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Review

Online Workbenches for Neural Network Connections

MIHAIL BOTA AND LARRY W. SWANSON*
University of Southern California, Los Angeles, California 90089-2520

ABSTRACT

The nervous system is the most complex object we know of. It is a spatially distributed, functionally differentiated network formed by axonal connections between defined neuron populations and effector cells. Computer science provides exciting new tools for archiving, analyzing, synthesizing, and modeling on the Web vast amounts of frequently conflicting and incomplete qualitative and quantitative data about the organization and molecular mechanisms of neural networks. To optimize conceptual advances in systems neuroscience, it is important for the research and publishing communities to embrace three exercises: using defined nomenclatures; populating databases; and providing feedback to developers about improved design, performance, and functionality of knowledge management systems and associated visualization tools. J. Comp. Neurol. 500:807–814, 2007.

Indexing terms: neural circuits; neural pathways; neural systems; neuronal cell types

Structure–function accounts of the mammalian body as a whole have been framed since classical antiquity in two distinct although ultimately interchangeable ways (Galen, 1968, 1999). One is topographic and deals with regions like the hand, tail, or nose; this is analogous to a geographic approach. In stark contrast, the other way deals with systems—alimentary, cardiovascular, skeletomotor, and so on—that together, in various combinations, form particular regions. It is analogous to placing transportation routes and demographic information on geographical maps and now includes on the order of 10 major systems. Around the middle of the nineteenth century this fundamental macroscopic account was supplemented with effective microscopic analysis, so that well-known organs and tissues could be described and analyzed histologically and functionally in terms of their distinguishing cellular units (Kölliker, 1854). And now, for the last half-century or so, the molecular machinery of individual cells has been analyzed in exquisite detail with a wide variety of histochemical methods on thin, pliable tissue sections viewed under the light and electron microscope (Pierce, 1980).

Of course, this cumulative progression from macroscopic to microscopic to molecular applies to the nervous system as well. Topographic analysis commonly recognizes peripheral and central divisions—with the latter subdivided into forebrain, midbrain, hindbrain, and spinal regions, which themselves are progressively subdivided—and a variety of sensory, motor, and other functional systems often spanning these regions are recognized (Nieuwenhuys et al., 1988; Swanson, 2000, 2003). It is also known that these regions and systems are formed structurally by chains of nerve cell (neuron) populations (neuronal cell types) whose divergent and convergent axonal pathways form neural networks with species-specific spatial distributions and functional properties (Cajal, 1909–1911; Kandel et al., 2000). And most recently, increasingly sophisticated histochemical and molecular methods are

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*Correspondence to: Dr. Larry Swanson, Hedco Neuroscience Bldg., Rm. 428, 3641 Watt Way, Los Angeles, CA 90089-2520.

E-mail: lswanson@usc.edu

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used to analyze the cell biology of individual neurons (Björklund and Hökfelt, 1983–2005; Markram, 2006).

It has also been appreciated since antiquity that nervous system structure and function is far more complex than any other bodily organ system. The nervous system generates consciousness, controls voluntary and reflex bodily interactions with the environment (behavior), maintains a relatively constant environment within the body itself (homeostasis), and generates and controls endogenous states associated with sleep–wake and reproductive cycles. In other words, the nervous system controls and coordinates, to a greater or lesser degree, activity within all of the other functional systems—and regions—of the body.

In view of this, it is hardly surprising that biological data has been accumulating at an exponential rate for many centuries, and because of its inherent complexity and importance, the sheer volume of data about the structure and function of the nervous system has been the greatest and most difficult to evaluate. It is now far beyond the grasp of individual investigators, no matter how brilliant, to remember, evaluate, and synthesize the neuroscience literature, even in restricted domains like network structure, physiology, or chemistry. The amount of literature involved has not been estimated, but it is sobering to realize that in a period as far back as 1895–1900 at least 1,700 studies of central nervous system anatomy alone were published (Rasmussen, 1947).

Fortunately, computer science has come to the rescue, and methods are now available, at least in principle, to represent neural systems information in databases, and to organize and model these data with inference engines in knowledge management systems (KMSs)—both of which can be made available to everyone on the Web. Expanding use of these three powerful tools (databases, KMSs, and the Web) is inevitable, and progress in the systems neuroscience domain remains relatively slow only because of the exceptional complexity intrinsic to this field, and its huge published literature (sometimes called legacy data).

But to facilitate major conceptual advances, the neuroscience community must do three critically important things. First, it must help computer science developers populate databases and analysis tools available freely on the Web—the job is simply too vast and the value of expert knowledge too great to proceed effectively without this input. Second, it must encourage the use of defined nomenclatures, which are a requirement of KMSs that use inference engines (see below). And third, an indispensable corollary is that the community must have mechanisms in place simultaneously to provide feedback on KMS design, usefulness, and functionality. The only alternative is a massive human genome-style, privately or publicly funded project that will pay to get the job done in a relatively timely and systematic way.

The actual scope of the problem facing the systems neuroscience database population is poorly defined. As a starting point, one recent qualitative analysis (Bota et al., 2003) suggests that for the mammalian central nervous system there are on the order of 500–1,000 different gray matter regions (three examples: the retina, dorsal lateral geniculate nucleus, and primary visual cortex); 2,500–5,000 neuron classes (three examples: retinal photoreceptors, bipolar cells, and ganglion cells); and 25,000–100,000 macroconnections between neuron classes (one example: from retinal ganglion cells to dorsal lateral geniculate projection neurons). However, there is controversy (conflicting literature) about the exact borders and identity of virtually every region, less that 100 neuron classes have been reasonably carefully defined, and the vast majority of known axonal connections are understood only in an incomplete, very qualitative way. Furthermore, this level of analysis is superimposed on estimates that the human brain contains on the order of 10^{11} neurons and 10^{14} synapses between neurons (see Swanson, 1995). It is little wonder that progress is slow and incremental in understanding the basic wiring diagram of the brain, gram for gram the most complex object known to us.

Another recent qualitative analysis of the basic wiring diagram problem is especially instructive in terms of both data quantity and reliability (Bota et al., 2003). Focusing on only one major brain region, the hypothalamus, it was estimated that in 1940 about 55 macroconnections (region to region) related to its known cell groups (regions or nuclei) 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 hypothalamic macroconnections had been described with an even newer generation of much more reliable pathway tracing methods—and that number approaches 5,000 today (with the vast majority analyzed in rat). Assessment of their reliability awaits the next generation of analysis, probably stimulated mostly by data from genetically engineered mice.

This example emphasizes that data conflicts, based on widespread false-positive and false-negative results, are a fundamental, serious, and widespread problem in systems neuroscience that cannot be ignored—that must be accommodated satisfactorily in databases and KMSs. There are at least two main reasons that published data conflicts in this field remain prominent. First, difficult and sometimes unreliable methods, combined with sparse sampling for practical reasons, often lead to alternative interpretations about the identity of neuronal regions, cell types, and connections between cell types—even within the same species, strain, age, sex, time of day, behavioral state, and endocrine status. And second, criteria for establishing homology of parts and connections between species are often even more controversial for lack of data and agreement about defining criteria (Bota and Arbib, 2004; Reiner et al., 2004). Thus, equally important data conflicts are of two major types—presumably resolved (improved analysis) and obviously unresolved (insufficient data)—with gradations between them.

In resolving the many problems of neural systems data management, there is a seeming paradox with profound implications. On one hand, neuroinformatics systems must support different ways of representing connectivity data and different interpretations of brain organization—it is not possible to eliminate all conflicting interpretations with data available at the moment. But on the other hand, employing inference engines to generate specific models of neural network organization requires that data be converted to, and stored in terms of, an internally consistent, explicitly defined framework of nomenclature and concepts (an ontology: Gruber, 1993; Gomez-Perez et al., 2003). Every author of an article in the primary scientific literature goes through this process informally, and in a very limited domain, when as-

sessing in the Discussion section their results with respect to the earlier literature.

In summary, it is essential that neuroinformatics applications dealing with neural networks allow for alternative interpretations of region, cell type, and connection identity, as well as for alternative classification schemes, for example, involving nomenclature hierarchies. In many if not most cases sufficient data to distinguish between certain alternative interpretations is not available or agreed upon, and one of the most important functions of KMSs is to provide comparisons of available information—to help make informed decisions and identify critical gaps in the data that require further research. Nevertheless, internally consistent subsets of information in the global database must be extracted and used when models are derived with various processing methods in KMSs. Obviously, neural network models are only as good as the (internally consistent subsets of) data they are based on. Once again, this emphasizes the fundamental importance of explicit definitions for all concepts and names used in neural network analysis.

COMPUTER SCIENCE STRATEGY

Neuroinformatics combines research in neuroscience and informatics to design, develop, and maintain tools for understanding brain structure and function (Beltrame and Koslow, 1999). Online-based neuroinformatics systems typically store data and metadata using a variety of approaches, from flat files to complex object and relational databases. These systems include display interfaces that allow users to access data and metadata online. Ideally, a mature neuroinformatics system integrates data over several levels of nervous system organization (that is, from gene expression patterns, to neurons and neuronal networks, to systems and behavior, and finally to normal life-cycle changes and disease) and in multiple species. It includes a set of visualization tools for displaying multimodal information and allows data analysis—and it should also be a knowledge provider, thus utilizing inference algorithms and data mining tools. Additional challenges addressed by an ideal neuroinformatics system include data sharing and federation (Ascoli, 2006), metadata completeness and complexity, a comprehensive and coherent data quality control policy (Amari et al., 2003), and the ability to maintain up-to-date information. Users of an ideal neuroinformatics system should also be able to interact with the system and provide feedback, as well as store and process their own data in personal accounts.

In this early stage of evolution, neuroinformatics systems (or applications containing neuroinformatics components) vary widely in scope and complexity, from simple Web-accessible image repositories, to tools for visualizing particular data modalities, to KMSs that relate data and metadata at different levels of nervous system organization. They include anatomy ontologies (Foundational Model of Anatomy: Rosse and Mejino, 2003) and controlled vocabularies (BrainInfo: Bowden and Dubach, 2003). With few exceptions they are prototypes, relatively sparsely populated, and in need of serious user feedback about improved functionality. They vary greatly in ability to associate molecular, functional, and behavioral data with information about neural regions, cell types, and connections, and in ability to archive and display qualitative and quantitative data as tables, graphs, and multidimensional maps. Table 1 characterizes 19 exemplary Web-accessible neuroinformatics systems according to species, levels of nervous system organization, and functionality. Additional systems are provided by Kennedy (2005) and the most complete list of Web-accessible neuroinformatics systems can be found at the Neuroscience Database Gateway (http://big.sfn.org/ndg).

Gene expression patterns and brain regions are the two nervous system levels of organization most thoroughly represented in Table 1. Two informatics systems are especially conspicuous in terms of data richness and integration across modalities. GENSAT includes expression pattern photos (digital images) for more than 5,000 genes in the adult *Cx3cl1* BAC transgenic mouse brain (Heintz, 2004), and the Allen Brain Atlas will shortly include photos of expression patterns for about 20,000 genes in the adult male *C57BL/6J* mouse brain. For the latter, gene expression photos can be compared qualitatively online with a reference neuroanatomical atlas incorporating a detailed parcellation scheme (Dong, 2006; for technical considerations associated with such comparisons, see Swanson, 1998, 2001).

As shown in Table 1, almost all listed systems include data management functionality, usually as search tools of varying complexity or as static tables. Visualization tools are also a common feature of these systems. Such tools range from simple applications for image display to complex multimodal 2D maps like those developed by the Allen Brain Atlas and the LONI Mouse Atlas Project (MacKenzie-Graham et al., 2004), and also include applications for displaying tract-tracing data in a standardized coordinate system (NeSys: Bjaalie, 2002) or annotated, high-resolution digital images (the BrainMaps system).

However, integration of different experimental results and of data modalities, which is a very important feature of any neuroinformatics system, is performed by few systems listed in Table 1. NeSys allows dynamic display of multiple tract-tracing experiments onto the same reference frame. Wormbase integrates gene expression data with neuron projections information, together with gene sequences information provided by external databases. The Allen Brain Atlas visualization tool allows display of three sets of gene expression pattern images, together with a corresponding atlas template. The LONI Atlas Project allows visualization of three data modalities taken in the same plane of section—fresh tissue section images, magnetic resonance microscopy, and a Nissl-stained section—together with a corresponding atlas template. BrainInfo associates gene expression data, cell type, and connectivity information with brain region records, but this information is provided by external sources, and the association is performed only on the basis of name identity and not species or brain nomenclature.

Many of these systems also include analysis tools that typically perform statistics on inserted data, either online or with downloadable software applications. However, inference engines and data mining algorithms are included in only three of the systems under consideration: Brede Database (Nielsen et al., 2004), WebQTL (Chesler et al., 2004), and Wormbase (Harris et al., 2004; Chen et al., 2005). Both Wormbase and WebQTL are well-established bioinformatics systems that include data about neural systems in various species. Thus, the Brede Database is the only application in Table 1 that is not part of a larger bioinformatics system but does include data mining functionality.

TABLE 1. Set of 19 Exemplary Neuroinformatics Systems with a Comparison of Key Functionalities

Neuroinformatic system	Nervous system level	Species	Data management	Visualization tools	Analysis tools	Inference engines/data mining	Data sharing
Allen Brain Atlas http://www.brainatlas.org/aba	Gene expression patterns, brain regions	Mouse	+	+	+	−	+
BrainMaps http://www.brainmaps.org	Gene expression patterns, brain regions	Human, macaque, cat, mouse	+	+	+	−	+
BrainMap http://brainmap.org	Brain regions, behavioral	Human	+	+	−	−	−
BrainInfo http://braininfo.rprc.washington.edu	Brain regions	Human, macaque	+	+	−	−	+
Brede Database http://hendrix.imm.dtu.dk/services/jerne/brede	Brain regions, behavioral	Human	+	+	+	+	+
Cell Centered Database (CCDB) http://ccdb.ucsd.edu	Gene expression patterns, neurons	Rat	+	+	−	−	−
CoCoMac http://cocomac.org/home.asp	Brain regions, neuroanatomical connections	Macaque	+	−	+	−	+
CoCoDat http://www.cocomac.org/cocodat	Neurons	Macaque	+	−	−	−	−
fMRI Data Center http://www.fmridc.org	Brain regions, behavioral	Human	+	+	+	−	−
Foundational Model of Anatomy http://sig.biostr.washington.edu/projects/fm	Brain regions	Human	+	−	−	−	−
Gensat http://www.gensat.org	Gene expression patterns, neurons, brain regions	Mouse, transgenic strain	+	+	−	−	−
L-Neuron Database http://krasnow.gmu.edu/L−Neuron/	Neurons	Rat	+	+	+	−	−
Mouse Atlas Project at LONI http://www.loni.ucla.edu/MAP	Brain regions	Mouse	−	+	−	−	+
Mouse Brain Library http://mbl.org	Gene expression patterns, brain regions	Mouse, different strains	+	+	+	−	−
NeSys http://www.nesys.uio.no	Brain regions, neuroanatomical connections	Rat	+	+	+	−	−
SenseLab http://senselab.med.yale.edu/senselab	Gene expression patterns, neurons, brain regions	N/A	+	−	−	−	+
SumsDB http://sumsdb.wustl.edu:8081/sums/index.jsp	Gene expression patterns, brain regions, neuroanatomical connections	Human, macaque, mouse, rat	+	+	−	−	+
WebQTL http://www.genenetwork.org	Gene expression patterns, brain regions	Mouse, several strains	+	+	+	+	+
Wormbase http://www.wormbase.org	Gene expression patterns, neurons	*C. elegans*	+	+	+	+	+

Senselab includes six interrelated databases: CellPropDB, NeuronDB, ModelDB, ORDB, OdorDB, and OdorMapDB.

Data Sharing functionality refers to tools or applications that allow systems to act either as an online data provider or as a client of other systems. Many neuroinformatics systems listed in Table 1 share information with other systems, with complexity of approach ranging from simple mapped URLs, to XML query outputs, to backend database connections (SenseLab).

Data richness associated with the neuroinformatics systems considered in Table 1 varies greatly. It ranges from more than 39,000 neuroanatomical connection details in the macaque brain (CoCoMac: Kötter et al., 2004) and mouse brain expression pattern photos for about 20,000 genes (Allen Brain Atlas: Dong, 2006), to the more than 15,000 neuroanatomical terms included in BrainInfo, the hundreds of entries for reconstructed neurons in L-Neuron Database (Ascoli et al., 2001), and the 32 neuron names in the NeuronDB database.

Although several systems in Table 1 are populated with enough data for large-scale analysis and data mining, virtually none have comprehensive metadata sets for experimental methods or an explicit quality control policy. These two features of any neuroinformatics system are critical for establishing data reliability, especially in the face of conflicting results. The problems of comprehensive metadata sets associated with data stored in databases, and of a specified quality control policy, are relevant to the field of neuroinformatics as a whole because a generally accepted framework is lacking, and neurobiological data is very complex.

Metadata provided by neuroinformatics systems listed in Table 1 usually derive from collated literature, and include experiment-related information that varies widely across systems with respect to completeness and complexity. Metadata about techniques employed in individual experiments are provided by the Allen Brain Atlas, BrainMaps, CoCoMac, NeSys, and Wormbase. Neurohistology metadata like plane of section and section thickness are provided by the Allen Brain Atlas, BrainMaps, Mouse Brain Library, and NeSys. Mapping metadata that document how experimental results associate with an internally consistent brain nomenclature (reference terminology) are provided only by the NeSys system. CoCoMac is the only neuroinformatics system in Table 1 capable of associating collated tract-tracing data with precision description codes that capture qualitatively complete and correct information, according to collators (Stephan et al.,

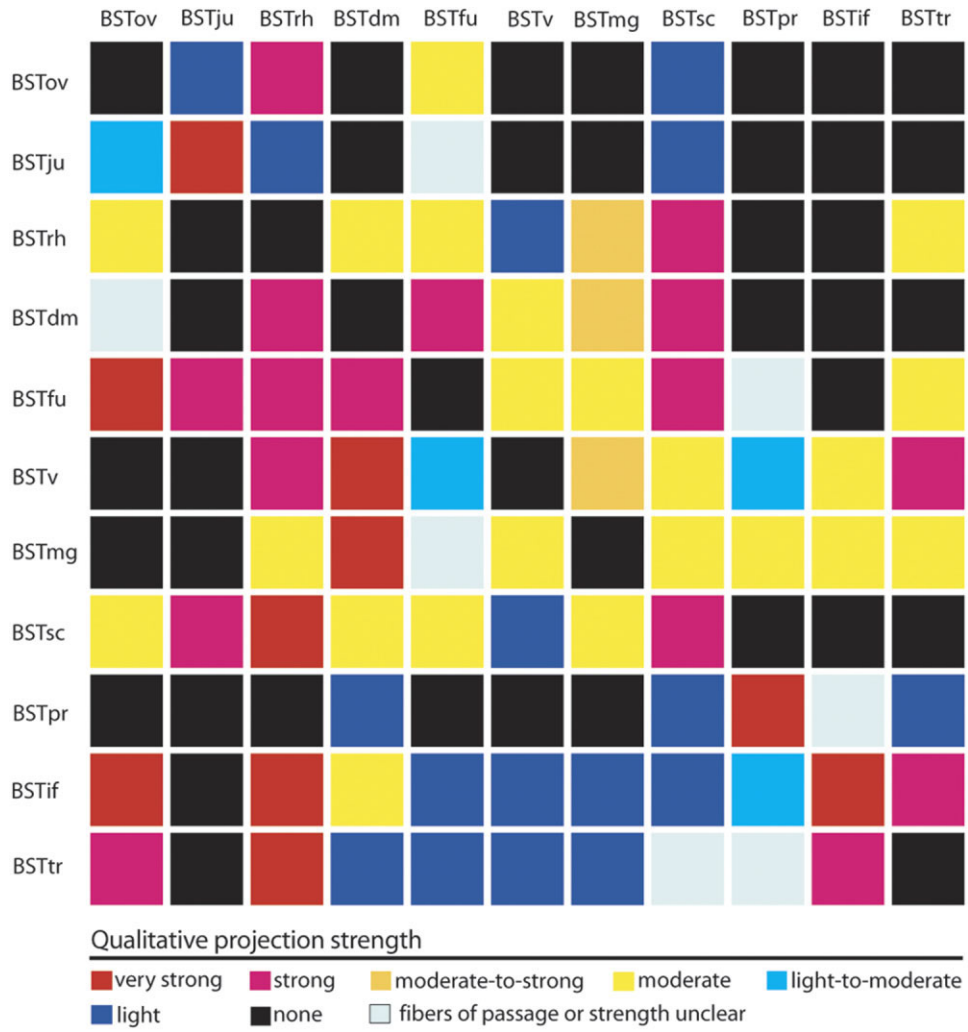

Fig. 1. A color-coded matrix of neuroanatomically defined axonal projections between the component regions of the bed nuclei of stria terminalis (BST) in the rat brain, defined in the Swanson (1998) nomenclature. This is a rare example of a complete matrix: there are experimental data for all cells in the matrix. BAMS can be queried for complete documentation of information in this connection matrix.

2001). Thus, none of the listed neuroinformatics systems include a complete set of metadata providing users with information related to experimental methods, neuroanatomy, mapping procedures, and quality assessment of inserted data.

BRAIN ARCHITECTURE MANAGEMENT SYSTEM (BAMS)

BAMS has been under development in our group since 2001. It can incorporate any vertebrate species and integrate qualitative and quantitative information over four successive, logically connected levels of nervous system organization: regions, cell types forming regions, axonal connections (structural pathways) between regions and cell types, and molecules expressed in regions and cell types (Bota et al., 2003, 2005; Bota and Swanson, 2006; http://brancusi.usc.edu/bkms). Complex online queries prompt inferences about nervous system connection patterns based on regional subdivision and cell type information, about topological relationships between nervous system regions defined in different atlases, about possible axonal connection matrices between regions and/or cell types, and about molecular expression patterns in different nervous system regions/cell types and under different physiological and experimental conditions. Thus, user-defined projection matrices can be constructed online from data in the system, and displayed in a variety of ways. Examples of recent additions include color-coded qualitative assessments of projection strengths (Fig. 1) and the display of projection networks as graphs (Fig. 2).

The database structure of BAMS, combined with the amount of information inserted, enables us to begin large-scale data analysis and display—attacking in a more systematic way the general problem of global nervous system organization principles alluded to above: ultimately, what is the basic wiring diagram of the nervous system? The rat central nervous system connectivity matrix as constructed from data inserted in BAMS is shown in Figure 3. The first steps in analyzing structure–function relationships within a systems neuroscience context include describing brain regions in terms of component cell types, each with char-

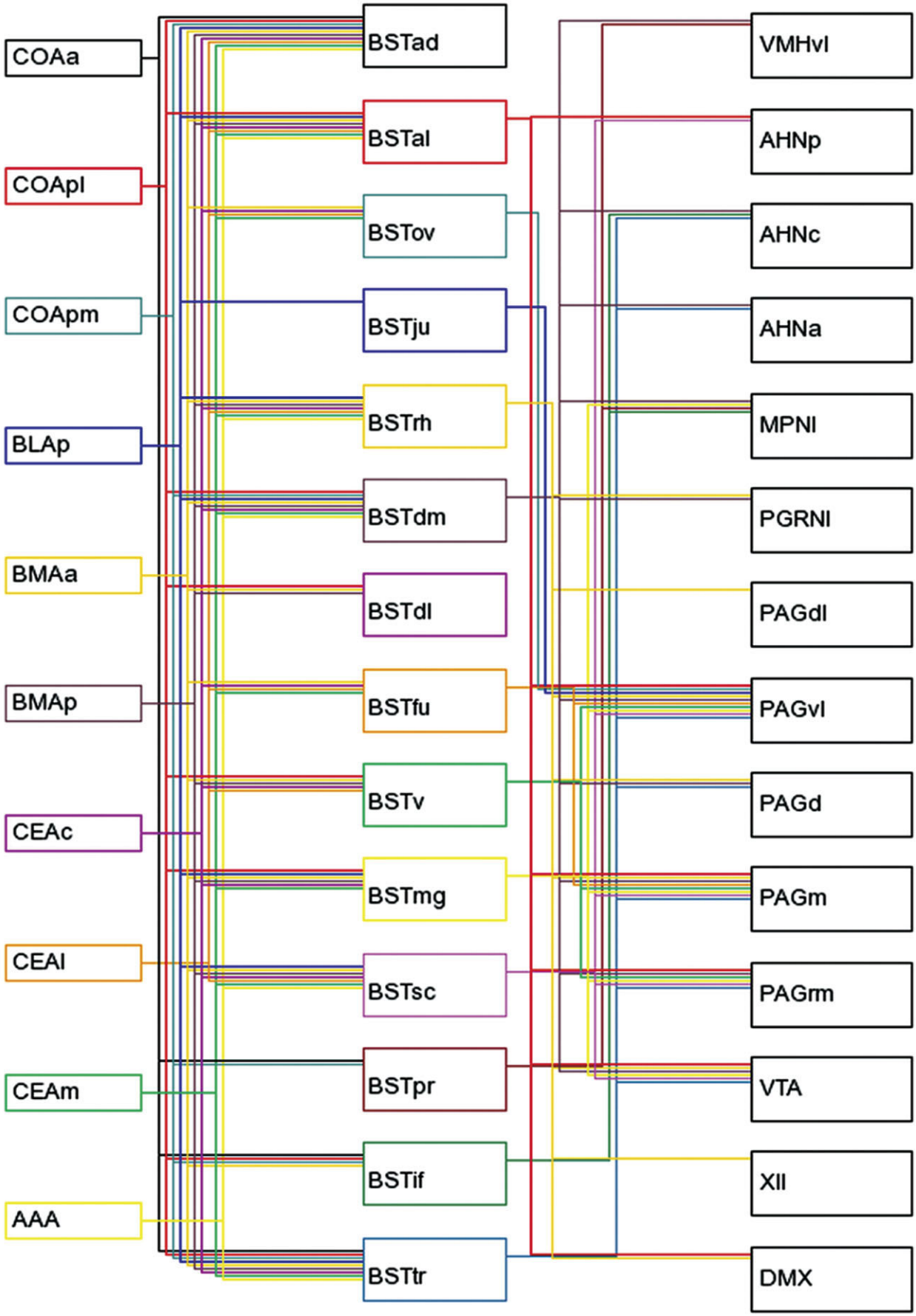

Fig. 2. A color-coded graph of neuroanatomically defined axonal projections from 10 regions of the rat amygdala to the various regions of the BST (see Fig. 1), and then from the BST regions to 14 user-defined regions of the brainstem. Generated from a query in BAMS, where full documentation of the graph's contents may be found.

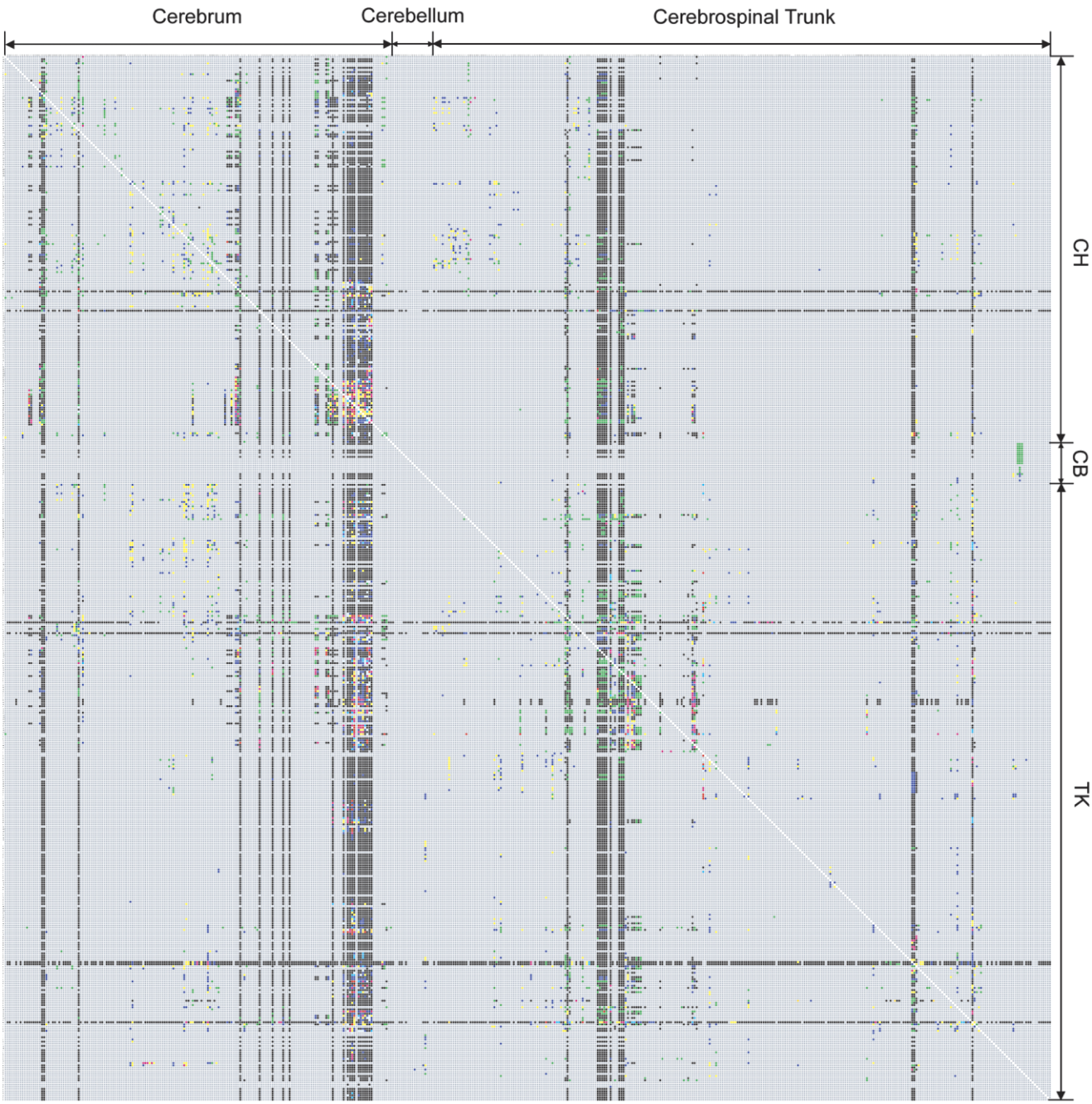

Fig. 3. The matrix of axonal projections interconnecting the rat central nervous system. It is based on the Swanson (1998) nomenclature hierarchy and constructed from data in BAMS. Projecting regions are on the horizontal axis, receiving on the vertical. The matrix is 486 × 486 neuronal regions and contains 22,178 cells labeled with a color other than gray (no data)—representing the number of distinct reports of neuroanatomically defined projections in BAMS's database. The color code is similar to that in Figure 1, with the addition that green represents projections of unknown strengths. The present coverage factor for BAMS's rat central nervous system projection matrix is 9.4%. This is based on 39,225 reports of projections collated from 324 references. Note the region of the matrix containing the BST (shown expanded in Fig. 1) in the cerebrum (near the center of the upper left quadrant).

acteristic patterns of axonal connections and gene expression; and the construction of projection matrices and neural network diagrams based on experimental data that is as quantitative as possible. The database structure and Web interface design of BAMS currently allow users to perform all of these operations.

CONCLUSIONS

We have pointed out that developing neuroinformatics resources is a heterogeneous enterprise, potentially involving individual research groups, the broader community of users, and public and private institutions with

substantial resources. It is also critically important that journals facilitate in a timely way the maturation of neuroinformatics tools on the Web. This can be done in a number of ways, at the outset by insisting on the rigorous definition of all nomenclature, and providing forms for the ready entry of systematic data about neural regions, cell types, and connections, in tabular and/or graphical formats, with associated information about species, age, sex, physiological condition, and so on.

A gold standard neuroinformatics system will include ontologies for defining and aligning concepts specific to the modeled system. It will also include rigorous data quality control, full description of metadata and experimental procedures, specification of collation and curation policy, and mapping between different experimental procedures included in the same system and across different KMSs (Amari et al., 2003). Besides ensuring data and metadata completeness, mapping across different experimental paradigms also allows inserting alternate definitions of neural regions and cell types and evaluating evidence quality. The eventual payoffs in understanding the functional organization of the brain—the organ of mind—in health and disease are enormous.

LITERATURE CITED

Ascoli GA. 2006. Mobilizing the base of neuroscience data: the case of neuronal morphologies. Nat Rev Neurosci 7:318–324.

Ascoli GA, Krichmar JL, Nasuto SJ, Senft SL. 2001. Generation, description and storage of dendritic morphology data. Philos Trans R Soc Lond B Biol Sci 356:1131–1145.

Beltrame F, Koslow SH. 1999. Neuroinformatics as a megascience issue. IEEE Trans Inf Technol Biomed 2:239–240.

Bjaalie JG. 2002. Localization in the brain: new solutions emerging. Nat Rev Neurosci 3:322–325.

Björklund A, Hökfelt T, editors. 1983-2005. Handbook of chemical neuroanatomy. Amsterdam: Elsevier.

Bota M, Arbib MA. 2004. Integrating databases and expert systems for the analysis of brain structures: connections, similarities, and homologies. Neuroinformatics 2:19–58.

Bota M, Swanson LW. 2006. A new module for online manipulation and display of molecular information in the brain architecture management system. Neuroinformatics 4(4) (in press).

Bota M, Dong H-W, Swanson LW. 2003. From gene networks to brain networks. Nat Neurosci 6:795–799.

Bota M, Dong H-W, Swanson LW. 2005. Brain architecture management system. Neuroinformatics 3:15–48.

Bowden DM, Dubach FM. 2003. NeuroNames 2002. Neuroinformatics 2:63–83.

Cajal SR. 1909–1911. Histologie du système nerveux de l'homme et des vertébrés. Paris: Maloine. For translation, see Swanson N, Swanson LW. 1995. Santiago Ramón y Cajal: histology of the nervous system in man and vertebrates. New York: Oxford University Press.

Chen N, Harris TW, Antoshechkin I, Bastiani C, Bieri T, Blasiar D, Bradnam K, Canaran P, Chan J, Chen CK, Chen WJ, Cunningham F, Davis P, Kenny E, Kishore R, Lawson D, Lee R, Muller HM, Nakamura C, Pai S, Ozersky P, Petcherski A, Rogers A, Sabo A, Schwarz EM, Van Auken K, Wang Q, Durbin R, Spieth J, Sternberg PW, Stein LD. 2005. WormBase: a comprehensive data resource for Caenorhabditis biology and genomics. Nucleic Acids Res 33:D383–D389.

Chesler EJ, Lu L, Wang J, Williams RW, Manly KF. 2004. WebQTL: rapid exploratory analysis of gene expression and genetic networks for brain and behavior. Nat Neurosci 7:485–486.

Dong H-W. 2006. The Allen atlas: a digital brain atlas of the C57BL/6J male mouse. New York: John Wiley & Sons.

Eckersley P, Egan GF, Amari S, Beltrame F, Bennett R, Bjaalie JG, Dalkara T, De Schutter E, Gonzalez C, Grillner S, Herz A, Hoffmann KP, Jaaskelainen IP, Koslow SH, Lee SY, Matthiessen L, Miller PL, da Silva FM, Novak M, Ravindranath V, Ritz R, Ruotsalainen U, Subramaniam S, Toga AW, Usui S, van Pelt J, Verschure P, Willshaw D, Wrobel A, Tang Y; OECD Neuroinformatics Working Group. 2003. Neuroscience data and tool sharing: a legal and policy framework for neuroinformatics. Neuroinformatics 1:149–165.

Galen. 1968. On the usefulness of the parts of the body. Translated from the Greek with an introduction and commentary by M.T. May. Ithaca, NY: Cornell University Press.

Galen. 1999. On anatomical procedures. Translation of the surviving books with introduction and notes by Charles Singer. Oxford: Oxford University Press.

Gomez-Perez A, Corcho O, Fernandez-Lopez M. 2003. Ontological engineering, with examples from the areas of knowledge management, e-commerce and the semantic web. New York: Springer.

Gruber TM. 1993. Toward principles for the design of ontologies used for knowledge sharing. Int J Human-Computer Studies 43:907–928.

Harris TW, Chen N, Cunningham F, Tello-Ruiz M, Antoshechkin I, Bastiani C, Bieri T, Blasiar D, Bradnam K, Chan J, Chen CK, Chen WJ, Davis P, Kenny E, Kishore R, Lawson D, Lee R, Muller HM, Nakamura C, Ozersky P, Petcherski A, Rogers A, Sabo A, Schwarz EM, Van Auken K, Wang Q, Durbin R, Spieth J, Sternberg PW, Stein LD. 2004. WormBase: a multi-species resource for nematode biology and genomics. Nucleic Acids Res 32:D411–D417.

Heintz N. 2004. Gene expression nervous system atlas (GENSAT). Nat Neurosci 7:483.

Kandel ER, Schwartz JH, Jessell TM (eds.). 2000. Principles of neural science. New York: McGraw-Hill.

Kennedy DN. 2005. The impact of neuroinformatics. Neuroinformatics 3:287–292.

Kölliker A. 1854. Manual of human histology. Translated and edited by George Busk and Thomas Huxley. London: Adlard.

Kötter R. 2004. Online retrieval, processing, and visualization of primate connectivity data from the CoCoMac database. Neuroinformatics 2:127–144.

Marenco L, Nadkarni P, Skoufos E, Shepherd G, Miller P. 1999. Neuronal database integration: the Senselab EAV data model. Proc AMIA Symp 1999:102–106.

MacKenzie-Graham A, Jones ES, Shattuck DW, Dinov ID, Bota M, Toga AW. 2003. The informatics of a C57BL/6J mouse brain atlas. Neuroinformatics 1:397–410.

Markram H. 2006. The blue brain project. Nat Rev Neurosci 7:153–160.

Nielsen FA, Hansen LK, Baslev D. 2004. Mining for associations between text and brain activation in a functional neuroimaging database. Neuroinformatics 2:369–380.

Nieuwenhuys R, Voogd J, Huijzen Chr van. 1981. The human central nervous system: a synopsis and atlas, 3rd ed. Berlin: Springer.

Pierce AGE. 1980. Histochemistry: theoretical and applied, 4th ed. New York: Churchill Livingston.

Rasmussen AT. 1947. Some trends in neuroanatomy. Dubuque, IA: Wm C Brown.

Reiner A, Perkel DJ, Bruce LL, Butler AB, Csillag A, Kuenzel W, Medina L, Paxinos G, Shimizu T, Striedter G, Wild M, Ball GF, Durand S, Gunturkun O, Lee DW, Mello CV, Powers A, White SA, Hough G, Kubikova L, Smulders TV, Wada K, Dugas-Ford J, Husband S, Yamamoto K, Yu J, Siang C, Jarvis ED; Avian Brain Nomenclature Forum. 2004. Revised nomenclature for avian telencephalon and some related brainstem nuclei. J Comp Neurol 473:377–414.

Rosse C, Mejino JL Jr. 2003. A reference ontology for biomedical informatics: the Foundational Model of Anatomy. J Biomed Inform 36:478–500.

Stephan KE, Kamper L, Bozkurt A, Burns GAPC, Young MP, Kötter R. 2001. Advanced database technology for the collation of connectivity data on the macaque brain (CoCoMac). Philos Trans R Soc Lond B Biol Sci 356:1159–1186.

Swanson LW. 1995. Mapping the human brain: past, present, and future. Trends Neurosci 18:471–474.

Swanson LW. 1998. Brain maps: structure of the rat brain. A laboratory guide with printed and electronic templates for data, models and schematics, 2nd ed. Amsterdam: Elsevier.

Swanson LW. 2000. A history of neuroanatomical mapping. In: Toga AW, Mazziotta JC, editors. Brain mapping: the applications. San Diego: Academic Press. p 77–109.

Swanson LW. 2001. Interactive brain maps and atlases. In: Arbib MA, Grethe JG, ediotrs. Computing the brain: a guide to neuroinformatics. San Diego: Academic Press. p 167–177.

Swanson LW. 2003. Brain architecture: understanding the basic plan. Oxford: Oxford University Press.