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Short Communication

NEUROINFORMATICS: THE INTEGRATION OF SHARED DATABASES AND TOOLS TOWARDS INTEGRATIVE NEUROSCIENCE

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There is significant interest amongst neuroscientists in sharing neuroscience data and analytical tools. The exchange of neuroscience data and tools between groups affords the opportunity to differently re-analyze previously collected data, encourage new neuroscience interpretations and foster otherwise uninitiated collaborations, and provide a framework for the further development of theoretically based models of brain function. Data sharing will ultimately reduce experimental and analytical error. Many small Internet accessible database initiatives have been developed and specialized analytical software and modeling tools are distributed within different fields of neuroscience. However, in addition large-scale international collaborations are required which involve new mechanisms of coordination and funding. Provided sufficient government support is given to such international initiatives, sharing of neuroscience data and tools can play a pivotal role in human brain research and lead to innovations in neuroscience, informatics and treatment of brain disorders. These innovations will enable application of theoretical modeling techniques to enhance our understanding of the integrative aspects of neuroscience. This article, authored by a multinational working group on neuroinformatics established by the Organization for Economic Co-operation and Development (OECD), articulates some of the challenges and lessons learned to date in efforts to achieve international collaborative neuroscience.

Keywords: Neuroinformatics; data sharing; analytical tools; integrative neuroscience.

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1. Introduction

The challenge of the 21st century is the understanding of the human brain, the most complex organ created during evolution. The abilities of information processing, decision making, perception, and action displayed by this biological system dwarf those of man-made systems. In order to understand the brain we need to bridge many different levels of description, from molecules to cells and from systems to organisms, which are addressed in diverse disciplines ranging from anthropology to molecular biology. While the accumulation of facts and data on the brain has been impressive, the depth of our insight regarding their meaning is much more limited. Similarly, over the last few decades we have seen tremendous advances in the area of information technology (IT), such that IT technologies are now being brought to bear on providing insights into the organization of the brain and in particular to understanding brain function.

The new interdisciplinary field of Neuroinformatics (NI) capitalizes on the potential synergies between neuroscience and IT, for example: by applying advanced IT methods to deal with the flood of neuroscientific data; by developing and applying data analysis methods for the study of the brain; by providing both analytical and numerical tools for theoretically modeling brain function; and by exploiting our insights into the principles underlying brain function to develop new IT technologies. Applications of NI can, therefore, be found in diverse areas ranging from clinical psychiatry to structural biology. In order to allow the potential of this development to be realized, however, a number of important challenges need to be faced both at the level of practical science as well as science administration and policy making. For instance, if we want to understand the brain and appreciate the intricate inter-relationship of its multiple levels of functional organization, as in integrative neuroscience, we need to communicate ideas and observations beyond the boundaries of particular disciplines in which individual researchers gather their data. Moreover, the aim of understanding the brain will require a truly global collaborative effort that will require completely new forms of science funding and communication.

There is a significant scientific movement to realize the opportunities provided by sharing data and tools [3, 10]. These include the ability to increase the statistical power of studies by capitalizing on others' data, rather than replicating it. Exchange of data between groups affords the opportunity to differently re-analyze previously collected data, as well as encourage new interpretation of it and foster otherwise uninitiated collaboration. In addition, sharing will ultimately reduce experimental and analytical error. The development of neuroscience databases will also contribute towards the further development of theoretical modeling techniques in order to enhance our understanding of the integrative aspects of neuroscience, namely the larger-scale functional organization of the brain, neural coding and signal analysis. This article, authored by a multinational working group on NI set up by the OECD (see App. 1), articulates some of the challenges and lessons learned to date in efforts to achieve a collaborative and integrative neuroscience.

2. Challenges

There is a pressing need for greater collaboration in the acquisition and analysis of experimental data, the creation and investigation of theoretical models of brain function and the design and development of software methodologies to support both these activities. Despite this clear need and the obvious opportunities that would arise from action to satisfy it, there are significant barriers in a variety of arenas that make progress difficult [1].

Cultural Issues: Major shifts in the sociology of scientific interaction must be made as we move into the mode of complete data and tool sharing. Current publication methods often do not provide sufficient detail that individual researchers can relate their own findings and methods with those published by colleagues. Most published scientific articles contain condensed fractions of the original raw data, and incomplete details of methods. While emerging systems such as electronic publications and databases that facilitate sharing show promise for addressing these problems, they often do not provide the same cachet as traditional publication methods [16].

Quality Assurance: Data quality control for neuroinformatics databases poses several problems that are unique to the field [2]. Compared to the established genome and protein sequence databases three main differences can be identified: (1) heterogeneity of data formats, (2) large variability of data and (3) differences amongst data providers. Each creates difficulties for quality control that are unlikely to be solved by standard recipes. Peer review of scientific results is not sufficient on its own when data is provided in a variety of formats and processed using a variety of naming schemes. Similarly, quality assurance for NI tools is not simple. While there have been some tool comparisons [27], many packages are not evaluated against a "gold standard", e.g., tools for brain imaging data analysis, data conversion, and model simulation.

Metadata: Neuroscience data tend to show a high degree of variability, both within experiments, across individuals and across experimental paradigms. Some sources of variability are well understood, some are physiological and some experimental. For example the firing properties of neurons may differ greatly between slice preparations and *in vivo* recordings [5] or between anaesthetized or awake animals. In functional brain imaging and neuropsychological studies it is well appreciated that small details in the study design may have a huge effect on the response. To ensure that meta-studies of the data are possible, it is essential to document, in full detail, the experimental procedures used to obtain them, which is not trivial.

First, there is the problem of how to standardize such methodological descriptions so that they can be put into database records, instead of the free text format used in journals. Second, methodological descriptions are often incomplete in important details. The BrainMap project [6, 12] has been a partial attempt to solve these problems for brain activation imaging experiments, but only published data are included, rarely sufficient to ensure comparability between studies performed in different laboratories. Models of brain function are often similarly varied in quality of description and comparability, in part due to the relatively small size of research groups developing software modeling tools [4]. Furthermore, there is a crucial need to develop integrative neuroscience modeling tools that take account of multiple levels of description of brain function. Standardized high quality multi-hierarchical neuroscience databases are needed to provide experimental data for use with these models. Recent developments in this regard include a database of macaque brain connectivity based on tracing studies (CoCoMac) [22], which provides flexibility for integration of large sets of partially redundant and contradictory data. The International Consortium for Brain Mapping (ICBM) database [26] is a repository for multiple types of human brain image data including MR scans, cyto- and myelo-architectonic data, as well as subject demographics and genetic information.

Tools: Software is among the most shareable of all neuroscientific tools. However, software development is often one of the most difficult and expensive aspects of collecting, analyzing and modeling neuroscientific data. The very creative nature of good software is often at odds with the rigor required of the science and often depends upon very different skills than those mastered by most neuroscientists. The amount of work that goes into making modular, portable, reusable code can be considerable and only rarely is it developed to serve a wide range of applications. Supporting it is not popular among scientists and only infrequently does non-commercial code reach the status of being widely accepted and used.

Ethical and Legal Aspects: There have been a number of developments in regulations covering data gathering, storing and access (see App. 2). In addition to these generic questions, three important aspects to the legal issues associated with data and tool sharing are: protection for the creator of the data or tool, protection for the user of them and protection for the subjects included in the data. In some cases there will be proprietary information that must be protected. It is clear that there will be legal and institutional requirements or regulations that need to be established and followed. Traditional considerations about intellectual property, equitable distribution of authorship and other forms of credit include whether an individual participates in the conception of an experiment, collection of data, analysis of data, integration of the results into a conceptual model, actual modeling of the experimental result, and development of a scientific manuscript. These factors and others will need to be reconsidered in creating new norms suitable for a collaborative and integrative era in neuroscience. The legal issues regarding responsibilities to human subjects involved in research are relatively precise, being articulated more or less clearly (and differently!) by state agencies. The ease with which information can be transmitted from databases and over electronic circuits has heightened the challenge to ensure human subject anonymity and avoid inappropriate sharing of information about them. International collaboration also presents new concerns regarding satisfaction of each nation's Ethical Review Board requirements, which can have a major impact on global cooperation in sharing data.

3. Solutions

Despite these barriers to greater cooperation and collaboration in neuroscience [16], there are encouraging developments in a number of areas that are pointing the way to wider solutions. One theme which emerges from the examples which follow is that, on the one hand, parallel, local efforts are the foundation for global cooperation and, on the other hand, high-level, top-down facilitation and encouragement can significantly speed the establishment and cementing of collaborative efforts. It is appropriate to start with the individual and collaborative efforts, and ensure that they are built with clear inter-operational capabilities. Inter-operation implies using similar and clearly defined fields, terminology and ontology for description of data, models, literature, experimental procedures, etc., and identical or equivalent application software for analysis, as well as developing appropriate standards relating to modeling neuroscience data. A natural progression for databases is the creation of federations of databases, based on either broad or narrow research problems, ultimately resulting in meta databases where data would be merged into large compatible collections. Similarly, for software environments a natural progression is the definition of common component-based software frameworks arising from identified commonality of interest across research problems. However, some of the problems described above are not amenable to organic solutions, even partially, (e.g., data-privacy issues) and will require high-level intervention.

Databases: In modern neuroscience there is a spectrum of exchange and sharing. Individual databases are emerging focused on (usually) one area of study. These typically serve manageable constituencies and remain successful independent efforts, although the ability to scale up in size, number of users or diversity of information is often untested. Several such examples can be found in [6]. Collaborative efforts where multiple databases, mirror sites, and complimentary efforts are linked are less common, but instructive examples exist, e.g., the ICBM effort (App. 3), and cooperation between some laboratories studying knockout mice. Problems include the lack of variability inherent in a genetically defined animal and the requirement for a defined common coordinate system in the construction of an atlas. Such focused collaborative efforts demonstrate the feasibility of multiple laboratories coming together and the sociological prerequisites for success. However, few examples exist of inter-operable databases developed to address the problem of understanding brain function across multiple hierarchical levels of description, either structurally or functionally. For example, databases for understanding the large-scale functional organization of the brain, neural coding and signal analysis are required. There is a crucial need for database developers to ensure inter-operability between multiple levels of spatial and temporal description as required by integrative neuroscience modeling efforts [11].

Ontologies: Neuroscientific data and models are complex and diverse, thus codifying them in standard formats represents a significant problem. An extensible and flexible index and description of experimental variables, protocols and models is needed. Clearly, a uniform taxonomy must be established to equate and differentiate the various data and model characteristics. Indeed, unequivocal nomenclature is essential at every level of data and tool sharing. Efforts are underway to address these issues in various domains of neuroscience, e.g., the Common Data Model [7] and NeuroML [8] (see App. 4).

Software Frameworks: Several laboratories are collecting and creating tool sets that can be assembled into useable programs or collections. These are typically component based frameworks, for example FisWidgets, LONI pipeline, the Biological Modeling Framework Core and NEOSIM (see App. 5). Integrative modeling of neuroscientific processes, for example using cable theory, modeling of biochemical processes, and large-scale realistic neural networks for understanding cognitive information processing, are being enhanced through the adoption of similar frameworks. As with databases containing data, software modules must also include sufficient descriptions about them to make them useful. They must be appropriately validated and documented. Legal considerations such as absolution of liability, copyright and credit requirements must be made clear.

Funding: Neuroinformatics projects have specific funding needs at multiple levels. Individual initiatives can be promoted by allowing an informatics development and maintenance budget in standard research grants from agencies supporting neuroscience research. Larger initiatives need specific support for multi-disciplinary and collaborative research. There are a number of successful funding models that have overcome the national barriers to multinational collaboration, and the disciplinary barriers to multidisciplinary collaboration (see App. 6). An alternative model which is proposed by the OECD Working Group (App. 1) would be to create a framework for national funding of international collaborations with international peer review.

4. Areas Where Progress Is Needed

Software Development: The open source movement (http://www.opensource.org/) provides a model of how to ensure quality and contribution, but there will need to be avenues developed for ongoing funding streams for development, maintenance and support of software. While there are several examples of governmental support, e.g., NiFTI (http://www.nimh.nih.gov/strategic/strategic.pdf) and Medline (http://www.nlm.nih.gov/databases) for maintenance of software and databases, new vehicles will need to be identified.

Quality Assurance: We have discussed quality control from the viewpoint of database management. The growth of many individual databases raises another problem: how to evaluate them from the prospective user's viewpoint. They do not receive the same peer review or other type of scrutiny as with traditional scientific reporting. Which are good databases and which are not? Are the data correctly annotated and cross-referenced? A similar problem exists with tools, most seriously with neuroscientific software: does it work properly, how does it compare to other tools claiming to perform the same function, is it relatively robust and bug free, are the results correct, etc.? The Internet will likely emerge as a spontaneous and free flowing version of peer review, as has been used in E-commerce: for example, booksellers encourage readers to write short online reviews of books.

Ethical and Legal Considerations: We will need to develop guidelines for sharing, analyzing and modeling data in an ethical and fair manner recognizing the due credit and responsibility for both the original "data provider" as well as the "data user", in the new research paradigm in which data are openly shared. It will be necessary to address the issues of who the researchers are, the rights of each researcher, the timing and purpose of the data sharing arrangement, access to data, allocation of rights/ownership and who bears what costs. Furthermore, researchers sharing analysis and modeling tools with a strong theoretical basis need the certainty that their software tools are being applied in appropriate ways. Ultimately, we must be accountable to all and ensure that all who contribute receive credit, and those who have no intellectual contribution do not. In particular, Ethical Review Board practices need to be made interoperable to enable maximum data sharing within a proper regulatory regime.

5. Conclusions

At a grass roots level much progress is being made as is evident in the plethora of small database initiatives appearing and in specialized software tools that circulate within neuroscience sub-fields. However, many of the challenges mentioned cannot be overcome at this level. There are increasingly significant challenges in further developing theoretical methods for integrating our diverse specialized understanding of aspects of neuroscience. These integrative analysis and modeling techniques are dependent upon experimental techniques to provide data that allow studies of integration in neuroscience. It is in this area that neuroinformatics can contribute significantly. Integrative modeling of biomolecular neuroscience processes as well as of theoretically based cognitive neuroscience processes, such as the psychodynamical foundations of neuroscience, are significant challenges. However, the application of our understanding of integrative neuroscience processes to innovations in biomedicine, neural engineering, robotics, machine vision, as well as in other computational based disciplines provide much promise. The large-scale international collaborations needed require new models of coordination and funding. Provided sufficient government support is given to such international initiatives, neuroinformatics can play a pivotal role in human brain research leading to innovations in neuroscience, informatics and treatment of brain disorders.

Disclaimer

This paper reflects the opinions and positions of the authors and is not an official policy or opinion of any government or the European Commission.

Appendix 1. The OECD Neuroinformatics Working Group

Scientific sharing and cooperation are global objectives with international efforts already underway. The goal of the OECD Neuroinformatics Working Group (NWG) is to provide a common resource for neuroinformatics tools and databases, establish guidelines and recommendations for their organization and interoperability and help with the communication and dissemination of worldwide efforts in collaborative neuroscience. These goals are broad (global) in their intent and participation and have been preceded by and will continue to include considerable national and international dialogue. The NWG grew out of previous efforts by the Organization for Economic Cooperation and Development (OECD), which aims to help develop and restore economies in the industrialized world and emerging nations. One of these efforts led to the Global Science Forum (GSF) that fosters cooperation in global large science programs and issues. On the basis of a report to the OECD in 1999, (http://www.oecd.org/dsti/sti/s_t/ms/prod/BIREPFIN.pdf), and recognizing the need for cooperative efforts in neuroinformatics, scientists and policy officials from member governments committed a two-year mandate to the Working Group on Neuroinformatics to help promote this field.

Appendix 2. National and International Data Privacy Regulations

Databases (primarily from non-neuroscientific fields) have received considerable legislative attention. The European Union introduced a directive on legal protection of databases in 1996 (Directive 96/9/EC; http://europa.eu.int/eur-lex/en/lif/dat/1996/en_396L0009.html). The EU legislation assigns copyright to the database authors. This legislation emphasizes that the maker of a database "may not prevent a lawful user of the database from extracting and/or re-utilizing insubstantial parts of its contents, evaluated qualitatively and/or quantitatively, for any purposes whatsoever". Similarly, U.S. Congress bill H.R. 354 of 1999 (http://www.uspto.gov/web/offices/dcom/olia/hr354.html) deals with legal protection against "commercial misappropriation of collections of information". This bill also emphasizes the need to avoid legislative obstruction of the free use and reuse of scientific data produced with governmental support. A continuing debate on copyright and ownership issues related to general aspects of data and tools sharing takes place in the World Intellectual Property Organization (http://www.wipo.org/).

Appendix 3. The International Consortium for Brain Mapping (ICBM)

ICBM is a database project where a number of brain image databases have been combined to take advantage of the large number of studies achieving significant statistical power for population-based studies. Initially established to create an anatomic and probabilistic framework that describes morphological variability, this international effort now incorporates functional measures using a variety of imaging modalities. This project includes data acquisition and software development for analysis, visualization and modeling [13–15, 24, 26]. ICBM scientists developed a variety of warping algorithms [25] enabling brain-to-brain to population comparisons. Statistics derived from these deformations have been applied to numerous subpopulations including Alzheimer's disease [17], Schizophrenia [18, 19] and normal development [23]. The database itself is an ever expanding repository of image data, demographics and genetic information.

Appendix 4. Ontologies: The Common Data Model and NeuroML

The Common Data Model (CDM) (http://cortex.med.cornell.edu) provides an ontology for describing data, literature, experimental methods, computational models, etc., across a wide spectrum of contemporary neurophysiology [7]. The evolving model is designed to become as well an open extensible standard for describing and sharing data models, metadata, dataset formats and model descriptions of a wide range of neuroscience resources: a blueprint for neuroscience information exchange. NeuroML (http://www.neuroml.org) is an extensible markup language for the neurosciences that adheres to the CDM [8]. Using XML as its surface form, and Java classes as its generating schemata, it is used for interoperation of a wide variety of software components, from databases through simulators to user-interface tools (see App. 5). Currently its main use is for information related to computational models, and it is expected that it will be extended to other types of data described in the CDM, such as anatomical data and experimental methods.

Appendix 5. Software Frameworks

Modern software engineering favors the use of component-based software frameworks for large, evolving systems. Such a framework defines a set of protocols and interfaces to enable combination and interaction of software components, and several such frameworks related to NI have been developed or are under development. NEOSIM (http://www.neosim.org) is a component-based software framework for portable, scalable high-performance simulation of computational models.

It implements NeuroML and currently includes components-based releases of the CATACOMB and NEURON modeling packages. The Biological Modeling Framework (BMF) Core [9] is a plug-in kernel supporting dynamic web-based loading and running of software components including databases, simulators and user-interface tools (e.g., NEOSIM), which interact via specialized communication protocols such as NeuroML. The LONI pipeline (http://www.loni.ucla.edu) includes a description language that provides a java based graphics interface to select and order processing modules from any source, controlling a client/server execution.

Appendix 6. Funding Models

The Human Brain Program (http://www.nimh.nih.gov/neuroinformatics/index.cfm) in the United States explicitly requires that projects have both an informatics and a neuroscience component. In Japan, a large collaborative integrative neuroscience project is focused on the visual system (http://www.neuroinformatics.gr.jp) and several other countries have national programs to promote NI research. The 5th Framework Program of the European Commission had a specific call for collaborative NI initiatives (http://www.cordis.lu/life/home.html), but at present it is uncertain whether this will be continued under the 6th Framework. This points to the general difficulty in finding support for international collaborative ventures. While the Human Frontier Science Program (http://www.hfsp.org) supports international research programs it is not focused on NI specifically, and because of its limited budgets it is not able to give significant support to the field.

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