not have to be discarded, indeed there must be a field in which all IDs are stored in parsable form. Nevertheless a simplifying, rational scheme for assigning names within a particular organism, or across similar species, should be encouraged. It was felt that a database itself would result in a standard nomenclature within appropriate areas as entries are made - since new entries must conform to the style of existing entries.

As stated above, atlases of the appropriate brains/nuclei/ganglia should be provided and entries should be mapped with respect to a particular atlas. This means that it may be valuable to support the development of resources for producing and standardizing high-quality atlases. There was an extended discussion on the development of techniques to store anatomical data in an atlas. An atlas would preserve the 3-D cytoarchitecture of the brain or ganglion as a template in which to view single neurons, groups of neurons, transmitter staining patterns, gene expression patterns or any other anatomical characteristic of the tissue. An atlas should allow one to search for patterns of structural interrelatedness among neurons such that functional or computational ensembles may be identified. The availability of interactive atlases for a number of organisms would be a very powerful tool for the study of the evolution of the nervous system. The panel recognized, however, that there are some organisms for which a detailed atlas may have less importance. This may be true for example of *Aplysia* and related molluscan species.

Databases should carefully consider ways to indicate circadian and developmental time. For some research communities, it will be essential that a database have separate anatomical atlases to provide a framework for entering data on adults, larvae, embryos, etc. Within these areas, there should be tags for finer grain temporal information (age of adult, stage number, % development etc.)

We noted that in providing molecular level information, it is not necessary for neural databases to provide all resources directly. For example, some information on mutants or gene sequences would best be provided by allowing connection to existing electronic stock listings and gene sequence databases.

Participants discussed a general plan where databases would have two layers. The first layer would comprise the electronic equivalent of a single-page in a flip chart, or browsing book, with general information on each neuron or class. Anatomical information here might be in terms of an idealized ball and stick model or perhaps projections into the 3 canonical planes. Behind that layer would be in-depth coverage of individual items. For anatomy, for instance, one might have confocal series or other computerized reconstructions of neurons or classes of neurons. This second layer should also include a detailed atlas of the brain. We do not envisage inclusion of analytical software initially. However, data stored in compatible formats should be made accessible for downloading into existing software applications (e.g. NEURON, GENESIS, etc.).

Each record in a database should include as wide a range of attributes as possible. The fields containing these attributes should diverge in a nested hierarchy from some general characteristics (e.g. morphology, physiology, development, genetics, etc.) to specific traits (e.g. channel characteristics, particular mutants). The hierarchy in each particular class of data would be best established by a group of researchers that are most familiar with the types of data included in the database.

Norms of Quality and Accessibility

It was widely agreed that it will be important to establish some norms for insuring the quality, free accessibility, and correct attribution of data.

There was a strong sense that many of the conventions for submission of data, and correct attribution of data sources, should follow the general forms in place for publishing in the printed literature. Entries should be tagged not only with accession numbers, but also with an identifier for the person submitting the data. Unpublished data should be acceptable, but there should be an indicator on the entry that it is unpublished. Published data should always be tagged with a proper literature citation, and when unpublished data become published the tag should immediately be changed. To use unpublished data from any database, the permission of the submitter should be obtained, and it should be described in other media as an unpublished observation, with a reference to the appropriate accession number.

While entry could be done through one person acting as an editor, or a committee to insure quality and uniformity, this is time consuming. The simplest solution for making new data rapidly available is to design the entry routine such that it can be accomplished directly by users — using well-known standards of quality. For example, how many times

must an observation be made before it is entered into a database (n=3)? Resolution of issues related to quality assurance should be done by a group from the scientific community that uses the database, perhaps in a format equivalent to a board of editors.

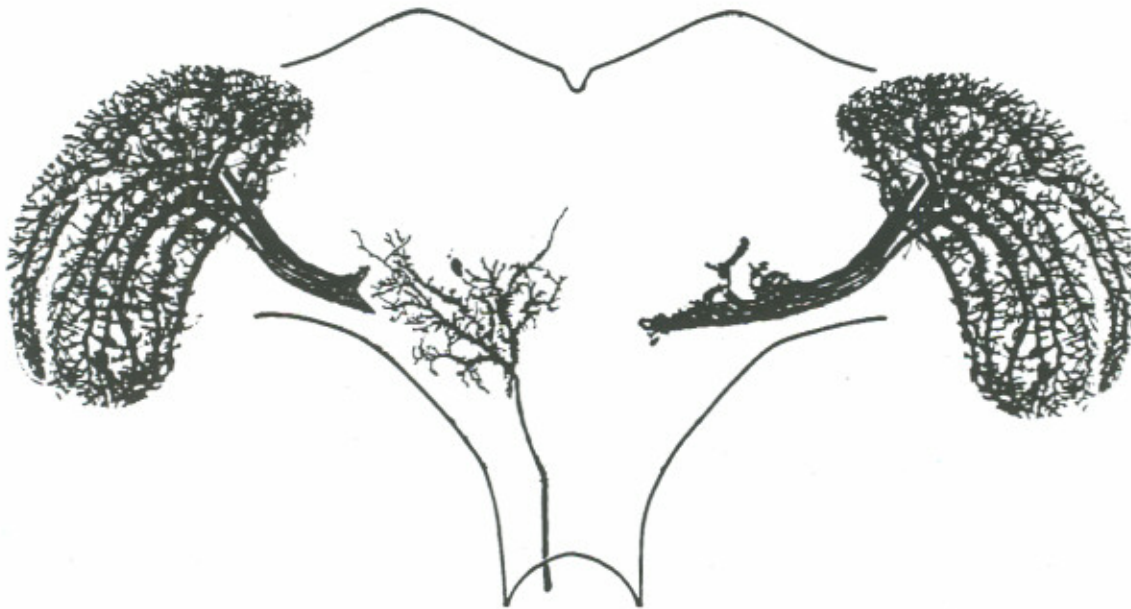
We also suggest that it will be important to keep track of the usage of each file, both for general documentation and to help the community determine what is most useful, how long different types of data should be preserved, etc.

Potential Funding Mechanisms

A willingness to fund databases for neurobiologists is important because it makes database development a research activity. This linkage is important in that it raises the status of the activity: These activities are creative and demanding enough not to be relegated to "spare time" efforts (or to be overlooked at time of promotion or tenure) as they have been in the past within the neuroscience community.

The workshop was attended by a number of NSF staff, particularly those from the Division of Integrative Biology & Neuroscience (IBN) and from the Division of Biological Instrumentation and Resources. These Divisions have programs to support neuroscience research and database activities, respectively. It was clear to the NSF staff that the type of projects being discussed would fit well into the existing database activities program in BIR, and that such projects would further the research efforts of communities that are targeted by programs in IBN.

Those interested in planning for submission of proposals on identified neuron database development are encouraged to contact program officers in one of the two divisions to discuss the availability of resources. In IBN contact: Christopher Comer (CCOMER@NSF.GOV); in BIR contact John Porter (JPORTER@NSF.GOV).



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SUMMARY

We envision that it would be desirable to encourage several efforts at database development: some might naturally spring from a research community working on one model system (e.g. zebrafish, *C. elegans*), but it would also be desirable to attempt developing databases that span several widely used systems (e.g. insects, molluscs, etc.). Because certain research communities are heavily oriented toward certain data types, this would naturally result in some efforts largely exploring the development of tools necessary to adequately display, store, map, or process one aspect of neurobiological data (e.g. anatomy, electrophysiology, biochemistry). Some efforts might explicitly focus on data type and attempt to devise generalizable ways of handling data across a wide spectrum of organisms. In any case we recommend that the individual identified cell or cell class remain the point of focus for all efforts, because it provides a way to unambiguously relate information from one database to that in another — and this is the ultimate goal — a federation of interactive databases that operate as one large resource for neuroscience researchers and educators.

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