BrainFrame: A Knowledge Visualization System for the Neurosciences

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Abstract

Neuroscience has benefited from an explosion of new experimental techniques; many have only become feasible in the wake of improvements in computing speed and data storage. At the same time, these new computation-intensive techniques have led to a growing gulf between the data and the knowledge extracted from those data. That is, in the neurosciences there is a paucity of effective knowledge management techniques and an accelerating accumulation of experimental data. The purpose of the project described in the present paper is to create a visualization of the knowledge base of the neurosciences. At run-time, this 'BrainFrame' project accesses several web-based ontologies and generates a semantically zoomable representation of any one of many levels of the human nervous system.

Categories and Subject Descriptors (according to ACM CCS): J.3 [Computer Applications]: Life and Medical Sciences

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1. Introduction

> *"We now have unprecedented ability to collect data about nature…but there is now a crisis developing in biology, in that completely unstructured information does not enhance understanding."* (Sydney Brenner, at [Dig03])

Biological data have been accumulating exponentially over the past few centuries [BS07]. To manage this situation, most biological sciences have incorporated data management techniques into their methodologies; fewer have adopted knowledge management techniques. For biology's most complicated organ system, the nervous system, this situation has become particularly problematic, and neuroscientists are currently overwhelmed with data.

Neuroscientists have begun to acknowledge that--even within relatively restricted neuroscientific research domains--no individual is smart enough to remember, evaluate, and synthesize the existing literature (e.g., [BS07]). As an illustration, a search using PubMed [Pub07] for the number of articles published in 2006 matching the term *hippocampus* (a temporal lobe structure) yields 5,042 published articles. Assuming a supernormal reading speed of 1 pg/min and a subnormal article-length of 10 pgs, it would still take 840 h to read the 2006 hippocampus-related literature. That leaves little time for conducting experiments or reading the other 69,327 hippocampus-related articles published prior to 2006.

In the face of overwhelming amounts of data, humans adopt heuristics. Some of those heuristics (e.g., the availability heuristic; see [TK74]) can produce unscientific syntheses of the available data. Accordingly, if the most talented neuroscientists are unable to handle the size of the existent literature, then there is a good chance they have a distorted understanding of their own research domain. This situation will, in turn, result in their adopting any one of three possible strategies when attempting to convey neuroscientific knowledge to the public: (1) they will simply not attempt to, (2) they will say "we don't know enough yet," or (3) they will provide their own distorted view. As the data sets and literature continue to grow, the danger they will adopt one of these strategies also grows.

In practice, most neuroscientists do not attempt to read every article in their domain. Many come to rely on published review articles as a means of synthesizing the literature. The problems with review articles aside (e.g., many do not use or identify a systematic methodology; see [MCvW*99]), the number of review articles about even "smaller" topics in the neurosciences has become unwieldy: Searching PubMed for hippocampus-related review articles yields 293 entries for 2006. When a researcher wonders if there are reviews of the review articles, there is a dangerous problem with the system.

There must be a better way of representing the literature than the traditional document. That is, how can the ever-increasing knowledge base of neuroscience be organized into a more penetrable format--one that is sensitive to the limitations of human cognition? The present article will next review some issues specifically related to knowledge management in the neurosciences; neuroscience database efforts will also be discussed. Next, several existent neuroscience ontologies and knowledge visualization efforts will be examined. Based on that review, a new vision for knowledge management in the neurosciences will be proposed and our first implementation of such a system will be presented.

2. Neuroscientific Knowledge

Before trying to solve the knowledge management issues in a particular domain, one should ask the following question: What is the means of knowledge acquisition within the domain? The answer should not be literal (e.g., collect data, enter data…publish paper, write review article); a useful answer should provide an abstraction of the domain's knowledge acquisition process.

We have found the following metaphor to be useful when characterizing the knowledge acquisition process in the neurosciences: *Neuroscience takes photos.* That is, each data set collected by a neuroscientist is a time-locked context-sensitive snapshot of information. The data are locked temporally (e.g., to the time the neurophysiological recording was obtained) and contextually (e.g., location, treatment, and species). Multiple temporal and contextual slots are common: For example, the calendar time of data collection (e.g., 1977), the time in the life of the organism (e.g., postnatal day 10) or the time after some treatment (e.g., 2-hr post-Valium-injection) are all important for a meaningful interpretation of the data.

But neuroscience wants more than just a photo album for its many snapshots: Its goals are to generalize findings across species, time frames, and places. To extend the photo analogy: *Neuroscience seeks a complete movie from an incomplete set of frames*. Accordingly, to obtain knowledge in neuroscience, a single experiment is insufficient. Neuroscience must rely on replication of an observed effect; not just in multiple labs, but also in multiple species, and at multiple times within the lifetime of the same species. Such observed effects are hoped to be transformable into knowledge about the human brain--although this is not always the desire (e.g., comparative neurobiology). Accordingly, the usefulness of a particular finding cannot be determined by the statistical tests applied within a particular neuroscientific study, nor even in the replication of a study within and between laboratories, but rather in the management of knowledge about the reproducibility of the observed effect in multiple labs, at multiple times, and in multiple species. In the neurosciences, a study is the datum, the results of many studies constitute information, and the meta-analysis—be it qualitative or statistical—of many studies constitute knowledge.

In addition to characterizing the mode of knowledge acquisition in the neurosciences, it is also useful to examine how various user groups currently access that knowledge. Each of the following three subsections examine a representative scenario faced by three common users of neuroscientific knowledge: (1) neuroscientists; (2) science journalists; and (3) patients.

2.1. User Scenario 1: The Neuroscientist

The primary goal of any neuroscientist is, of course, to conduct meaningful and useful research. Let us examine the simple scenario of a neuroscientist who wishes to study a specific disease process within the hippocampus. More specifically, this researcher wants to know if the ablation of a specific cell type in the hippocampus is a necessary and sufficient cause of the anterograde amnesia observed following bilateral temporal lobe resection (e.g., as was observed in famous case study of patient H.M. [SM57]).

The researcher begins by searching PubMed for articles related to their question. They are immediately overwhelmed with textual information. After considerable time and effort, they settle upon several dozen review articles; they download them; they read each of them thoroughly; they seek out select references from each review article and then read each of those. After completing those readings, the researcher decides their original hypothesis is valid and testable, and that their question has not been addressed in the existent literature. Still, there are nagging questions in the neuroscientist's mind: Were those review articles outdated or biased? Is someone else working on the same research question right now? Could the answers I am seeking be inferred from the existing knowledge base?

Such questions will usually remain unanswered. Yet the fiscal and ethical stakes involved in not answering them are high: large sums of public funds and animal suffering are associated with most neuroscience experiments.

2.2. User Scenario 2: The Science Journalist

Journalists seek out the major scientific (e.g., *Science*, *Nature*) and neuroscientific journals (e.g., *Journal of Neuroscience*) for studies they hope will be of interest to the general public. The results of such studies are usually represented in the press as new knowledge. For example, a study showing a protective effect of a drug in a mouse model of Alzheimer's disease might be represented as: "Scientist identifies treatment to prevent Alzheimers." Such news reports are problematic for several reasons. First, for the reasons outlined earlier, neuroscience experiments do not represent knowledge; such reports encourage the mistaken idea that complex problems in the neurosciences are solvable with single experiments. Second, they generate public mistrust when the inevitable conflicting reports are subsequently published and reported on.

2.3. User Scenario 3: The Patient

Patients read the scientific literature for experimental studies and review papers in the hopes of improving their understanding of their illness and their treatment options. Most internet-using patients do considerable amounts of research on their illness (e.g., [ABC*07]). For the reasons outlined in the previous scenario, many patients come to believe that the results of individual experiments represent knowledge. Mistrust in both the medical community and in the neuroscience literature arises when the patient's assessment of their health and/or treatment options differs from that of a medical professional.

3. Databases in the Neurosciences

In contrast to other biological sciences, neuroscience has been plagued by a lack of data sharing [Asc06]. The reasons for this problem range from the ethical (e.g., human brain-imaging data can contain identifiable characteristics of an individual, [Asc06]) to the practical (e.g., the heterogeneity of neuroscientific techniques means that metadata entry can be extremely time-consuming; see [vHG05] for a full discussion of this and other practical issues). Whatever the reasons, the result is that neuroscience has been slower to implement database technology relative to many other biological sciences.

Still, efforts have been made by the neuroscience community to build repositories for previously collected data as well as live data (e.g., [Gar04]). These databases have been reviewed elsewhere [KS05]. Unfortunately, neuroscience databases suffer from sparse population and/or misrepresentative population [Asc06].

4. Ontologies in the Neurosciences

An ontology is a "formal explicit specification of a shared conceptualization" [GLG*03]. Biology and medicine have produced many ontologies. Some of the more populous examples include the Gene Ontology [Gen02] and the Unified Medical Language System (UMLS) [Nat03]. A small number of ontologies have also been constructed specifically for the neurosciences.

The use of ontologies in the neurosciences has been explored for some time in the context of the development of large neuroscience database projects [MGE04] (e.g., [Cel07], [Bio07]) and with the support of granting-agency initiatives aimed at improving data sharing practices in the neurosciences (e.g., [Gar04]). It is beyond the scope of the present paper to review every ontology for the neurosciences (see [Nie07] for a complete list). Instead, we will examine four projects—each representative of a particular knowledge domain within the neurosciences. However, before doing so, we outline three design considerations that are unique to neuroscience ontologies.

4.1. Design Considerations

First, any ontology for the neurosciences has to take into account the possibility of multiple perspectives. That is, neuroscience comprises a heterogeneous group of researchers. For example, a clinician might study epilepsy in human patients, a biopsychologist might study epilepsy in an animal model, and a neurophysiologist might study it in an *in vitro* model. In each case, the meaning of the term *seizure* can be subtly different. At the same time, we want to be able to relate commonalities in the three usages of the term; since, for example, the goal of an animal model is to make inferences about a human condition. Thus, an epilepsy ontology would need to preserve the separate meanings of *seizure* while still allowing us to relate them in meaningful ways.

Second, and closely related to the first design consideration, is that any ontology for the neurosciences needs multiple levels of detail. Neuroscientists, like many biomedical scientists (e.g., [KH07]) operate at multiple granularities. A cognitive neuroscientist could be studying the neurological underpinnings of memory using functional magnetic resonance imaging (fMRI) and find that the hippocampus is important for explicit memory formation. A neurophysiologist could be studying the same question, and find that it is the pyramidal cells of the dorsal hippocampus that are important. The ontology needs to be constructed so that these different conclusions do not conflict, but rather reflect the different levels of analysis.

Third, an ontology for the neurosciences needs to be designed as a mutable thing. Many of the classifications and conclusions in the neurosciences are in flux. Bota and Swanson highlight that instability in the context of neuroanatomical interconnectivity:

> "*Focusing on only one major brain region, the hypothalamus, it was estimated that in 1940 about 55 macroconnections…were considered reasonably established, whereas by today's criteria some 80% of these results were false-positive technique artifacts. Thirty years later, about 75 macroconnections were regarded as established with new analytical tools, whereas today half of them appear to be false-positive artifacts. By 2002, on the order of 3,000 hypothalamus macroconnections had been described...that number approaches 5,000 today…*[BS07]"

One needs to design flexible neuroscience ontologies so that information shifts are incorporated without disrupting the structure and portability of the ontology.

There are other design considerations one must take into account when designing neuroscience ontologies However, many are subdomain specific and may not apply to all neuroscience ontologies. Gupta et al [GLG*03] provide an excellent overview of the numerous design considerations associated with the development of a Parkinson's-disease-specific ontology.

4.2. Gross Neuroanatomy Ontology: NeuroNames

One of the oldest ontology projects in the neurosciences is the NeuroNames project [BM95], which is now available as a source vocabulary for the UMLS [HS03]. Most recently, it has been integrated with BrainInfo [Bra07] to include a stereotactic atlas interface that allows users point-and-click navigation of the ontology. The NeuroNames ontology comprises over 15,000 neuroanatomical terms.

4.3. Neurophysiology Ontology: BrainML

Another project, BrainML, was built as part of an effort to encourage data sharing amongst neurophysiologists [GAK*05]. BrainML has a layered architecture: It is built on top of a metalanguage (BrainMetaL), which is in turn built on top of XML Schema and XML [GAK*05].

4.4. Systems Neuroscience Ontology: BAMS

A more recent effort, the Brain Architecture Management System (BAMS) is an ontology that incorporates quantitative and qualitative data on nervous system connectivity [BS07]. BAMS is particularly impressive as it was able to incorporate a notoriously conflicting set of data on nervous system structural connectivity.

BAMS also aims to be a knowledge management system. Accordingly, it has a number of associated features that contribute to that goal: Information visualization tools and databases. Unfortunately, BAMS suffers from the same issues that plague much of the neurosciences: It relies on data contributions from individual researchers, yet those data are not appearing.

4.5. A synapse ontology: SynO

The most recent neuroscience ontology is the synapse ontology (SynO). SynO was constructed in parallel with a database of proteins known to exist in the synaptic clefts between neurons (i.e., SynDB). SynO contains a total of 177 terms, hundreds of synonyms, and is currently eight levels deep [ZZZ*07].

4.6. Summary

Although there are several large ontologies already available to neuroscientists, there is one marked failing in these ontologies. Specifically, it has been previously observed (e.g., [WA03]) that most biomedical ontologies do not satisfy the requirements of being a formal ontology. That is, they cannot be subjected to automated logical interpretation or plugged into inference engines. The ontologies reviewed above are no exception to that observation. Despite being called "ontologies," many of them are simply controlled vocabularies and none were constructed using modern tools (e.g., Protégé [Prt07]). The reasons for this shortcoming are unclear. It might be that the design criteria for neuroscience ontologies (discussed above) are prohibitive to the construction of well-formed ontologies.

There has been at least one effort to build a true formal ontology for a domain of knowledge within the neurosciences: A disease-specific ontology of Parkinson's disease [GLG*03]. However, because the published description [GLG*03] was of an unfinished project, and no articles have appeared since that initial report, it is presently unclear if the designers have continued building it.

From the above survey, it is clear that the current set of available neuroscience ontologies is insufficient. If neuroscience is going to solve its knowledge management problems, it will need to take steps to construct formal ontologies (e.g., using the Web Ontology Language (OWL)[Ow07]; see Protégé [Prt07]); ones that can be subjected to reasoning engines (e.g., Jess [Jes07]). One way of solving this problem is to remap [KS03] the existing neuroscience ontologies into an OWL-based format.

5. Information Visualization in the Neurosciences

There are many data visualizations in the neurosciences. The most obvious examples are those used in human brain imaging projects (e.g., MRI, fMRI, and positron emission tomography). There are fewer examples of information visualization in the neurosciences. The following subsections will review two notable examples.

5.1. Brain Explorer

The Allen Institute for Brain Science [All07] has been working on several projects with a collective goal of creating a new atlas of the brain that is based on the functional organization of the brain as assessed via gene expression profiles within the brains of several species (e.g., mouse, human) and under several behavioural conditions (e.g., sleep, wakefulness). The large scope of this undertaking required that information management and visualization techniques be integrated into their research agenda from the outset. Accordingly, they developed a data basing system for searching the existent data sets and a free downloadable visualization tool: Brain Explorer.

Brain Explorer constitutes a visualization tool for those data sets generated by the Allen Institute for Brain Science. It permits the user to rotate a model of the mouse brain that displays the expression profiles of the various genes expressed in particular brain regions. As a tool for the neuroscientist it has several notable and useful features: (1) It permits the user to restrict their view only to those brain areas of interest, thereby limiting the information presented so that they are not overwhelmed; (2) …

5.2. Nodes3D

Nodes3D is a visualization tool for the brain connectivity information contained at brainmaps.org [brm07]. It uses spheres to represent brain regions, lines to represent connections between those regions, and arrowheads to represent the directionality of those connections. It allows the user considerable control over the various aspects of the display of the information.

5.3. Summary

Although these two examples of information visualization within the neurosciences constitute important steps forward in the way we look at and neuroscience information, they do not constitute examples of knowledge visualization. That is, these examples do not support the transfer of knowledge [Bur05] so much as they permit the summary of large amounts of data. They do support interaction on the part of the user, but that interaction is relatively limited and does not affect the system or the database.

6. BrainFrame

We would like to propose a particular vision for knowledge management in the neurosciences. This "BrainFrame" vision is an extension of that proposed for virtual observatories (VOs) by Fox et al. [FMM*06]:

> *"The virtual observatory (VO) vision includes a distributed, virtual, ubiquitous, semantically integrated scientific repository where scientists (and possibly lay people) can access data."*

The BrainFrame vision comprises several components, each of which is discussed in some detail in the subsections that follow. The current iteration of the BrainFrame project represents a first step in our efforts to achieve that vision. It is also discussed in each of the following subsections.

6.1. New Ontologies for the Neurosciences

The BrainFrame vision will necessitate the production of several new neuroscience ontologies written in OWL. Some of these ontologies will serve as remappings of existing neuroscience ontologies into a format useable by OWL-DL-based reasoning engines such as Jess [Jes07], while others will be new ontologies for the neurosciences.

The current iteration of the BrainFrame system focused on the construction of 9 fundamental ontologies whose relationships are illustrated in Figure 1.

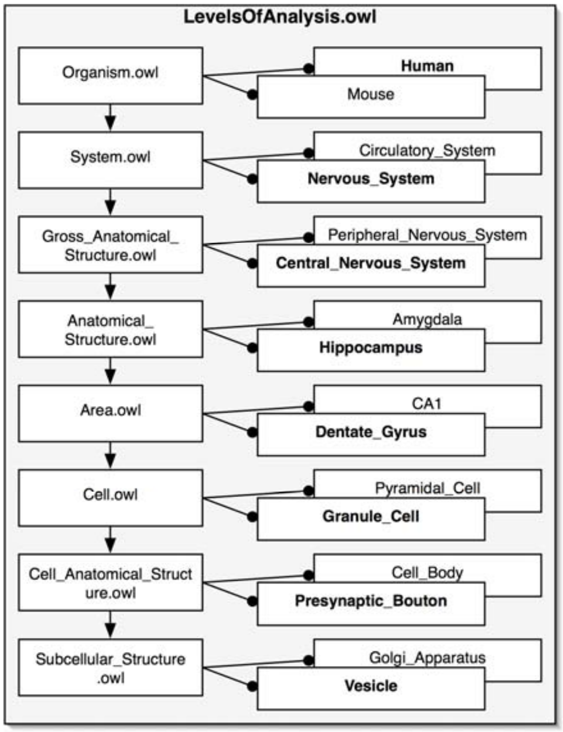

Figure 1: *The nine fundamental ontologies of the current BrainFrame system. The Levels_Of_Analysis.owl ontology defines eight classes (left); each of those classes are elaborated within their own ontology. Also shown are two example classes (right) from each of these eight ontologies.*

The first ontology, *Levels_Of_Analysis.owl*, has a class for each fundamental level of analysis someone might want to look at. These classes currently comprise several spatial levels of analysis ranging from the *Organism* class to the *Subcellular Structure* class. The class list is by no means complete (e.g., proteins could be added at the bottom, behaviour could be added at the top) and will be extended in future versions of the system and by user interactions with the system.

The 8 levels of analysis currently defined in the *Levels_Of_Analysis.owl* ontology are further elaborated within their own respective ontologies. For example, the *Organism* class has a property (i.e., *hasUrl*) that links to its respective ontology: *Organism.owl*. Figure 1 also illustrates examples of two classes within each of those 8 ontologies.

We anticipate that future versions of the system will contain even more ontologies. This is because any attempt to integrate all of the ontologies into a single ontology (we attempted this in a prior version) would create several practical issues. For example, such a unified ontology would be (1) less extensible, (2) slow to load over a network, and (3) have large memory demands once it is loaded as a Jena [Jen07] model. In short, we designed the ontologies to be modular and extensible by making them as shallow as possible.

6.2. Implementation

The BrainFrame system is implemented in Java and uses several libraries: (1) the Processing [Pro07] library for its graphical interface, (2) the Jena [Jen07] library for building ontology models, and (3) the RETE-based Jess [Jes07] rule engine for performing reasoning on the Jena-based models.

The BrainFrame system employs the XML-based scalable vector graphics (SVG) format for all of its images (see Figure 2). This was an important design decision, since using this format will encourage future extensions of the system. For example, since each of the graphical elements are written as a parsable XML file, a user can write new graphical representations into the system at run-time that can be read into the system by another user and displayed without requiring any new code. In addition, references to the images are stored as a property (i.e., *hasImageURL*) of the class (e.g., human or mouse in Figure 2) within a particular ontology (e.g. *Organism.owl* in Figure 2).

Ultimately, each entity (e.g., any of the elements on the right side of Figure 1) in the BrainFrame system is represented as an object of the class *Entity.java.* Each object of this class stores information derived from the ontologies about its respective entity, and that entity's immediate children and parents in the Jena ontology model. It also stores information about its visual representations (i.e., its SVG files) and any other properties or relationships it has with the other entities in the current ontology model.

6.3. Interface and Representations

The present iteration of the BrainFrame system presents the user with an entry screen that depicts each of the organisms (e.g., human and mouse in Figure 2) represented in the *Organism.owl* ontology. When the user hovers their mouse over a particular organism, the entities existent at the next level of analysis (e.g., the nervous and circulatory systems in Figure 2) are revealed so the user has a sense of their trajectory. The user can then click on that organism (e.g., to zoom into the next level of analysis.

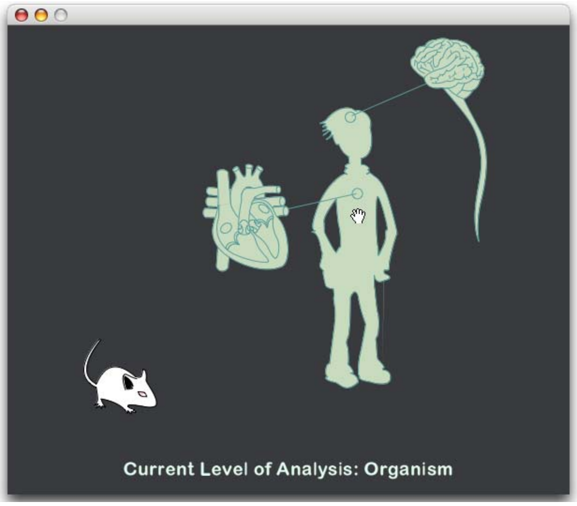

Figure 2: *Current start screen for the BrainFrame system.*

6.4. Semantic Zoomability

Semantic zooming occurs when a user clicks on a particular entity and expands the contents of that entity. For example, choosing the human entity in Figure 2 will restrict the next level of analysis (i.e., the System level) to that of human systems (e.g., the nervous or circulatory systems in Figure 2). The major purpose of the semantic zooming in the BrainFrame system is to limit the amount of information that the user is presented with. Our goal wasn't to construct a visualization of our ontologies—which would simply impart a sense of complexity on the viewer. Our goal was to present the user with an interface that allowed them to control the granularity and details of the information presented to them. If the user is a neuroscientist, they are free to delve deeper into the ontologies; whereas, if the user is a journalist or patient they can obtain the knowledge they seek with a minimum amount of extraneous information.

6.5. Summary and Future Goals

The BrainFrame system is not a tree or graph visualization, nor is it similar to any available ontology visualization (see [WA07] for a review). In fact, the amount of information in the present and future iterations of BrainFrame would make such a visualization cluttered, and therefore relatively useless as knowledge visualization [AW02]. An important goal of the BrainFrame system is not to overwhelm the user with information. Rather, the BrainFrame system aims to limit the amounts of information to that which is reasonable given the constraints on human sensation, perception, and cognition. Accordingly, the BrainFrame system uses semantic zooming to allow the user to reveal only those details they desire to entertain.

The immediate goals for the next iteration of the BrainFrame system are three-fold: (1) allowing the user to directly modify the underlying ontologies--in addition to empowering the user this addition will be important for the growth of the system and is consistent with the vision for the BrainFrame system in particular and for virtual observatories in general; (2) expanding the underlying ontologies so as further to enable the former goal, and (3) incorporating a sketchpad metaphor into the interface of the system. The sketchpad interface will serve two purposes. Its primary purpose will be to allow the representation of degrees of certainty of knowledge within the system. In contrast to the knowledge that is currently represented in the BrainFrame system, most of the knowledge base in the neurosciences is in a state of flux. It is critical that users are made aware of the putative nature of many of the facts in the system. A secondary purpose of the sketchpad metaphor is to allow the user to propose changes to the system via sketching, and to pose common queries to the system via simple gestures rather through textual commands or menu navigation.

The BrainFrame system has several long-term development goals. The first is to incorporate or link existent databases and references as supporting materials for the representations in the system. This wasn't as important for the current version of the system since the facts represented in the system are not in considerable flux--they were derived from a comparative analysis of two introductory texts (i.e., [SRS*03, KSJ00]. As the system evolves to incorporate more and more information, and once it comes to support user modifications, it will become increasingly important to provide a means of referencing and linking sources. Protégé [Prt07] permits the creation of annotation properties. Ideally these annotations will use either the Digital Object Identifier [Doi07] for journal articles and other resources and the International Standard Book Number [Isb07] for books. An additional requirement necessitated by that development is a means of representing degrees of certainty about information represented in the system. Accordingly, we are currently developing an ontology that seeks to explicitly define the types of information (e.g., experiments, review articles, meta-analyses) that comprise knowledge in the neurosciences and the degrees of certainty that might be associated with each of those types.

7. General Discussion

The present paper examined the current status of knowledge management within the neurosciences: The neurosciences are clearly in need of better knowledge management techniques. The BrainFrame system is currently in the earliest stage of its development. The current iteration of BrainFrame comprises several high level ontologies that are navigable by users using a semantically zoomable interface. Some of the steps that will be taken in the next iteration of the BrainFrame system will be support for user modifications, expansion of the BrainFrame ontologies, and the incorporation of a sketchpad metaphor into the interface.

The human brain is a massively parallel system. This system tends to be organized hierarchically within particular domains (e.g., visual sensation and perception), but is ultimately a fundamentally recursive system in terms of its integration of ongoing incoming sensory information with concurrent outputs (e.g., motor signals). For example, any motor output from the system always creates new sorts of sensory inputs that immediately feedback into the system. It will be important not to lose sight of this complexity when designing a computational system that seeks to provide knowledge management for the neurosciences.

8. References

[ABC*07] ANDREASSEN, H. K, BUJNOWSKA-FEDAK, M. M, CHRONAKI, C. E., DUMITRU, R. C., PUDULE, I., SANTANA, S., VOSS, H., WYNN, R.: European citizens' use of E-health services: A study of seven countries. *B.M.C. Pub. Health 7* (2007), 53.

[All07] *Allen Institute for Brain Science.* http://www.allen-institute.org/default.htm

[AW02] AHLERS, J., WEIMER, H.: Challenges in interactive visualization for knowledge management. *Proceedings of the Sixth International Conference on Information Visualization* (2002).

[Asc06] ASCOLI, G. A.: Mobilizing the base of neuroscience data: The case of neuronal morphologies. *Nat. Rev. Neurosci., 7* (2006), 318-324.

[Bio07] *Biomedical Informatics Research Network*. http://www.nbirn.net/.

[BM95] BOWDEN, D. M., MARTIN, R. F.: NeuroNames brain hierarchy. *Neuroimage, 2* (1995), 63-83.

[Bra07] *BrainInfo.* http://braininfo.rprc.washington.edu/menumain.html

[Brm07] *Brainmaps.org.* http://brainmaps.org/.

[BS07] BOTA, M., SWANSON, L. W.: Online workbenches for neural network connections. *J. Comp. Neurol., 500* (2007), 807-814.

[Bur05] BURKHARD, R.: http://www.knowledge-visualization.org/. (2007).

[Cel07] *Cell Centred Database.* http://ccdb.ucsd.edu/CCDBWebSite/index.html.

[Dig03] *Post-conference web site for "Digital Biology: The Emerging Paradigm."* http://www.bisti.nih.gov/2003-meeting/.

[Doi07] *The digital object identifier system.* http://doi.org/

[FMM*06] FOX, P., MCGUINESS, D., MIDDLETON, D., CINQUINI, L., DARNELL, J. A., GARCIA, J., WEST, P., BENEDICT, J., SOLOMON, S.:

Semantically-enabled large-scale science data repositories. In CRUZ, I. (ed.): *ISWC 2006, LNCS 4273,* 2006, 792-805.

[GAK*05] GARDNER, D., ABATO, M., KNUTH, K. H., ROBERT, A.: Neuroinformatics for neurophysiology: the role, design, and use of databases. In KOSLOW, S. H. AND SUBRAMANIAM, S. (eds.): *Databasing the Brain*. John Wiley & Sons Inc., Canada, 2005, 47-67.

[Gar04] GARDNER, D.: Neurodatabase.org: networking the microelectrode. *Nat. Neurosci., 7* (2004), 486-487.

[Gen02] GENE ONTOLOGY CONSORTIUM: Creating the gene ontology resource: design and implementation. *Genome Research, 11* (2002), 1425-1433.

[GLG*03] GUPTA, A., LUDASCHER, B., GRETHE, J. S., MARTONE, M. E.: Towards a formalization of disease-specific ontologies for neuroinformatics. *Neural Netw., 16* (2003), 1277-1292.

[HS03] HOLE, W. T., SRINIVASAN, S.: Adding NeuroNames to the UMLS metathesaurus. *Neuroinformatics, 1* (2003), 61-63.

[Isb07] *International ISBN agency.* http://www.isbn-international.org/

[Jen07] *Jena: A Semantic Web Framework for Java.* http://jena.sourceforge.net/.

[Jes07] *Jess: The Rule Engine for the Java Platform.* http://www.jessrules.com/

[KH07] KASHYAP, V., HONGSERMEIER, T.: Can semantic web technologies enable translational medicine? In BAKER, C. J. O., CHEUNG, K. (eds.): *Semantic web: Revolutionizing knowledge discovery in the life sciences.* Springer Science and Business Media, New York, 2007, 249-279.

[KS03] KALFOGLOU, Y., SCHORLEMMER, M.: Ontology mapping: the state of the art. *The Knowledge Engineering Review, 18* (2003), 1-31.

[KS05] KOSLOW, S. H., SUBRAMANIAM, S. (eds.): *Databasing the Brain.* John Wiley & Sons Inc., Canada, 2005.

[KSJ00] KANDEL, E. R., SCHWARTZ, J. H., JESSELL, T. M.: *Principles of Neural Science, 4th Edition.* McGraw-Hill, USA, 2000.

[MCvW*99] MCALISTER, F. A., CLARK, H. D., VAN WALRAVEN, C., STRAUS, S. E., LAWSON, F. M. E., MOHER, D., MULROW, C. D.: The medical review article revisited: has the science improved? *Ann. Intern. Med., 131* (1999), 947-951.

[MGE04] MARTONE, M. E., GUPTA, A., ELLISMAN, M. H.: E-neuroscience: challenges and triumphs in integrating distributed data from molecules to brains. *Nat. Neurosci., 7* (2004), 467-472.

[Nat03] NATIONAL LIBRARY OF MEDICINE: *UMLS documentation.* (2003).

[Nie07] NIELSEN, F. A.: Bibliography on Neuroinformatics: Neuroscience Terminology. (2007).

[Owl07] *OWL Web Ontology Language Reference.* http://www.w3.org/TR/owl-ref/.

[Pro07] *Processing 1.0 Beta.* http://processing.org/

[Prt07] *The Protégé Ontology Editor and Knowledge Acquisition System.* http://protege.stanford.edu/.

[Pub07] *PubMed.* http://www.ncbi.nlm.nih.gov/sites/entrez?db=PubMed.

[SM57] SCOVILLE, W. B., MILNER, B.: Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiatry, 20* (1957), 11-21.

[SRS*03] SQUIRE, L. R., ROBERTS, J. L., SPITZER, N. C., ZIGMOND, M. J., MCCONNELL, S. K., BLOOM, F. E.: *Fundamental Neuroscience, Second Edition.* Academic Press, San Diego, 2003.

[TK74] TVERSKY, A., KAHNEMAN, D.: Judgment under uncertainty: heuristics and biases. *Science, 185* (1974), 1124-1131.

[vHG05] VAN HORN, J. D., GAZZANIGA, M. S.: Maximizing information content in shared and archived neuroimaging studies of human cognition. In KOSLOW, S. H., SUBRAMANIAM, S. (eds.): *Databasing the Brain*. John Wiley & Sons Inc., Canada, 2005, 449-458.

[WA03] WILLIAMS, J. AND ANDERSEN, W.: Bringing ontology to the gene ontology. *Comparative Functional Genomics, 4* (2003), 90-93.

[WA07] WANG, X., ALMEIDA, J. S.: Techniques for ontology visualization. In BAKER, C. J. O., CHEUNG, K. (eds.): *Semantic web: Revolutionizing knowledge discovery in the life sciences.* Springer Science and Business Media, New York, 2007, 249-279.

[ZBL*99] ZIGMOND, M. J., BLOOM, F. E., LANDIS, S. C., ROBERTS, J. L., SQUIRE, L. R. (eds.): *Fundamental Neuroscience.* Academic Press, San Diego, 1999.

[ZZZ*07] ZHANG, W., ZHANG, Y., ZHENG, H., ZHANG, C., XIONG, W., OLYARCHUK, J. G., WALKER, M., XU, W., ZHAO, M., ZHAO, S., ZHOU, Z., WEI, L.: SYNDB: a synapse protein database based on synapse ontology. *Nucleic Acids Res., 35* (2007), D737-D741.