Foundational Model of Neuroanatomy:
Implications for the Human Brain Project

Richard F. Martin, Ph.D., José L.V.Mejino Jr., M.D., Douglas M. Bowden, M.D.,
James F. Brinkley III. M.D., Ph.D., and Cornelius Rosse, M.D., D.Sc.
Structural Informatics Group,
Department of Biological Structure and Regional Primate Research Center
University of Washington, Seattle, WA 98195

ABSTRACT

In order to meet the need for a controlled terminology in neuroinformatics, we have integrated the extensive terminology of NeuroNames into the Foundational Model of anatomy. We illustrate the application of foundational principles for the establishment of an inheritance hierarchy, which accommodates anatomical attributes of neuroanatomical concepts and provides the foundation to which other information may be linked.

INTRODUCTION

A primary mission of the Human Brain Project (HBP), an interdisciplinary initiative of NIH coordinated by the National Institute of Mental Health, is to support the development of web-based resources and methods that enable the sharing, modeling and mining of the ever increasing quantity of highly specialized neuroscience data, and facilitate their integration at different levels of analysis in order to understand the biological substrates of whole brain function in health and disease.[1] A controlled neuroscience terminology is a fundamental requirement for assuring the inter-operability of the unique and diverse components of the HBP's information domain. Although several controlled medical terminologies (CMT) include a large number of concepts relating to neuroanatomy and neurological diseases (e.g., SNOMED, GALEN), they have neither the comprehensiveness nor the specificity needed by investigators in basic or clinical neuroscience, or in neuroinformatics. Thus there is a need to develop a terminology that models the structure of knowledge in the neuroscience domain. The level of concept representation in such a knowledge source should be more comprehensive, as well as deeper and richer, than that found in terminologies that primarily target clinical medicine. Moreover, a terminology for this interdisciplinary domain should benefit from experience gained during the development of other structured vocabularies.[2,3]

The backbone of this terminology must be an inheritance hierarchy or ontology since an ontology allows the thousands of individual terms to be organized into comprehensible categories. The first challenge is to determine how to accommodate structural and functional contexts in the ontology, since this will have a bearing on the transitive inheritance of the characteristics that define the concepts to be included in the ontology.[3] We have previously argued that the anatomy (structure) of biological systems can serve as a foundation for organizing other biomedical information, including normal and abnormal functions.[4,5] The rationale for this hypothesis is that biological processes may be conceptualized as attributes of anatomical structures, ranging in size from molecular to macroscopic levels. The logic and comprehensiveness of the conceptualization will be assured if the ontology symbolically models the physical organization (i.e., anatomical structure) of a biological organism and its parts. Motivated by such considerations, we established the Foundational Model (FM) of anatomy,[5,6] which represents the concepts and relationships that describe the physical organization of the body. We regard this model as *foundational* for two reasons: 1. the science of anatomy is fundamental to all biomedical domains; and 2. the structural concepts and relationships encompassed by the FM generalize to all these domains.

The above considerations imply that in order to meet the specific need for a controlled neuroscience terminology, an ontology of neuroanatomical concepts must first be established. For reasons explained below, we contend that the most effective way to accomplish this objective, both scientifically and fiscally, is to enhance the FM by neuroanatomical concepts. To test this hypothesis, we have begun to map such concepts

to the FM from the NeuroNames Brain Hierarchy,[7] which was developed at the University of Washington independently of the FM. The objective of this communication is to illustrate the challenges entailed by merging these two knowledge sources. We begin by describing these sources.

NEURONAMES

Although *Terminologia Anatomica,* the official anatomical terminology, includes an extensive term list for macroscopic neuroanatomy, it is nevertheless less comprehensive than other sources. Moreover, if it were adopted as the basis for a neuroanatomy ontology, it would present problems because its semantic structure lacks consistency.[8] Of the alternative neuroanatomy terminologies, NeuroNames Brain Hierarchy[7] is the most comprehensive. It has been incorporated as one of the source vocabularies of UMLS. The hierarchy is constructed predominantly on the basis of *PART_OF,* rather than *IS_A,* relationships between terms. These terms represent anatomical subvolumes of the primate brain identifiable with the naked eye or on Nissl-stained histological sections. The vocabulary includes more than 6500 neuroanatomical terms, about 4000 of which are synonyms. Structures found solely in the human or macaque brain are identified.

NeuroNames, however, is limited to the brain: it excludes the spinal cord and the peripheral nervous system. Furthermore, attributes currently associated with NN terms are insufficient as bases for a neuroanatomy ontology. However, its extensive vocabulary and the explicit part-whole relationships facilitate reuse of its terms in an inheritance hierarchy.

FOUNDATIONAL MODEL

The Digital Anatomist Foundational Model (FM) is a conceptualization of the physical organization (structure) of the human body. The symbolic modeling of the material objects (anatomical structures) that constitute the body, and the structural relationships that exist between them, are dictated by a set of declared principles.[5,6] The concept domain of the current model encompasses all anatomical structures (with the exception of the brain and spinal cord) to the resolution of 1 mm. These concepts are arranged in classes based on the structural characteristics they share with one another. The inheritance hierarchy of these classes was established in accord with explicit definitions,

which specify the defining attributes of groups of anatomical entities.[3] This hierarchy, known as the Anatomy Ontology (AO), is one component of the FM. It currently includes approximately 50,000 concepts. The terms and relationships of the model are stored in a relational database which is manipulated by a frame-based knowledge acquisition system known as Protégé.[9] The AO of the FM was initially conceived as an anatomical enhancement of UMLS and is currently accessible through UMLS as the University of Washington Digital Anatomist (UWDA) vocabulary. It is now being extended to include tissues, cells and subcellular anatomical structures.

The relationships that specify the part-whole and spatial arrangements of anatomical structures and spaces constitute the Anatomical Structural Abstraction (ASA), the second component of the FM. In addition to parts, the ASA specifies boundary, location, orientation, connectivity and spatial adjacency relationships. The ASA is currently being instantiated for classes of organs in Protégé, which supports inheritance of taxonomic and ASA relationships.[9] Modeling of a third component of the FM, Anatomical Transformation Abstraction (ATA), has been deferred for the time being; it will describe morphological transformations, starting with the fertilized ovum through embryonic and fetal development, as well as during postnatal growth and aging. The fourth component of the FM, Metaknowledge (Mk), comprises the principles, rules and definitions according to which relationships are represented in the FM's other three components. Thus the FM may be stated as a four-tuple:

$$Fm = (AO, ASA, ATA, Mk)$$

All anatomical information associated with any anatomical structure, be it a cell component, an organ, or a part of the body such as the head, is encapsulated by this equation. Therefore, this scheme should also capture anatomical information relating to the nervous system and its component parts.

MODELING NEUROANATOMY

All nerves and nerve plexuses that constitute the peripheral nervous system are already represented in the FM. Comprehensive modeling of these nerves requires that their nuclei of origin and termination also be represented. These nuclei are located in the brain and spinal cord.

Similarly, when these nuclei are modeled as parts of the brain and spinal cord, their relationships to the respective nerves must also be modeled. There is structural continuity between spinal nerves and the spinal cord and between cranial nerves and the brain. In addition, arteries and veins associated with the brain and spinal cord, as well as anatomical structures that are adjacent to subdivisions of the brain and spinal cord, are critical concepts for educational and clinical applications of neuroanatomy. These and other considerations argue persuasively for integrating an ontology of neuroanatomy with a symbolic model of the whole body.

How can the semantic structure of the FM accommodate neuroanatomical concepts? In consonance with UMLS, the FM represents concepts rather than terms. Each concept is designated by a unique numerical identifier (UWDA-ID) and one or more terms. One of these terms is designated as the preferred name and the others as synonyms. NeuroNames is a comprehensive source for structures comprising the brain, one of which is designated as 'standard term', the most likely candidate for 'preferred name' in the FM. The challenge lies in the classification of neuroanatomical concepts and the merging of these classes with those of the FM. Although it is intuitive to think anatomically in terms of *PART_OF* relationships, it is most critical to define class inclusion (taxonomic) or *IS_A* relationships as a prerequisite for an inheritance hierarchy. Class assignments must be guided by the foundational principles on which the classification of anatomical entities in the FM is based.[5,6] The application of these principles can be illustrated by the process of identifying the FM class to which the brain and the spinal cord should be assigned.

Class Assignments. One of the foundational principles declares 'organ' to be the organizational unit of macroscopic anatomy. Transferring concepts from the part-of hierarchy of NeuroNames to the FM must conform to this principle. The spinal cord and the brain might each be regarded intuitively as an organ. Do they satisfy the FM definition of 'organ'?

Organ
is an **anatomical structure**,
　　　　which *consists of* the maximal set of
　　　　　organ parts
　　so *connected* to one another that together they
　　　constitute a self-contained unit of
　　　　macroscopic anatomy

morphologically distinct from other such units.

Neither the brain nor the spinal cord alone satisfies this definition; however, together they do. They are made of the same kind of components (gray matter and white matter), and all these components are so connected together that the brain and spinal cord constitute a whole: they can only be separated from one another by an arbitrarily placed transection. This feature results from their mode of development: both the brain and cord develop from the neural plate, an uninterrupted embryonic structure. There is no other morphological entity in the body that is comparable to 'brain+cord'. Thus, this 'brain+cord' structure (thing) is a unique concept and needs to be designated by a single UWDA-ID as well as by one or more terms. Although the brain and the spinal cord have long been regarded as the 'central nervous system', using this term as the preferred name of the organ we just "discovered" is in conflict with the FM definition of 'organ system':

Organ system
is an **anatomical structure**
　　which *consists of* members of
　　　　predominantly one organ subclass
　　　　　interconnected by zones of continuity.

Examples: skeletal system, cardiovascular system, alimentary system, urinary system.

The brain and the spinal cord are organ parts (subdivisions of neuraxis), rather than organs, and hence the term 'central nervous system' cannot be applied to them logically. Instead, we propose 'neuraxis' as the preferred name of the 'brain+cord' organ. In accord with the definition principle[3] we define this organ by the structures that constitute it:

Neuraxis
　is an **organ with organ cavity**
　　which *consists of* gray matter and white matter.

Although this classification and preferred name may be justified on embryological, structural and logical grounds, the concept 'brain+cord' must also be retrievable from the FM by the term 'central nervous system' since in current usage, this is the term usually associated with the concept. Entering this term as a synonym of 'neuraxis' will lead a search to the same concept, as will the UWDA-ID 55675, or any other value that is entered in the 'has synonym' slot of the frame 'neuraxis' in Protégé.[9]

These points are illustrated by Figure 1, the right-hand side of which shows the neuraxis frame in Protégé, whereas the left side shows part of the AO, with the Neuraxis in context with other subclasses of Anatomical structure.

NeuroNames lists 'neuraxis' and 'central nervous system' as synonyms. However, the dictionary to which NeuroNames points defines 'neuraxis' as "the axial, unpaired part of the central nervous system....in contrast to the paired cerebral hemispheres" (Stedman's). Dorland's dictionary, on the other hand, assigns two meanings to the term: 1. an axon; 2. the central nervous system. Thus 'neuraxis' is currently a homonym for at least three different concepts. Such situations obtain for many neuro- and other anatomical terms.[8] This circumstance emphasizes the importance of 1. constructing an ontology with concepts rather than terms; and 2. explicitly defining each concept consonant with the ontology's context.[3] The explicit definition of 'neuraxis' in the FM, together with the values of

the slot 'Has Part' (Brain, Spinal cord), eliminates any ambiguity about the meaning of the term 'neuraxis' in this ontology.

A similar process needs to be pursued in assigning all parts of the 'neuraxis' to classes of the AO, taking into account that it has been subdivided in a number of overlapping ways. The FM defines a hierarchy of organ parts, partly shown in the left side of Figure 1 [Tissue (e.g., neural tissue, ependyma), Organ component (e.g., parenchyma, stroma, cortex, medulla, gray matter), Organ subdivision. As a preliminary structural classification we have grouped the various white matter and gray matter structures as subclasses of 'Organ subdivision of brain', which is a "Subdivision of neuraxis', which is an "Organ subdivision'. These classes will be more precisely defined in accord with the desiderata we established for definitions.[3,10]

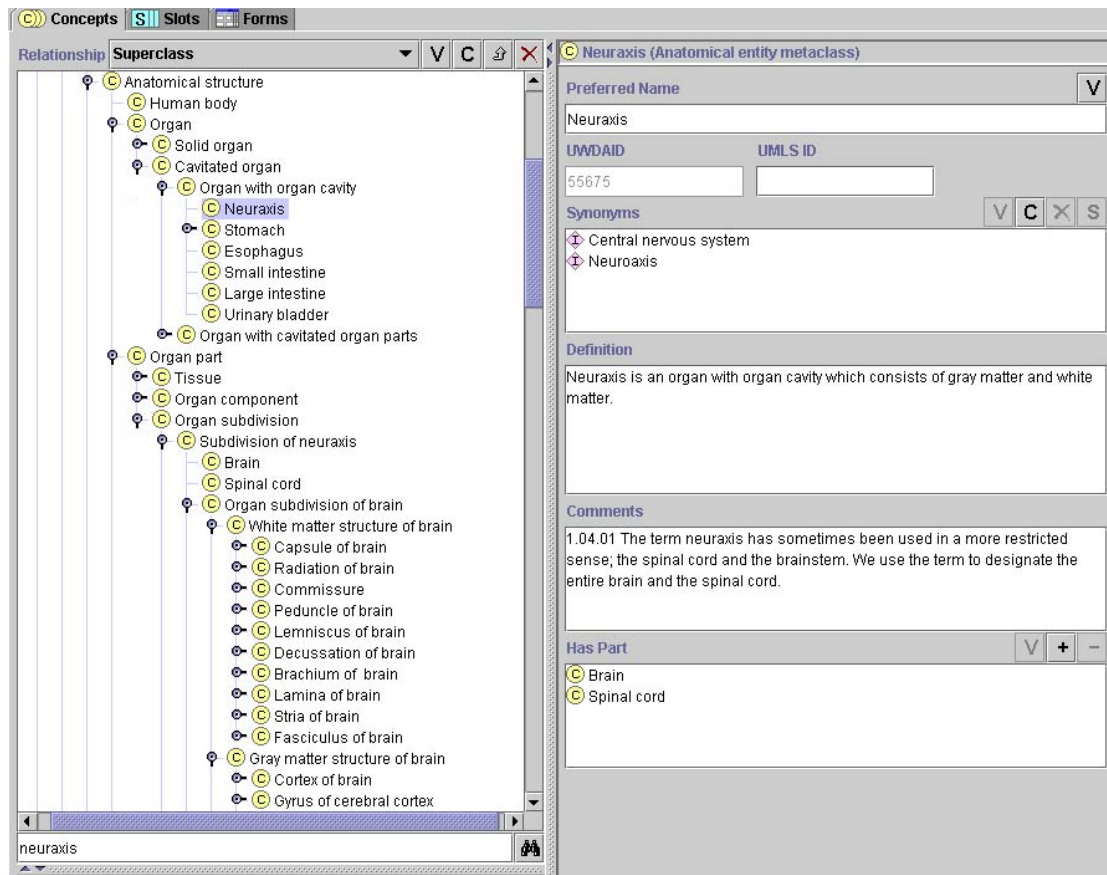**Inheritance.** Because the concept 'neuraxis' is assigned to a particular class of the AO, it

Figure 1. Protégé frame-based knowledge acquisition tool. Left: Anatomy Ontology, with neuraxis highlighted. Right: attributes of the neuraxis frame.

inherits the defining attributes of all of its parent classes. Therefore, the AO specifies not only that the neuroaxis is an organ which contains a continuous cavity ('Organ with organ cavity'), but also that it is a self-contained macroscopic anatomical unit, which has been generated through the coordinated expression of groups of genes, a defining attribute of the class 'anatomical structure'.[3,5] Both inherited and direct attributes are represented as slots in the Protégé frame of an AO class, and are displayed when the frame is selected. For example, the right hand side of Figure 1 shows some of the attributes for the neuraxis frame. The attributes added to a subclass beyond the inherited attributes are the attributes which distinguish it from its siblings in the AO.

Implementation. We have rearranged the majority of NeuroNames terms in a preliminary ontology and have represented them in Protégé, based primarily on implicit rather than explicit definitions. We have integrated this neuroanatomy ontology with the AO of the FM. We are currently validating and rearranging this ontology through explicit definitions formulated in accord with FM principles.[3] The next tasks will be to represent the explicitly stated defining attributes in Protégé frames and begin to model ASA relationships of neuroanatomical concepts, including those that are unique to these concepts.

The FM is stored in a relational database that is accessed both by Protégé and by a foundational model server (FMS) that is accessible over the Internet[11]. As the FM of Neuroanatomy is further developed it will become available via the FMS to various Brain Project applications, including our own brain map experiment management system[12].

DISCUSSION

This report suggests that the integration of neuroanatomical concepts with the Foundational Model of anatomy will establish a scalable resource that could meet the neuroinformatics needs of investigators in the Human Brain Project. Whether viewed structurally or functionally, the neuraxis is inextricably integrated with other parts of the body. Therefore, the foundational model of neuroanatomy must also be conceived and implemented as an integral component of whole body anatomy. We have illustrated that the guiding principles of the FM also assure the non-ambiguous and logical representation of neuroanatomical concepts. The ontology of these concepts supports the inheritance of structural characteristics and can also accommodate the kinds of information unique to neuroanatomy. When made accessible over the Internet via the Foundational Model Server, the FM of Neuroanatomy can become an important tool for organizing and retrieving the vast amount of data being generated about the human brain.

References
1. Koslow SH, Huerta MF (editors). Neuroinformatics: an overview of the Human Brain Project. Mahwah, N.J.: L. Erlbaum, 1997.
2. Cimino JJ. Desiderata for controlled medical vocabularies in the twenty-first century. Methods Inf Med 1998;37:394-403.
3. Michael J, Mejino JL, Rosse C. The role of definitions in biomedical concept representation. Proc AMIA Symp 2001. Submitted.
4. Brinkley JF. Structural informatics and its applications in medicine and biology. Acad Med 1991;66:589-91.
5. Rosse C, Mejino JL, Modayur BR, Jakobovits R,Hinshaw KP, Brinkley JF. Motivation and organizational principles for anatomical knowledge representation: the Digital Anatomist symbolic knowledge base. J Am Med Inform Assoc 1998;5:17-40
6. Rosse C, Shapiro LG Brinkley JF. The Digital Anatomist Foundational Model: principles for defining and structuring its concept domain. Proc AMIA Symp 1998;820-4.
7. Bowden DM, Martin RF. NeuroNames Brain Hierarchy. Neuroimage 1995;2:63-83. <http://braininfo.rprc.washington.edu>
8. Rosse C. Terminologia Anatomica: considered from the perspective of next-generation knowledge sources. Clin Anat 2001. In press.
9. http://protégé.stanford.edu
10. Mejino JLV, Fridman Noy N, Musen M, Rosse C. Representation of structural relationships in the Foundational Model of anatomy. Proc AMIA Symp 2001. Submitted.
11. Brinkley, J.F., Wong, B.A., Hinshaw, K.P. and Rosse, C. Design of an anatomy information system. IEEE Computer Graphics and Applications. 1999;19(3):38-48.
12. Jakobovits, R., Soderland, S., Taira, R.K. and Brinkley, J.F. Requirements of a web-based experiment management system. Journal of the American Medical Informatics Association, Symposium Supplement, 2000;374-378.