

# Neuroinformatics

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## Original Article

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### Brain Architecture Management System

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#### Abstract

The nervous system can be viewed as a biological computer whose genetically determined macrocircuitry has two basic classes of parts: gray matter regions interconnected by fiber pathways. We describe here the basic features of an online knowledge management system for storing and inferring relationships between data about the structural organization of nervous

system circuitry. It is called the Brain architecture management system (BAMS; <http://brancusi.usc.edu/bkms>) and it stores and analyzes data specifically concerned with nomenclature and its hierarchical taxonomy, with axonal connections between regions, and with the neuronal cell types that form regions and fiber pathways.

**Index Entries:** Neuroanatomy; connections; inference engines.

#### Introduction

The large quantity of information that exists in any field of neuroscience makes searching and interpretation a difficult task. Further difficulties with the interpretation and integration of data arise from the different levels of central nervous system (CNS) organization. Any region of the mammalian brain can be described with respect to a series of levels of organization: from patterns of gene expression under specific

experimental conditions, to structural, chemical, and physiological characteristics of its constituent neurons and glial cells, to specific roles in functional networks of brain regions in a particular species.

The mammalian CNS can be parceled differently, depending on methods and mapping criteria. Therefore, neuroanatomy has to address the problem of many parceling schemes for a single species (Stephan and Kotter, 1998; Bota et al., 2003; Bota and Arbib, 2004). Moreover,

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the naming of brain regions leads to further problems because a particular name or term can designate partly or completely different regions, or the same region can have different names in alternative parceling schemes (Bota et al., 2003). The comparison of brain regions across different parceling schemes and species can be performed in different ways, and can be addressed by inference algorithms implemented in neuroinformatics systems.

Brain part classification is also an important aspect of neuroanatomy in the sense that it provides taxonomies of brain parts (Bota et al., 2003). The hierarchical organization of neuroanatomical nomenclatures is seldom addressed in current neuroinformatics knowledge management systems (Bowden and Martin, 1997; National Library of Medicine, 2003). Nevertheless, the hierarchical organization of neuroanatomical nomenclatures must be based on criteria that represent the approaches followed by authors, by cited references, and by collators.

The advent of modern pathway tracing techniques has either confirmed or invalidated many previously identified brain circuits and has enabled researchers to identify vast numbers of new ones (Bota et al., 2003). Thus, another problem in neuroanatomy that must be addressed is related to the accuracy, reliability, and completeness of pathway tracing data found in the literature.

To solve these problems we have started to develop an online knowledge management system, the Brain Architecture Management System (BAMS, <http://brancusi.usc.edu/bkms>) for systematizing, organizing, and processing neuroscience information relevant to different levels of CNS organization.

The structure of BAMS allows insertion of data about brain regions, cell types, and neural pathways collated from the literature or recorded by researchers. BAMS user interfaces allow searching for information in different ways, and utilize inference engines that

1. relate connectivity and cell type data,
2. establish general qualitative topological relations between brain regions, and
3. construct possible networks of brain region interactions from connectivity data entered in the system.

BAMS contains another module designed for inserting and processing results of pathway tracing experiments. This module is currently used by researchers in our laboratory to construct complex tabular summaries of connectivity experiments that are inserted in papers sent for publication.

We describe here the structure of BAMS and its user interfaces for searching and manipulating data collated from the literature or entered by researchers. We describe in the Materials and Methods section the structure of BAMS's relational database and the algorithms implemented to date. The Results section includes a description of the most important web accessible parts of BAMS and how information can be retrieved from the system. We conclude with a short discussion of BAMS tools and features that are new relative to other online neuroinformatics systems.

## Materials and Methods

### *The General Structure of BAMS*

BAMS is hosted on a Dell 8200 desktop computer with a Pentium III processor running under the Windows 2000 operating system, with IIS 6.0. The backend relational database of BAMS was created in MySQL, and the PHP scripting language is used to query the database and run inference engines included in the system. Thus, the architecture of BAMS is constructed on three levels: a set of tables constructed in MySQL that store data collated from the literature, or inserted by neuroanatomists, an intermediate level encoded in PHP that includes queries and algorithms for processing data populating BAMS, and an output level that is mainly in an HTML tabular format and

graphics. The backend MySQL database of BAMS consists of 63 tables and the most important ones are listed in Table 1.

The data included in BAMS can be grouped in two major categories: data collated from the literature and experimental data. Data collated from the literature can be further divided into "original" data and "support information." The category *original data* refers to experimental results collated from the literature, and to the information inferred by collators from the original literature. The category *support information* includes references used by the authors of neuroanatomical nomenclatures to define different brain parts, and the associated annotations inserted by collators. The category *experimental data* refers to the results of tract tracing experiments entered in BAMS by registered users, and to the associated metadata (information about experimental animals, employed techniques, annotations).

Conceptually, BAMS contains four basic modules: *Brain Parts*, *Cell Types*, *Relations*, and *Connections*. The object-relationship structure of BAMS is centered on the object "Brain Part" as defined in different neuroanatomical nomenclatures. A brain part is uniquely identified in BAMS by name, species, atlas (nomenclature, defined broadly), and version of atlas or nomenclature. An additional attribute, the type of brain part, specifies whether it is a neural region or mass (gray matter), major fiber pathway (white matter), or ventricle. The term "Brain Part" is used for convenience; it can also include the other part of the CNS, the spinal cord, as well as the nerves and ganglia of the peripheral nervous system (PNS).

The general object-relationship (OR) schema of BAMS is presented in Fig. 1. Each of the objects and relations shown in the figure can be captured in more than one table. The object "Reference" and the "Brain Part" module in Fig. 1 are in a 1:n (one-to-many) relation, because atlas and atlas version are two attributes that uniquely define any brain record and refer

to a single source. The allowed types of references in BAMS are described in Bota (2001) and Bota and Arbib (2004).

The object "Brain Part" is in a 1:n relation with the "Collator" part of BAMS because a collator can insert information related to many brain parts, and a uniquely identified brain part can be entered by a single collator.

Any brain part recorded in BAMS can be associated with a number of cell type reports. The "Cell Types" module is constructed in an *m:n* (many-to-many) relation with "Brain Part." A neuronal cell type may be distributed in several brain regions, and a region typically contains several types of neurons. This module allows the qualitative description of a neuronal cell type in terms of distribution within the associated brain region, and in terms of numerical data (cell counts, cell density, percentages of cell types compared to the total number of neurons found in the associated brain region, and range of neuron number over a set of experiments).

### **Relations in BAMS**

The object "Brain Part" has three types of relations: Hierarchy, Connections, and Nomenclatures. The hierarchies of neuroanatomical nomenclatures and connectivity reports have been inserted by collators, and are considered in BAMS as original data. The relations included in Nomenclatures are either entered by collators as original data, or established by the BAMS inferences engines.

### **Hierarchies**

The "Hierarchy" part of BAMS refers to the set of tables and relations that allows collators to construct ordered sets of brain parts. The OR structure of the BAMS Hierarchy part is shown in Fig. 2. The structure of the BAMS Hierarchy part allows the ordering of brain nomenclatures according to alternative organization criteria, which are represented

Table 1  
The Most Important Tables of the BAMS Backend Database

Table	Encodes for
<i>Nomenclatures</i>	
brain_part	Unique identification and basic information (name, abbreviation, species, atlas or nomenclature, atlas or nomenclature version, collator, textual description) about brain parts collated from different neuroanatomical atlases or nomenclatures
brain_parts_support	References and associated annotations cited by authors of neuroanatomical nomenclatures to define different brain parts
hierarchy	Parent–children relationships between different brain parts defined in the same species and neuroanatomical nomenclature. It is similar to the Hierarchy module of NHDB described in Bota and Arbib (2004)
hierarchy_construction	Specifies the mode of construction of hierarchical trees of neuroanatomical nomenclatures inserted in BAMS. It is described in detail in Table 2 and Fig. 2
topology	Topological relations as defined by Egenhofer and Franzosa (1991)
atlas_levels	Atlas levels associated to a brain part in a neuroanatomical atlas
atlas_method	The experimental and sectioning methods employed in the associated atlas
topological_data	Topological relations between two brain regions defined in different atlases and identified in pairs of Atlas Levels, and inserted by collators
<i>Connections</i>	
connections	Connectivity reports as collated from the literature. This table is described in detail in Table 3
topographical_location	Values of topographical locations allowed in BAMS
connection_strengths	Values of connectivity strengths allowed in BAMS
extension_outside	Values of extensions of injections outside of target regions that are allowed in BAMS
technique	Tract-tracing techniques allowed in BAMS
hemisphere	Hemispheric location of the injection, and of the label
fiber_tract	Relationships between connectivity reports and major fiber tracts, which are entered in the table <i>brain_part</i>
assignment_criteria	Allows mapping of numerical data to qualitative assessments of projections strengths
<i>Cell types</i>	
celltype	Names of neuronal cell types identified in different brain regions
celltype_details	Qualitative descriptions of neuronal cell types as collated from the literature
celltype_numerical	Numerical descriptions of neuronal cell types as collated from the literature
<i>Tract-tracing experimental data</i>	
experimental_animal	Information such as species (strain), sex, age, and weight of experimental animals used in tract-tracing experiments
connections_processed	Results of qualitative processing of different tract tracing experiments by registered users
<i>Reference and collators</i>	
references	Information about the references that were used to collate information in BAMS. It is described in detail in Bota and Arbib (2004)
collators	Basic information about the researchers allowed to insert data in BAMS

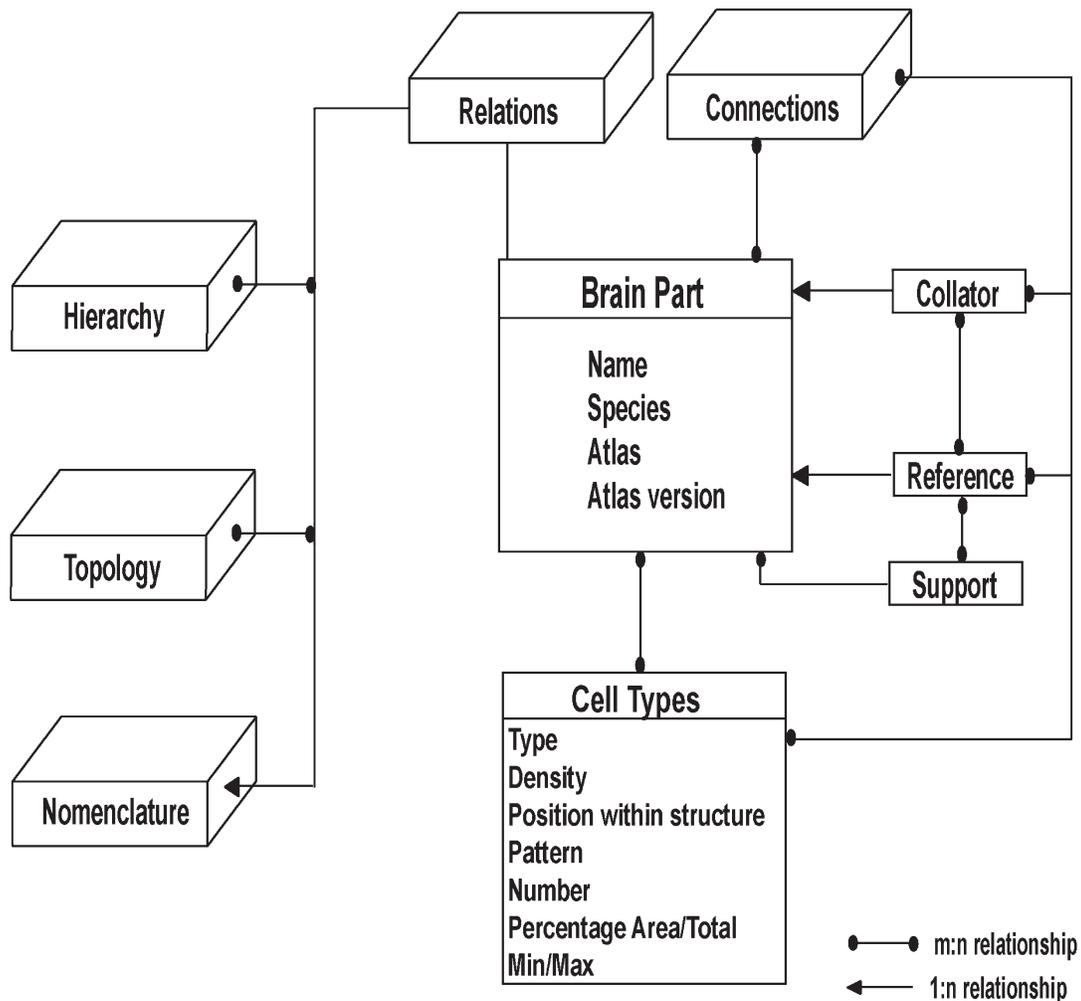


Fig. 1. The general OR schema of BAMS.

in Fig. 2 by the “Hierarchy criteria.” A brain nomenclature is considered here as a set of neuroanatomical terms that refers systematically to different parts of the CNS, and that is usually provided in an atlas or in a terminology book. The neuroanatomical atlas, or the reference that contains this list of terms is encoded in BAMS as “primary source” and the set of neuroanatomical terms as original data, whereas the references used for naming of different parts of the CNS are encoded as “support,” and the annotations inserted by collators as support information.

The Hierarchy part of BAMS contains three additional constraints:

1. If a brain part A has a subpart B, then A is not a subpart of B;
2. If A is a subpart of B, then B is the only parent of A;
3. If A has a subpart B, then there is a brain part C that is also a subpart of A.

The first constraint avoids inconsistencies (cycles) in the hierarchical tree. The second constraint ensures that the hierarchical organization of a brain nomenclature is not ambiguous: any

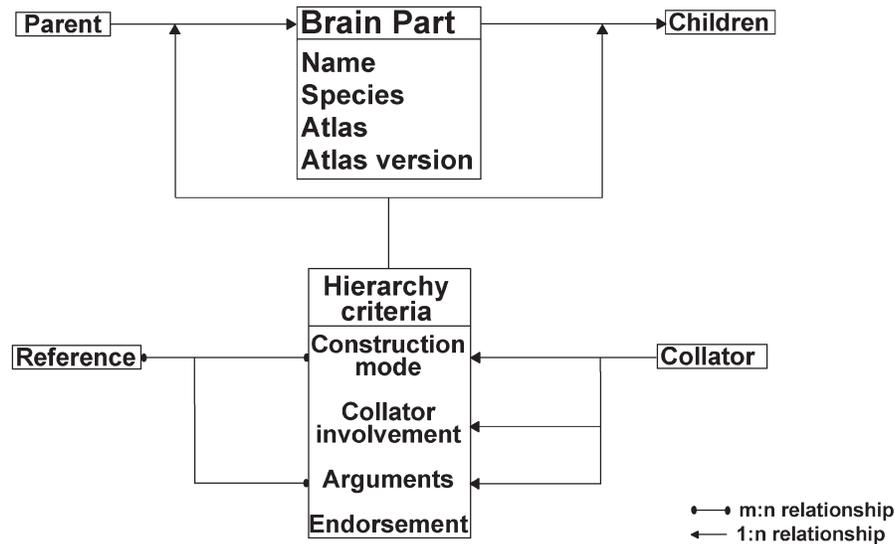


Fig. 2. The OR structure of the Hierarchy part of BAMS.

brain part defined in a nomenclature can have in BAMS only one parent and may have many children. The second constraint refers to the minimal number of children of a parent: any brain part that can be further subdivided, has at least two subparts. This constraint ensures that the hierarchy path of any brain part is complete.

The insertion of the hierarchy of any neuroanatomical nomenclature in BAMS follows the constraints discussed. If the authors of a neuroanatomical nomenclature have also provided a hierarchy, then collators are allowed to alter the original hierarchies only when any of the constraints are not fulfilled. The actions that can be taken by collators and the allowed construction criteria of a brain hierarchy in BAMS that are encoded in the MySQL backend database are summarized in Table 2.

If a neuroanatomical nomenclature was not hierarchically organized by its authors, the collators are allowed to organize it according to references cited by the authors, and to their expertise. If the references cited by the authors of the nomenclature contain information about the hierarchical organization of different CNS

parts, this will be adapted to the nomenclature and entered in BAMS. The authors of the neuroanatomical nomenclatures that are added to BAMS are consulted whenever collators perform changes in the original hierarchies. The decisions of authors of nomenclatures are encoded in BAMS by the attribute "Endorsement" shown in Fig. 2 and in Table 2.

### Connections

For simplicity, we currently view the neuroanatomical projections identified in a brain nomenclature as relations between pairs of brain regions. The OR schema of the BAMS "Connections" module is shown in Fig. 3. The attributes "Topological position injection site/labeled site," "Size position injection site/labeled site," "Extension injection site/labeled site," "Technique," "Type of connection," and "Associated annotations" are identical to those used in describing connectivity reports in the NeuroHomology Database system (NHDB; Bota, 2001; Bota and Arbib, 2004).

The BAMS "Connections" module also contains a set of attributes and relations that enables

Table 2  
The Attributes of Criteria Allowed for Construction of a Brain Hierarchy by Collators in BAMS

Criteria Attributes	Encodes for	Allowed values	Additional Information
Construction mode	Approach used to add the associated brain region to the hierarchy	Small integer	1 Position of the brain part in the hierarchy is specified in the associated reference 2 Position of the brain part in the hierarchy is specified in references cited by the authors of the nomenclature 3 Position of the brain part in the hierarchy is inferred by the collator using a set of references different from those cited by the authors 4 Position of the brain part is not supported by references
Collator involvement	The action taken by the collator in adding the associated brain part to the hierarchy	Small integer	0 Collator inserted directly the hierarchy from the reference associated to the nomenclature 1 Collator inferred the position of the brain region based only on his or her expertise 2 Collator used personal expertise and information collated from a set of references to construct the hierarchy tree of the associated brain region 3 Collator constructed the hierarchy tree of the associated brain region directly from a set of references
Arguments	The set of text fragments as support for the construction of hierarchy tree		Text
Endorsement	Refers to whether the author of the nomenclature agrees with the inferred hierarchical relationships hierarchy. It is characteristic of trees constructed by collators.	Small integer	0 Authors of the brain nomenclature do not endorse the hierarchy tree 1 Authors of the brain nomenclature endorse the constructed hierarchy tree

it to represent comprehensively connectivity reports collated from the literature, or inserted by neuroanatomists. Attributes of the Connections module that are specific to BAMS are summarized in Table 3. Attributes of the BAMS "Connections" module that are identical to those of NHDB (Bota, 2001; Bota and Arbib, 2004),

together with the first two attributes presented in Table 3, allow the full qualitative spatial description of a pathway tracing experiment. Attributes that allow representation of connectivity numerical data, together with associated Atlas Levels, enable graphical display of connectivity data. An example of the graphical display

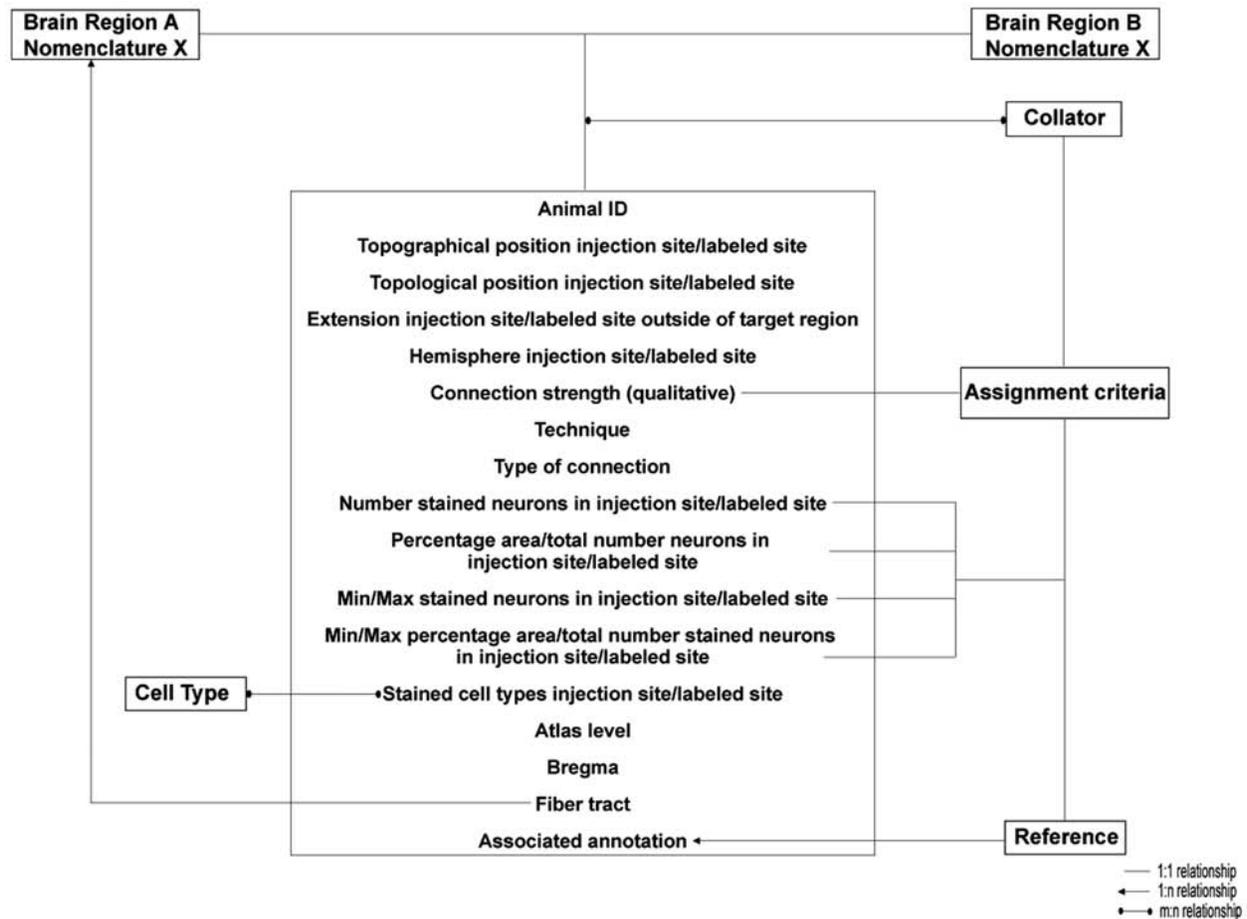


Fig. 3. The OR schema of the BAMS “Connections” module.

(histograms) of labeled neurons per Atlas Level is presented and discussed in the Results section.

We refined in BAMS the set of possible projection strength values of connections as collated from the literature, or as entered by neuroanatomists, by adding two strengths: “fiber of passage” (fp) and “exists.” The value “exists” is associated with any connectivity report stating that there is a projection pathway from brain region A to brain region B, without a specific strength being assessed in the report, or inferred by the collator.

The Connections module also allows mapping of numerical data to qualitative assessments of projection strength, represented in

Fig. 2 by “Assignment criteria.” The qualitative evaluation of numerical data is labeled as to whether it was collated from the associated reference, or was inferred by the collator.

The attribute “Stained cell types” of the Connections module allows the association of projection reports with neural cell types that were labeled in either the injection site or in the labeled site. In this way, the projection pattern of a cell type identified in a brain region can be reconstructed from an unrelated set of connectivity reports.

Finally, the attribute “Fiber tract” associates a pathway tracing report with a predefined set of fiber tracts, and allows reconstruction of

Table 3  
The Major Attributes of the BAMS Connections Module

Connections Module Attribute	Encodes for	Allowed Values	Additional Information
Hemisphere injection site/labeled site	The brain hemispheres (left or right) where the injection was performed and the labeled site was identified, respectively	String	The terms “unilateral” and “bilateral” are also allowed
Topographical position injection site/labeled site	The position of the injection site and labeled site, respectively, relative to the target regions	String	Codes for the neuroanatomical topographical terms, and combinations of them; more than 70 allowed possibilities
Number stained neurons in injection site/labeled site	The absolute number of stained cells in the region where the injection was performed and the labeled regions, respectively	Integer	
Percentage area/total numbers of neurons of stained cells in injection site/labeled site	Percentages of stained neurons in the region where the injection was performed and the labeled regions, respectively, as ratios of stained cells over total area, or number of neurons	Decimal	
Min/max stained neurons in injection site/labeled site	The minimal and maximal values of stained neurons in the region where the injection was performed and the labeled regions, respectively	Integer	
Min/max percentage area/total numbers of neurons of stained cells in injection site/labeled site	The minimal and maximal values of ratios of stained neurons in region where the injection was performed and the labeled regions, respectively	Decimal	
Stained cell types in injection site/labeled site	The identified neuron types that were stained in the region where the injection was performed and the labeled regions, respectively	Integer	Allows an <i>m:n</i> relationship with the “Cell Types” module
Atlas level	The Atlas Plates used to identify a neuroanatomical projection, and shown in the associated reference	Integer	Allows the three types of sections: coronal, lateral, and horizontal
Bregma	The bregma level of each of the atlas plates associated with the neuroanatomical projection	Decimal	
Fiber tract	Associates a set of neuroanatomical projections reports with major fiber tracts recorded in the associated nomenclature	Integer	

the major CNS pathways from connectivity information recorded in BAMS.

### Nomenclatures

The relation “Nomenclatures” shown in Fig. 1 refers to relationships that can be established between a pair of brain parts identified in the same species, and in different neuroanatomical nomenclatures. BAMS allows either insertion or deletion of three types of relationships: name identity, topological relations, and common references.

“Topological relations” refers to the set of eight possible topological relations between a pair of 2D objects as defined by Egenhofer and Franzosa (1991):  $U = \{d, m, o, cv, cvBy, co, isCo, i\}$  namely, disjoint (d), meet (m), overlap (o), covers (cv), is covered (cvBy), contains (co), is contained, or inside (isCo), and identical (i). These relations are inserted by collators who must compare different neuroanatomical atlases or nomenclatures. BAMS allows inferences of general spatial relations between pairs of brain structures by comparing sets of Atlas Levels. This inference engine is described below.

### Inference Engines in BAMS

BAMS is not simply a repository of neurobiological data pertaining to brain parts defined in different nomenclatures and species, cell types, and connections. It also contains a series of inference engines that relate data. Each BAMS module (Brain Parts, Cell types, Connections, and Relations) employs several inference engines.

#### Inferring a Brain Region’s Cellular Profile

This inference engine uses the hierarchical organization of a brain nomenclature and answers queries of the type: “What are the neuronal cell types found in the thalamus?” It relates all neuronal cell types associated with subdivisions of the searched brain region

and returns the set of cell types in tabular format.

#### Inferring a Brain Region’s Connectivity Pattern

This inference engine is similar to that used to reconstruct the cellular profile of a brain region from data associated with its substructures, and answers queries of the type: “What are the connections of the thalamus?” The inference engine reconstructs the projection pattern or profile of a brain region defined in a hierarchically organized nomenclature by taking into account the projections of each substructure with all the other brain regions defined in the associated nomenclature.

#### Inferring a Brain Region’s Possible Networks of Connections

The inference engine for constructing networks of parts from connectivity data that populate BAMS answers queries of the type: “What are the possible paths to get from region A to region B, given a number X of intermediate regions?” Each brain region that receives or sends projections is considered a black box, and the spatial characteristics of injection sites and labeled sites are not taken into account. Because of processing speed limitations, the number of intermediate regions is currently limited to a maximum of three. Here is the process for inferring networks of brain regions (from connectivity data inserted in BAMS) with two intermediate regions between A (the “start” brain region) and B (the “end” brain region).

*Step 1.* Given region A, find the set of first-order intermediate regions  $\{A_{1i}\}_{i=1,\dots,n}$  that receive a projection from A, and impose the feed-forward constraint  $A_{1i} \neq A$  for any  $i=1,\dots,n$ .

*Step 2.* For any  $A_{1i}$  find the set of second-order intermediate regions  $\{A_{2j}\}_{j=1,\dots,m}$  that receive a projection from  $A_{1i}$  and impose the feed-forward constraint  $A_{2j} \neq A_{1i}$  and  $A_{2j} \neq A$  for any  $i=1,\dots,n$  and  $j=1,\dots,m$ .

*Step 3.* Find the subset of brain regions  $\{A_{2k}\}_{k=1,\dots,p}$  that send a projection to B from the set  $\{A_{2j}\}$ .

To reduce further the number of possible networks that can be established between any two brain regions A and B defined in a given brain nomenclature, the brain networks inference engine currently takes into account only those projection reports with at least moderate strength. However, we do include projection reports with the value “exists” for the attribute “Connection strength,” because the actual projection strength may be “strong” or “very strong.” The inference engine allows A=B and thus possible networks with the same start and end point can be constructed.

### The Topology Inference Engine

The BAMS OR structure allows for the insertion of topological relations between brain regions identified in the same species and in different neuroanatomical nomenclatures as found in the literature, or as inferred by collators. BAMS also allows multiple topological relations for a pair of brain regions defined in two different nomenclatures. A pair of brain regions defined in two different nomenclatures can have more than one topological relation whenever each region is identified in several Atlas Levels. In this case, the topology inference engine evaluates general spatial relations by taking into account the set of topological relations established over the investigated set of Atlas Levels pairs. Thus, the topology inference engine answers queries like “What is the relation between two brain regions defined in different nomenclatures and extending across a set of Atlas Levels?”

The set of rules used to infer a general spatial relation from a set of topological relations describes in qualitative terms the relation between two brain regions, and covers all possible configurations of topological relations that can be established when pairs of Atlas Levels are compared, regardless of the completeness of sets.

The algorithm for inferring general topological relations works under three assumptions: the angle at which the brain section pairs were cut in each of the compared atlases is identical, any brain region of interest is represented in at least two Atlas Sections, and each set of Atlas Levels is a representative sample of the brain sections used to construct the compared atlases.

The assumption of the identical cutting angle ensures that same brain parts are represented in both Atlas Levels. Thus, topological relations between brain regions identified in different neuroanatomical atlases are entered by collators only when the difference between angles of cutting is negligible or stated as such by authors of atlases, or in related references. Errors in assigning topological relations increase in proportion to increasing difference in the cutting angles. The second assumption allows inferring general relations from individual topological relations and ensures that the compared brain parts are 3D structures. The third assumption is necessary because neuroanatomical atlases are generally constructed from representative sets of brain sections rather than serial sections (sections are typically only 15–50  $\mu\text{m}$  thick). This assumption ensures that the topological inference engine yields unequivocal answers when complete sets of Atlas Levels are compared.

The inference engine implemented in BAMS first checks the constraint of completeness for those brain regions that are compared: at least one brain region is completely represented in the compared Atlas Levels. Thus, for any pair of brain regions that is topologically compared, a complete set of Atlas Levels that represents one of the regions is compared with at least a subset of those Atlas Levels that represent the other region. If this rule holds true, then the inferred general topological relations will be unequivocal and the rules for inferring topological relations between two brain regions include the following:

$$gt_{AB} = \begin{cases} t_{ABi} & \text{if } t_{ABi} = t_{ABl} \forall i, l = 1, \dots, n; l \neq i \\ m & \text{if } t_{ABi} = m \wedge t_{ABl} = d \\ & \forall i, l = 1, \dots, n; l \neq i \\ cvBy & \text{if } t_{ABi} = i \wedge t_{ABl} \\ & = \{cvBy, isCo\} \\ & = \forall l = 1, \dots, n; l \neq i \\ cv & \text{if } t_{ABi} = i \wedge t_{ABl} = \{cv, co\} \\ & \forall l = 1, \dots, n; l \neq i \\ 0 & \text{otherwise} \end{cases} \quad (1)$$

where “ $\wedge$ ” stands for logical AND.

The general topological relation between regions A and B ( $gt_{AB}$ ) is of the same type with any of the topological relations  $\{t_{AB}^i\}$  established across a set of Atlas Level pairs if all elements of the set are identical. If the set of topological relations contains at least one “meet” relation and the rest are all disjoint, then the inferred general spatial relation is “meet.” The converse of this rule is also true: the general spatial relation is “meet” if there is at least one “disjoint” topological relation and the remaining relations are “meet.” The general topological relation is considered to be “covered by” when the set of topological relations is formed by the relations “identical” and either “covered by” or “is contained.” The converse of this rule is also true. The general topological relation is considered to be “overlap” if there is at least one topological relation “overlap” in the set  $\{t_{AB}^i\}$ , or the set  $\{t_{AB}^i\}$  contains at least one “covers” or “contains” relation and at least one complementary relation (cvBy, or isCo, respectively). The general relation “overlap” is also inferred when there is one “disjoint,” or “meet” relation and the rest are any combination of the set  $\{i, co, cv, isCo, cvBy\}$ .

Brain regions defined in different neuroanatomical nomenclatures may be difficult to compare topologically because of their complex spatial relations, or because there is a paucity of landmarks, and thus the completeness constraint defined earlier may not be satisfied. In this case, the inference of topological relations does not always yield unequivocal

answers. Rules for inferring qualitative spatial relations when the completeness constraint is not fulfilled are given in Eq. (2)

$$g_{t_{AB}} = \begin{cases} \{i, cv, cvBy, o\} & \text{if } t_{ABi} = i \forall i = 1, \dots, n \\ \{t_{AB}, o\} & \text{if } t_{ABi} = \{cv, cvBy\} \\ & \forall i = 1, \dots, n \\ \{cv, co, o\} & \text{if } t_{ABi} = co \forall i = 1, \dots, n \\ \{cvBy, isCo, o\} & \text{if } t_{ABi} = isCo \\ & \forall i = 1, \dots, n \\ \{d, m, o\} & \text{if } t_{ABi} = \{m, d\} \\ & \forall i = 1, \dots, n \\ \{m, o\} & \text{if } t_{ABi} = d \wedge \exists t_{ABl} = m \\ & \forall i = 1, \dots, n, l \neq i \\ \{cvBy, o\} & \text{if } \exists t_{ABi} = i \wedge t_{ABl} \\ & = \{cvBy, isCo\} \\ & \forall l = 1, \dots, n; l \neq i \\ \{cv, o\} & \text{if } \exists t_{ABi} = i \wedge t_{ABl} \\ & = \{cvBy, isCo\} \\ & \forall l = 1, \dots, n; l \neq i \\ 0 & \text{otherwise} \end{cases} \quad (2)$$

The results of the first rule in Eq. (1) become equivocal in Eq. (2) because the set of compared Atlas Levels is not complete. Therefore, relationships between the interiors and boundaries of the brain regions established across Atlas Levels are not necessarily true in those pairs of Atlas Levels that are missing from the complete set. For example, the result of the first rule in Eq. (2) can be “identical,” “covers,” “covered by,” or “overlap,” even though all topological relations are “identical.” Because the set of Atlas Levels is incomplete, one must assume that there may be a pair of Atlas Levels where the relationship between the compared regions is “disjoint” or “meet.” Thus, the general topological relation is not only “identical,” but it can also be “overlap,” because the boundaries of the compared region intersect in at least one pair of Atlas Levels. In a similar way, the result of the third rule can be “covers,” “contains,” or “overlap” when all the topological relations are “covers.” One may assume that there is a

Table 4  
Brain Nomenclatures Inserted to Date in BAMS (the code for each nomenclature in BAMS is constructed by merging the authors and the year of publication)

Species	Nomenclature Code in BAMS	Hierarchically Organized	Collator Involvement in Hierarchy Construction
Human	Bowden-Human-2002	Yes	None
	Mai-1997	Yes	Solved the ambiguity constraint for three brain regions
Macaque	His-Nomina Anatomica-1895	Yes	None
	Bowden-Macaque-2002	Yes	None
Cat	Berman/Jones-1982	Yes	None
Rat	Swanson-1992	Yes	Solved the completeness constraint for 19 brain regions
	Swanson-1998	Yes	Solved the completeness constraint for 19 brain regions
Mouse	Paxinos/Watson-1998	No	None
	Paxinos/Franklin-2001	Yes	Arranged hierarchically the nomenclature based on the information provided in the atlas and on the references cited by authors. Added 44 brain parts to the nomenclature
	Hof et al.-2000	Yes	Solved the ambiguity constraint for 30 brain regions

pair of Atlas Levels where the boundaries of regions meet, and therefore the general topological relation is “covers,” or where the interior of one region is the exterior of the other and thus the general topological relation is “overlap.”

The set of rules used to infer a general spatial relation from a set of topological relations describes in qualitative terms the relation between two brain regions, and covers all possible configurations of topological relations that can be established when pairs of Atlas Levels are compared, regardless of the completeness of sets.

### Inserted Data

The public part of BAMS contains neuroanatomical data collated from more than 350 references. We have entered 10 brain nomenclatures from five species: human, macaque

(*Macaca fascicularis*), cat, rat, and mouse. Table 4 summarizes the nomenclature data currently present in BAMS. The hierarchies constructed by the authors of the inserted brain nomenclatures have been checked for inconsistencies, ambiguities, and incompleteness, and have been modified from the original whenever any of the conditions discussed in the Methods section were not fulfilled. Changes performed on those hierarchies entered in BAMS are listed in the last column of Table 4. Generally, we avoided adding new brain parts to the nomenclatures; we added new names only when the constraint of completeness was not fulfilled, or when we constructed the brain hierarchy. As discussed in *Methods*, the hierarchical organization of brain nomenclatures by collators is primarily based on information found in the associated atlases (if any) and in the cited references. Using this approach, we organized

hierarchically the mouse brain parcellation scheme Paxinos/Franklin-01, using information found in the atlas and in references cited by authors. We have added 44 neuroanatomical names (*see* Table 4) to the mouse brain nomenclature listed in Paxinos and Franklin (2001), based on at least one of the following references: the atlas itself (20 brain parts names were listed in different Atlas Levels, but not in the nomenclature list), Paxinos and Watson (1986) (21 brain part names), Swanson (1992) (9 names), Shipley et al. (1995) (9 names), Price (1995) (6 names), Simerly (1995) (4 names), and Alheid et al. (1995) (1 name). The descriptions of the newly added brain parts include references that were used.

The system contains to date more than 15,000 reports of connections between different brain regions, as collated from the literature since 1962 and related generally to the visual and limbic systems of the rat.

BAMS contains support information for defining different brain regions in the rat brain nomenclatures of Swanson-1992, Swanson-1998, and in the mouse brain nomenclatures Paxinos/Franklin-2001, and Hof et al.-2000.

The system also contains data referring to 19 cell types identified in 23 rat brain regions that are defined in the Swanson-1998 rat brain nomenclature.

## Results

The BAMS user interface contains four modules for searching and manipulating information inserted in the system: Brain Parts, References, Evaluation, and the Personal Account.

### Searching the Brain Parts Module

This module includes several ways to search for information in BAMS that can be performed by name of brain part, full text search, species, or nomenclature. Full text search refers to queries that allow users to retrieve brain parts information from the knowledge base of BAMS

based on a partial match of the searched string with the textual description of regions, or with the names of regions in different nomenclatures. The option of search for information by species or by nomenclature retrieves those sets of brain regions that are associated with the searched species or nomenclature, respectively, alphabetically arranged.

The search for information by name retrieves brain parts that partly match the searched string. Steps involved in retrieving information by searching with the name of a region are shown in Fig. 4. The search by name first returns a list of all nomenclatures recorded in BAMS that contain terms partially matching the searched string, organized by species and neuroanatomical nomenclature, as shown in Fig. 4A. We have included this intermediate step in searching for brain parts by name to avoid displaying many identical results and thus reduce time required for processing and displaying information. Brain parts records retrieved by this query may appear in different nomenclatures and species, and therefore the result of the query may be a long list of identical terms. Users can choose the brain nomenclature of interest from the list associated with the searched term. Once the user chooses a brain nomenclature, the system displays all entries for brain parts that partially match the searched string, as shown in Fig. 4B. Fields associated with each retrieved entry provide information about the name, abbreviation, and type (region, pathway, or ventricle) of the retrieved brain part; the species; the reference used to collate the information, and the description of the region as found in the associated reference. Users can access further information by clicking on the link associated with the retrieved brain region name. The result of this action is shown in Fig. 4C. The screen shown here represents the main page for summarizing data that populate BAMS, or for inferring relationships between brain regions.

If the retrieved brain region is captured in a hierarchical tree, then the tree of super-

**A**

The term **cerebellum** (partial match of the string) is related to several brain nomenclatures. Click on the "Atlas version" to view all those records that are associated with **cerebellum**.

Structure to be searched (partial match)	<input type="text" value="cerebellum"/>
<input type="button" value="Search!"/> <input type="button" value="Reset"/>	

Species	Atlas/Version
Rat	Swanson-1998
	Swanson-1992
	Swanson-2004
	Paxinos
	Paxinos/Watson-1998

**B**

Your search retrieved a number of 1 structures that exactly match the string "cerebellum"

Structure	Type	Abbreviation	General Description	Inserte
<a href="#">Cerebellum</a>	gray matter	CB	According to Larsell 1952, Voogd et al. 1996.	2001-1

and 36 structures that partially match the string "cerebellum".

Structure	Type	Abbreviation	General Description
<a href="#">Bulbocerebellar tract</a>	fiber tract	bct	According to Voogd 1995, Voogd et al. 1996.
<a href="#">Cerebellar commissure</a>	fiber tract	cbc	According to Voogd 1995, Voogd et al. 1996.
<a href="#">Cerebellar cortex</a>	gray matter	CBX	According to Larsell 1952, 1970, Palay and Chan-Palay 1974, Voogd et al. 1995. The cerebellar cortex has three layers: molecular (CBXm), Purkinje (CBXp), and granule cell (CBXg). The surface map provided by Campbell and Armstrong (1983) was particularly useful in constructing the flatmap. Note that the brain used for this atlas had one apparently unusual feature in the cerebellum (not illustrated in the above references): a very large fissure that we have called the pyramidal fissure (atlas levels 64-70).

Fig. 4. The result of searching for information by partial matching of names in BAMS. **(A)** Users can search for information by names of brain parts. The first result of this type of search is a list of species and the associated brain nomenclatures that contain exact or partial matches of that searched string. **(B)** Users can choose the species and brain nomenclature of interest and the regions that partially match the searched string are displayed. Fig. 4. (continued) **(C)** By choosing one of the listed brain parts, users can access details about the region of interest, its hierarchical organization, those brain parts with identical names but defined in different nomenclatures and species, and links to its patterns of efferent and afferent connections as collated from the literature. **(D)** Further details about the brain region of interest as defined in the associated nomenclature, the criteria for including the region in a hierarchical organization, and support information, can be accessed by users. The brain region Hypothalamus is identified in the mouse brain nomenclature Paxinos/Franklin-2001 and it was added by a collator, based on information and references cited in the atlas. See text for details.

## C

Details about CB, Swanson-1998, in Rat.  [Tree](#) Same term found in other nomenclatures [Help?](#)

+ Cerebellum

Hierarchy level in atlas Swanson, version Swanson-1998 is 2: 1 superstructure includes it.

Major Subparts

Part	Type
<a href="#">Cerebellar cortex</a>	gray matter
<a href="#">Deep cerebellar nuclei</a>	gray matter
<a href="#">Cerebellar commissure</a>	fiber tract
<a href="#">Cerebellar peduncles</a>	fiber tract
<a href="#">Arbor vitae</a>	fiber tract

Tree of Cerebellum:

Brain

## D

Name of Structure	Type of Structure	Abbreviation	Species	Atlas	Version of Atlas	Reference	General Description of Structure	Collator
Hypothalamus	gray matter	Hy	Mouse	Paxinos/Franklin	Paxinos/Franklin-2001	The mouse brain in stereotaxic coordinates.	Our delineation of the hypothalamus is based on the description of Simerly (1995). The general cytoarchitecture of the mouse hypothalamus has been described by Broadwell and Bleier (1977). The distribution of aromataseimmunoreactive cells in the hypothalamus and other areas has been mapped by Foidart et al. (1995). See Ruggiero et al. (1984) and Baker et al. (1993) for a description of catecholaminergic cells in the hypothalamus of the mouse.	Mihail Bota

The hierarchy of the Hypothalamus was constructed partially from the information found in the associated reference, as well as using additional criteria. The approach used by the collator [Mihail Bota](#) is not endorsed by the author of the nomenclature.

Collator argument: The hierarchy of this region was constructed using the rat atlas Paxinos and Watson 1998 and Simerly 1995. See also Swanson 1992.

References: Same as for the associated structure  
Anatomical substrates of hypothalamic integration (1995) \*

\*: the reference was used by both collator and author

Fig. 4. (continued)

structures including it and the set of sub-structures that lie immediately under it are returned. Users can navigate along the hierarchy of a nomenclature by accessing any structures that are either superstructures or substructures of the retrieved brain region. If the searched region's hierarchical tree is reconstructed up to level 0 (e.g., the CNS for the rat brain nomenclature, Swanson-1998), then users can view the position of the retrieved region in the reconstructed hierarchical tree

by clicking the button "Tree," as shown in Fig. 4C.

Criteria used to include a retrieved brain region in an internally consistent hierarchy can be inspected by hitting the button "More," as shown in Fig. 4C. The result of this action is a web page exemplified in Fig. 4D. In this example, the position in the hierarchy of the brain region "Hypothalamus" identified in the mouse and defined in the neuroanatomical atlas Paxinos/Franklin-2001 (Paxinos and

Details about MB-HB, Swanson-1998, in Rat. [More](#) [Tree](#) [Help?](#)

Hierarchy level in atlas Swanson, version Swanson-1998 is 2: 1 superstructure includes it.

**Major Subparts**

Part	Type
<a href="#">Midbrain-Hindbrain, Sensory</a>	gray matter
<a href="#">Midbrain-Hindbrain, Motor</a>	gray matter
<a href="#">Reticular core</a>	gray matter
<a href="#">Pre-Post Cerebellar nuclei</a>	gray matter

**Tree of Midbrain-Hindbrain:**

```

graph TD
    Brain[Brain]
  
```

**7 cell types associated to Midbrain-Hindbrain**

Part	Cell type
<a href="#">Substantia nigra compact part</a>	<a href="#">stellate</a>
	<a href="#">fusiform</a>
	<a href="#">round</a>
	<a href="#">inverted pyramid</a>
	<a href="#">neurogliaform</a>
<a href="#">Substantia nigra reticular part</a>	<a href="#">large sized neuron</a>
	<a href="#">medium sized neuron</a>

Fig. 5. The cellular profile of a brain region can be inferred from neuron types information associated with subparts.

Franklin, 2001), is based on a reference cited by the authors of the nomenclature and on a reference used by the collator. Users can thus view the modes of hierarchy construction for the brain region of interest, as well as arguments and references used by collators, in a textual format, along with references that were used.

The output web page containing information about the searched brain region (Fig. 4C) also includes links to several BAMS inference engines. Thus, brain parts having an identical name with the part of interest, but identified

in other neuroanatomical nomenclatures and species, are displayed as a list in tree-format with the title "Same term found in other nomenclatures." These links can be used to access details about brain parts with names identical to the retrieved part. If the retrieved brain part of interest contains a set of subparts, and there are cell type records associated with them, then the cell types inference engine automatically reconstructs the cell type profile of the parent brain region. An example of a cell type profile reconstruction is provided in Fig. 5.

Cell type details						
There are 2 reports about the cell type medium spiny						
Report	Reference	Topological relation with the region	Localization within the region	Appearance within the region	Description	
1	<a href="#">Fallon &amp; Loughlin</a>	identical	medio-dorsal	patchy	In the rat, these neurons have an ovoid or roughly polygonal spine free soma with four to seven or sometimes eight primary dendrites that extend about 200-300 micrometers from the soma.	
2	<a href="#">Chang et al</a>	N/A	N/A	scattered	This was the most frequently impregnated neuronal type in our Golgi preparation. The morphology of cell type appeared to be identical to the medium spiny neurons described in the previous Golgi studies.	

Basic information about the cell population						
Report	Qualitative information	Quantitative information absolute numbers	Quantitative information percentage	Range information absolute numbers	Range information percentage	Average count
1	the density is considered to be dense	none provided	none provided	none provided	none provided	not specified
2	the density is considered to be very dense	none provided	none provided	none provided	none provided	not specified

Fig. 6. Users can inspect details about each of the inserted cell types, collated from different references. The medium spiny cell type is associated with the brain region caudoputamen, identified in the rat brain nomenclature Swanson-1998.

The brain part “Midbrain–Hindbrain” defined in the rat brain nomenclature Swanson-1998 (Swanson, 1998) has seven cell types associated in BAMS, but none of them are directly related to it. The association of a set of cell types with the brain part “Midbrain–Hindbrain” is possible because the whole brain nomenclature Swanson-1998 has an internally consistent hierarchical organization and two subparts of the Midbrain–Hindbrain are directly associated with reports of cell types. Users can view detailed reports of each cell type by accessing the links associated with each of them, as shown in Fig. 6.

If the brain part of interest is associated in BAMS with projection reports, matrices of afferent (input) or efferent (output) connections are

automatically constructed whenever the links “Afferent connections” or “Efferent connections” shown in Fig. 4C are accessed. An example of how a reconstruction of the afferent connection pattern of the caudoputamen, as defined in the rat brain nomenclature Swanson-1998, may be reconstructed is shown in Fig. 7.

Users can view more information about efferent or afferent connections of a brain region by clicking the corresponding buttons as shown in Fig. 7. Details of each retrieved connectivity report can be accessed through the field “Number of reports,” as shown in Fig. 8.

Users can view the main attributes of a projection report inserted in BAMS, the projection strength as collated from the associated reference or inferred by the collator, the type of projection,

List of regions which send projections to: Nucleus accumbens			
	Efferent region	Number of reports	Collator(s)
Cortical nucleus of the amygdala posterior part lateral zone (COApl)	COApl	1	Larry Swanson
Cortical nucleus of the amygdala posterior part medial zone (COApm)	COApm	1	Larry Swanson
Entorhinal area, lateral part (ENTI)	ENTI	1	Larry Swanson
Subiculum ventral part (SUBv)	SUBv	3	Gully Burns, Larry Swanson
Field CA1 (CA1)	CA1	3	Gully Burns, Larry Swanson
Secondary motor area (MOs)	MOs	1	Gully Burns
Agranular insular area posterior part (Alp)	Alp	1	Gully Burns

Fig. 7. Users can inspect patterns of afferent and efferent connection of brain regions of interest, which can be accessed by clicking on either the “Afferent connections” or “Efferent connections” links shown in Fig. 4C. We show here a part of the pattern of afferent connections of the nucleus accumbens identified in the rat brain nomenclature Swanson-1998.

## A

Details about the neuroanatomical projections from VTA to CP						
Sending structure	Receiving structure	Strength of projection	Type of connection	Technique	General description	Collator
Ventral tegmental area	Caudoputamen	light	not known	autoradiography	Case pg62, fig10. Soma notes 3Hproline/3Hleucine injections. Terminal notes ventromedial half, throughtout rostrocaudal extent.	Gully Burns
Ventral tegmental area	Caudoputamen	moderate	not known	autoradiography	Case pg198, fig3. Soma notes 3H proline/3H leucine inj. Terminal notes not specified..	Gully Burns
Ventral tegmental area	Caudoputamen	exists	not known	fluorescent tracers	earlier: see Beckstead, Domesick, & Nauta BR 175:191-217, 1979, rat, autoradiography; Simon, Le Moal, & Calas BR 178:17-40, 1979, rat, autoradiography. Collator note: label found just lateral to BST around atlas levels 16-18.	Larry Swanson

Fig. 8. Users can inspect details associated with retrieved connectivity reports. **(A)** Details of reports associated in BAMS with the projection between ventral tegmental area (VTA) and caudoputamen (CP), identified in the Swanson-1998 brain nomenclature. **(B)** An example of connection reports with qualitative strengths assigned from numerical data. Users can also inspect spatial characteristics of the injection site and terminal field, respectively, as well as criteria used to map numerical data to qualitative projection strengths.

## B

Details about the neuroanatomical projections from InWh to CL

Report ID	Sending structure	Receiving structure	Projection strength	Associated code	Type of connection	Technique	General description projection	Collator	Associated reference
6020	intermediate white layer of the superior colliculus	centrolateral thalamic nucleus	very strong*	6.00	not known	CTB	No description provided. Collator note: case 2227, Figure 4C, page 60, level 42 from Paxinos atlas.	Mihail Bota	Krout K.E., Belzer R.E., Loewy A.D., 2002
6021	intermediate white layer of the superior colliculus	centrolateral thalamic nucleus	very strong*	6.00	not known	CTB	No description provided. Collator note: case 2227, Figure 4D, page 60, level 45 from Paxinos atlas.	Mihail Bota	Krout K.E., Belzer R.E., Loewy A.D., 2002
6022	intermediate white layer of the superior colliculus	centrolateral thalamic nucleus	very strong*	6.00	not known	CTB	No description provided. Collator note: case 2227, Figure 4E, page 60, level 49 from Paxinos atlas.	Mihail Bota	Krout K.E., Belzer R.E., Loewy A.D., 2002
6023	intermediate white layer of the superior colliculus	centrolateral thalamic nucleus	moderate*	3.00	not known	CTB	No description provided. Collator note: case 2227, Figure 4F, page 60, level 51 from Paxinos atlas.	Mihail Bota	Krout K.E., Belzer R.E., Loewy A.D., 2002

\*: The projection strength is based on quantitative data

General description technique/protocol: CTb injections were made in 18 different thalamic sites. Each injection site was composed of two areas: the "core" region where neurons were filled with tracer, and a halo region where CTb was found only in the neuropil. The injection targets were divided into the intralaminar thalamic nuclei—central lateral (CL, Fig. 4)..

Further details associated to record number 6020:

Position of injection: everywhere	Position of terminal field: everywhere
Topological position of injection: identical	Topological position of terminal field: overlap
Extension of injection outside: none	Extension of terminal field outside: small
The injection was performed in: right hemisphere	The terminal field was found: ipsilateral

Criteria used to assign projection strengths:

No projection	Light	Light/Moderate	Moderate	Moderate/Strong	Strong	Very strong
0-1cells	2-5 cells	no information	6-15 cells	no information	16-25 cells	26 or more cells

These criteria have been found in the associated reference.  
Supporting fact(s): The criteria are found in page 55

Fig. 8. (continued)

the description of it, the name of the collator, and the associated reference. Fig. 8B shows a typical example of projection strengths that are assessed with numerical data. Here, criteria of connection strength assignments were extracted from the associated paper. Users can also inspect short descriptions of protocols employed and spatial characteristics of the injection site and labeled sites, respectively, as reported or as collated from the associated references.

If the brain region of interest is captured in an internally consistent hierarchy, and it contains at least one substructure with associated

reports of direct connections in BAMS, then the inference engine for reconstructing connection patterns can be accessed by two additional links: "Inferred efferent connections" and "Inferred afferent connections," as shown in Fig. 4C. The output web pages contain information about inferred patterns of afferent or efferent connections, respectively, in tabular format.

BAMS also allows the association of major fiber pathways defined in different brain nomenclatures with connectivity reports collated from the literature. Therefore, the major CNS fiber pathways of different species can

be reconstructed from reports of neuroanatomical connections collated from the literature. The OR structure of BAMS allows two different ways of associating connection reports with records of major fiber pathways: collated directly from the associated references, or inferred by collators. If a connection report is associated with a fiber pathway, users can inspect the motivation for relating the fiber pathway record with the set of connectivity reports as collated from the associated reference and illustrated in Fig. 9. Otherwise, the association between fiber pathway and a set of neuroanatomical projection reports is labeled with the statement "inferred by collator," and collator names are provided.

The BAMS topology inference engine can be accessed from the output page shown in Fig. 4C, using the button "Relations." An example of a spatial comparison of two brain regions (substantia innominata defined in the rat neuroanatomical atlases Swanson-1998 and Paxinos/Watson-1998, respectively) that can be performed in BAMS is shown in Fig. 10.

Information related to the qualitative spatial comparison of regions across different nomenclatures that is available to users includes: methodology used by the collator for making comparisons (either collation of data from different references or direct comparison of neuroanatomical atlases), compared regions, the set of pairs of topological relations, the Atlas Levels and their spatial coordinates, and the general spatial relations inferred. Users can also view the criteria used by collators to compare each pair of Atlas Levels (e.g., the landmarks used) in a textual format and associated with each of the entered relations.

### **Searching References in BAMS**

We discuss separately this type of search for information in BAMS because it has several specific features.

Searching for information by reference can be performed using any combination of three attributes: author, book or journal, and year of publication. An example of the result of searching by author regardless of journal or year is shown in Fig. 11. Searching the BAMS knowledgebase by author, regardless of specific journal or publication year retrieves all references associated in the system with the searched author, ordered by type of reference (e.g., books, book chapters, articles). This type of search retrieves not only details about references recorded in BAMS but also details about what kinds of neurobiological information can be found in each of them (e.g., brain part definitions, fiber pathway reports).

If a search by author retrieves references associated with information of the type "fiber tract," then users can view reconstructed connectivity matrices from the related references. The representation of connection matrices based on data collated from individual references is similar to that described for the reconstruction of connectivity data for a region from information associated with the set of its substructures. Users can organize connectivity data in two additional ways: they can view the connection matrix as reported in a given reference in terms of connection existence or absence, or in terms of maximum strength. The part of BAMS allowing representation in tabular format of neuroanatomical connections reported in an individual reference is not restricted to the construction of matrices based on combined results. Instead, it also allows the display of data from individual experiments. Reconstruction of connectivity matrices from individual references has an additional feature: the ability to create a composite profile of all experiments reported in that reference. In the example shown in Fig. 12, the retrieved reference (Dong and Swanson, 2003) is associated with a reconstructed matrix of projections, and with data for each of four individual experiments.

**A**

Details about apd, Swanson-1998, in Rat.  [Tree](#)

Same term found in other nomenclatures

- Ansa peduncularis
  - [ansa peduncularis\(Human\), Mai-1997](#)
  - [ansa peduncularis\(Human\), Bowden-Human-2002](#)
  - [ansa peduncularis\(Macaca fascicularis\), Bowden-Macaca-2002](#)
  - [Ansa peduncularis\(Rat\), Swanson-1992](#)
  - [ansa peduncularis\(Rat\), Swanson-2004](#)

Hierarchy level in atlas Swanson, version Swanson-1998 is 2: 1 superstructure includes it.

No other subparts of apd.

Tree of Ansa peduncularis:

Medial forebrain bundle system

[Component projections](#)

**B**

Component projections of Ansa peduncularis:

Efferent region	Afferent region	Details
	SI	<input type="button" value="View!"/>
BSTov	→ CEAm	<input type="button" value="View!"/>
	CEAI	<input type="button" value="View!"/>
BSTfu	→ SI	<input type="button" value="View!"/>

**Motivation for projection from Bed nuclei of the stria terminalis oval nucleus (BSTov) to Central nucleus of amygdala medial part (CEAm) to be a part of Ansa peduncularis, collated from the reference *Basic organization of projections from the oval and fusiform nuclei of the bed nuclei of the stria terminalis in adult rat brain*, authors Dong HW, Petrovich GD, Watts AG, Swanson LW, published in *J Comp Neuro*:**

Page 435: Caudally, this projection extends into CEA, whereas the rest of the amygdala is almost free of PHAL labeling...

**Details about the neuroanatomical projection from BSTov to CEAm**

Report ID	Sending structure	Receiving structure	Strength of projection	Associated code	Type of connection	Technique	General description	Collator	Associated reference
4795	Bed nuclei of the stria terminalis oval nucleus	Central nucleus of amygdala medial part	very strong	6.00	not known	PHAL	The CEAm is very densely innervated by abundant, highly branched bouton-laden fibers	<input type="button" value="Mihail Bota"/>	<a href="#">Dong HW, Petrovich GD, Watts AG, Swanson LW, 2001</a>

Fig. 9. The major fiber pathways identified in a brain nomenclature can be associated with reports of neuroanatomical connections as collated from the literature. **(A)** If a fiber pathway is associated with reports of connections, then a link to the page that displays its component projections becomes available to users. **(B)** Users can inspect information related to the connections included in fiber systems, and the association criteria.

1 General approach: We have topologically compared the substantia innominata (SI) defined according to the rat brain nomenclature Swanson-98 with a series of brain structures defined according to the rat brain nomenclature Paxinos-Watson-98. We have compared the closest atlas levels in terms of distance from bregma, from the associated atlases, respectively.

Collator: [Mihail Bota](#) [Explanation](#)

The inferred relations of substantia innominata (SI), defined in Paxinos/Watson-1998 are as follows:

overlaps with the [Substantia innominata\(SI\)](#), parcellation Swanson-1998

Details of topological relations of substantia innominata (SI), defined in Paxinos/Watson-1998 as collated by [Mihail Bota](#)  
In order to see the associated annotations for each of the established topological relation, go with the mouse over the relation.

Structure(abbreviation)	Identified in:	Topological relation:	Atlas plate used for SI (Bregma)	Atlas plate used for related structure (Bregma)
Substantia innominata (SI)	Swanson-1998	overlap	25 (-1.53)	25 (-1.60)
		overlap	26 (-1.78)	26 (-1.80)
		overlap	27 (-2.00)	27 (-2.12)

Collator note: as landmarks we have taken the internal capsule, the external capsule, the stria terminalis, the optic tract, and the fornix.

Fig. 10. Output of the BAMS topological inference engine. Users can inspect the methodology for inserting topological relations employed by users, relations between different regions across corresponding sets of Atlas Levels, and inferred general relations between the related regions.

The reconstruction of projection information from individual references has an additional feature: dynamic construction of graphical data representations. If connectivity reports in BAMS are associated with quantitative data, the textual information is augmented with graphical reconstructions (histograms) of labeled cells per Atlas Level.

Composite tables of individual experiments, along with graphical display of numerical connectivity data, provide for a richer representation of information collated from the literature.

### Processing Tools in BAMS

BAMS processing tools can be used to construct customized connection matrices, compare neuroanatomical nomenclatures in terms of common references, and construct possible networks of interconnected brain regions.

Users can choose sets of brain regions and construct customized connection matrices from data inserted in BAMS. Because of limitations

of processing speed and data display, this option is currently limited to a reconstructed matrix with a maximum of  $100 \times 100$  elements. The reconstructed connection matrix can be displayed in different ways including a color coded format of the maximal strengths, shown in Fig. 13.

Comparison of neuroanatomical nomenclatures evaluates sets of references associated with each nomenclature and cited in support of various brain region definitions. This comparison is performed in two complementary ways. First, lists of references specific to each of the compared nomenclatures are displayed in a tree format with first-order branches made out of each of the retrieved references. Second-order branches composed of those brain region subsets that are associated with each of the retrieved references are shown in Fig. 14.

Users can access details associated with each retrieved reference, as well as information about the brain regions referred to. Any given reference

Search of information by reference

Author

Journal

Year

**Books**

Author	Title of Book	Volume	Series	Year	Pages	Edition	Publisher	Editor	URL	Type of information
Swanson L.W.	Brain Maps: Structure of the Rat Brain	N/A	N/A	1992	196-212	first	Elsevier	N/A	Not available	brain structures
Swanson L.W.	Brain Maps: Structure of the Rat Brain	N/A	N/A	1998	196-213	second	Elsevier	N/A	Not available	brain structures
Swanson L.W.	Brain Maps: Structure of the Rat Brain, Third Edition	N/A	N/A	2004	166-179	third	Elsevier	N/A	Not available	brain structures

**Book Chapters**

Author	Title of chapter	Title of Book	Volume	Series	Year	Pages	Edition	Publisher	Editor	URL	Type of information
Swanson L.W.	The hypothalamus	Handbook of chemical neuroanatomy	5		1987	1-124	First	Elsevier	Bjorklund A., Hokfelt T. & Swanson L.W.	Not available	brain structures

**Journal articles**

Authors	Title of Article	Journal	Year	Volume	Issue	Pages	URL	Type of information
Dong H-W & Swanson L.W.	Projections from bed nuclei of the stria terminalis, posterior division: implications for cerebral hemisphere regulation of defensive and reproductive behaviors.	J Comp Neurol	2004	471	4	396-433	<a href="#">Abstract</a>	fiber tracts reports
Dong H-W. & Swanson L.W.	Projections from the rhomboid nucleus of the bed nuclei of stria terminalis: implications for cerebral hemisphere regulation of ingestive behaviors	J Comp Neurol	2004	463	4	434-472	<a href="#">Abstract</a>	fiber tracts reports
Thompson R.H., Swanson L.W.	Structural characterization of a hypothalamic visceromotor pattern generator network	Brain Res Brain Res Rev	2003	N/A	M/A	N/A	Not available	fiber tracts reports
Dong H-W & Swanson L.W.	Organization of axonal projections from the anterolateral area of the bed nuclei of the stria terminalis	J Comp Neurol	2003	N/A	N/A	N/A	<a href="#">Abstract</a>	fiber tracts reports
Dong HW, Petrovich GD, Watts AG, Swanson LW	Basic organization of projections from the oval and fusiform nuclei of the bed nuclei of the stria terminalis in adult rat brain	J Comp Neurol	2001	5	436	430-55	<a href="#">Abstract</a>	fiber tracts reports

Fig. 11. The output of a search for references in BAMS. Users can inspect details of each retrieved reference, and the types of neurobiological information found in it are inserted in BAMS.

may appear under each of the compared nomenclatures, but as support for definitions of different brain regions. The same reference being used in two different nomenclatures to define regions with different names does not necessarily imply that the associated brain regions are identical. Relationships between these regions can be established by the topology inference engine if qualitative spatial information was entered in the BAMS knowledge base.

The second evaluation displays in tabular format those references common to the compared nomenclatures, as shown in the lower part of Fig. 14.

### Constructing Networks of Brain Regions in BAMS

Users can infer possible feed-forward brain region networks that are defined in a given nomenclature from the set of direct projections inserted in BAMS. As described in *Methods*, the network of brain regions inference engine allows up to three intermediate steps between the starting region and the final region. Once these two regions, the starting point or origin of the network and the final endpoint, have been specified by users, the system prompts users to choose any of the three possible types of processing (Fig. 14 inset). The inference engine returns the set of possible networks that can be constructed

Summary of fiber tracts information collated from the reference *Organization of axonal projections from the anterolateral area of the bed nuclei of the stria terminalis*, authors Dong H-W & Swanson L.W., published in *J Comp Neurol*

Associated cases

Cases\_composite

Individual case (Injection site)

BST74(BSTsc)

BST19(BSTal)

BST178(BSTal)

BST124(BSTal)

Efferent	BSTsc	BSTal
Afferent		
PIR3	2	2
TR	1	1
COApl	1	1
COApm	1	1
SUBv-m	1	1
BLAp	1	11
BMAa	1	3
BMAp	3	5
CP	1	3
ACB	4	11

Fig. 12. Users can reconstruct matrices of neuroanatomical connections as reported in individual references. If a reference is associated in BAMS with connectivity data for individual experiments, this information also becomes available to users. This connectivity matrix was obtained by search for information by author and accessing the associated “fiber tract reports” link as shown in Fig. 11.

from connectivity information inserted in BAMS and by applying the algorithm described in *Methods* and illustrated in Fig. 15.

Support information for each inferred network can be accessed by clicking on the network number. An example of support information used to infer one of the possible networks between the lateral part of the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus—with the lateral hypothalamic area and bed nuclei

of the stria terminalis as intermediate regions and defined in the rat brain nomenclature, Swanson-1998—is shown in Fig. 16.

### Experimental Data Processing in a Personal Account

Registered users have the option to create personal accounts where they can store and process results of pathway tracing experiments. We describe in this section the most important features of the BAMS Personal Profile module.



Fig. 13. Users have the option of creating customized connectivity matrices that can be displayed in different formats, including a color-coded table of maximal strengths. The matrix shown in this figure represents the maximal strengths of the outputs of several regions of the bed nuclei of the stria terminalis identified in the rat brain nomenclature Swanson-1998 with several amygdalar regions. The option of creating user customized connectivity matrices can be found under the category “Evaluate” of BAMS’s menu.

The insertion of the results of a pathway tracing experiment can be performed with different degrees of complexity: from very simple reports of existence or absence of a specific connection, to the specification of those cell types that send or receive axonal projections. Registered users have the possibility of adding new features to any previously entered report.

Once a registered user inserts the results of a pathway tracing experiment, the data can be viewed and processed in three different ways. Users can view the results of an inserted experiment in simple tabular format, process the entered connectivity data, or organize in complex table experiments that were already processed. An example of experimental pathway tracing data processing is shown in supplemental Fig. S1 (<http://brancusi.usc.edu/neuroinformatics/s1.html>).

Users can choose to process any of their inserted experiments as shown in the inset of Fig. S1, where experiments coded green already have been processed, whereas data associated with those coded red are not

processed yet. The structure of the BAMS Personal Profile module allows registered users to enter connectivity data with different degrees of complexity: from simple data records with no assessment of features characterizing defined projections, to very complex insertions where all the attributes of a neuroanatomical projection described in the Methods section are specified. The example presented in Fig. S1 displays pathway tracing data qualitatively assessed by the user and inserted per Atlas Level, using the rat brain atlas, Swanson-1998.

Registered users can choose any of three modalities for the qualitative processing of connectivity data. “Maximal” processing evaluation refers to an assessment of the greatest strength of a projection across a set of Atlas Levels. The “Mode” evaluation detects that strength having the highest frequency of appearance for a pair of brain regions across multiple Atlas Levels. This option also detects bimodal or multimodal staining intensity distributions, as shown in supplemental Fig. S2

Expand

- Swanson-1992 (Rat)
  - Graybiel, A.M. & Ragsdale C.W., 1979
    - Corpus striatum
    - Striatum
  - Ju G. & Swanson L.W. (I), 1989
  - Haberly, L.B. & Price J.L., 1978
- Swanson-1998 (Rat)
  - Graybiel, A.M. & Ragsdale C.W., 1979
  - Ju G. & Swanson L.W. (I), 1989
  - Alvarez-Bolado & Swanson L.W., 1995
  - de Olmos J., Alheid G.F. & Beltramino C.A., 1985
  - Petrovich GD, Risold PY, Swanson LW, 1996
  - Ju G., Swanson L.W. & Simerly R.B., 1989
  - Haberly, L.B. & Price J.L., 1978
- Paxinos/Franklin-2001 (Mouse)

Please choose at least two nomenclatures from the list below to compare in terms of supporting citations:

Swanson-1992  Swanson-1998  Paxinos/Franklin-2001

Submit Reset

Common references:

Reference	Is common for the following nomenclatures:
Fiber Connections of the Basal Ganglia by Graybiel, A.M. & Ragsdale C.W., published in Development and Chemical Specificity of Neurons, year 1979	Swanson-1992 and Swanson-1998
Studies on the cellular architecture of the bed nuclei of the stria terminalis in the rat: I. Cytoarchitecture by Ju G. & Swanson L.W. (I), published in J Comp Neurol, year 1989	Swanson-1992 and Swanson-1998
Association and commissural fiber systems of the olfactory cortex of the rat. II. Systems originating in the olfactory tubercle by Haberly, L.B. & Price J.L., published in J Comp Neurol, year 1978	Swanson-1992 and Swanson-1998 Swanson-1992 and Paxinos/Franklin-2001 Swanson-1998 and Paxinos/Franklin-2001

Fig. 14. Neuroanatomical nomenclatures can be compared in terms of common references and brain regions referred to. The option of comparing neuroanatomical nomenclatures can be found in the category “Evaluate” of BAMS’s menu under the name “Nomenclatures.”

(<http://brancusi.usc.edu/neuroinformatics/s2.html>). Bimodal and multimodal distributions are displayed in red, and users have the option to save the results (encoded in BAMS as “mode, not processed”), or further processing them by choosing the most appropriate connection strengths for the bimodal and multimodal distributions (“mode, processed”).

The processing mode “Your choice” shown in Fig. S2 refers to the user’s assessment of overall projection strength from a set of density estimates associated with a pair of brain regions distributed across several Atlas Levels. The qualitative evaluation of connectivity strength assessed by users takes the value of “fiber of passage” (fp; axons without terminals) as a separate category.

Therefore, the results of experimental connectivity data processing will include this as a separate category, whenever there is at least one report of fibers of passage for a pair of brain regions.

The results of processing can be saved by users in their personal account for future use. Users also have the option to construct composite tables from any number of previously processed experiments, per type of processing (supplemental Fig. S3 [<http://brancusi.usc.edu/neuroinformatics/s3.html>]).

Finally, user-defined composite tables can be downloaded onto personal computers in Excel format. This option provides a copy of the composite tables to registered users, who can then rearrange them as desired.

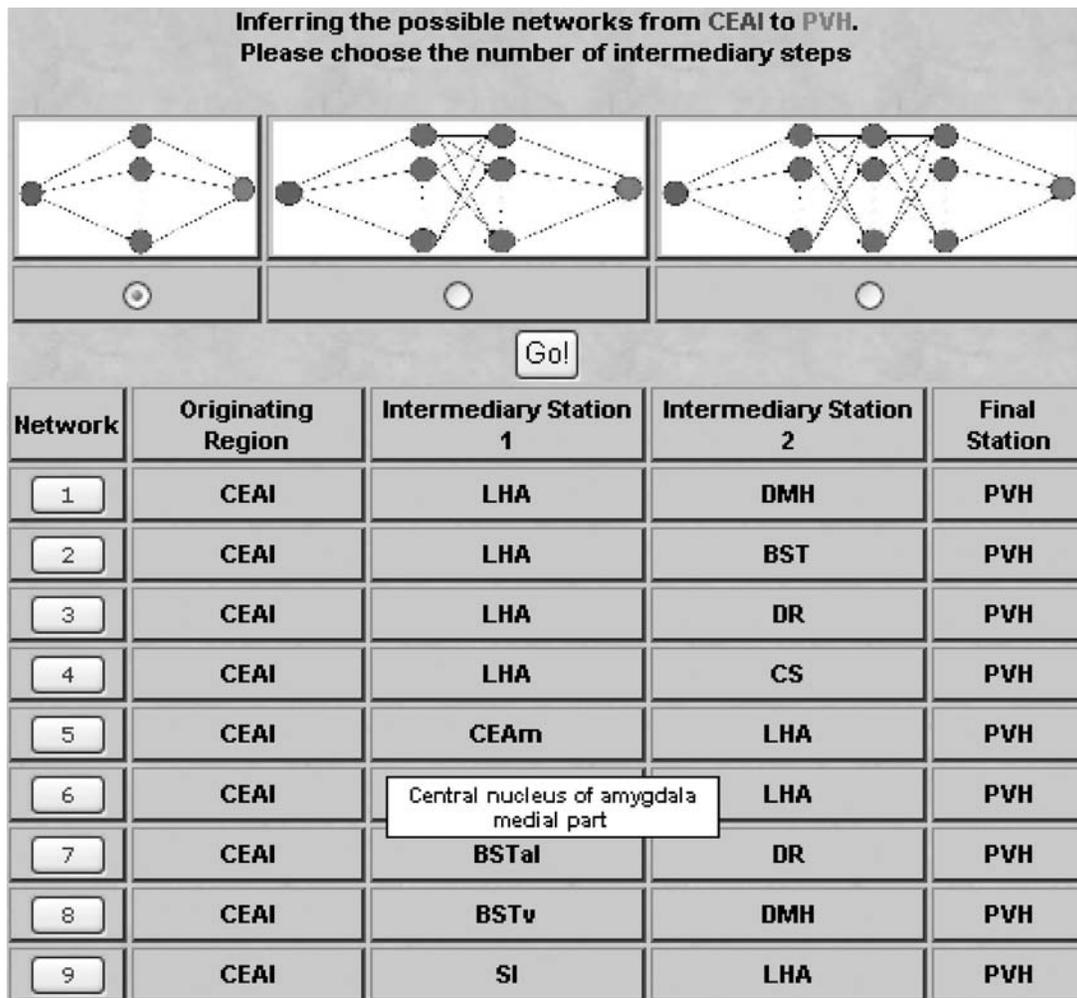


Fig. 15. Inferring possible networks of brain regions from connectivity data recorded in BAMS can be performed for up to three intermediary steps. The output of the networks inference engine (shown here for two intermediate steps) includes abbreviations and names of regions related by direct projections, and links to support information for each reconstructed network. The option of inferring possible networks of brain regions is found in the category “Evaluate” of BAMS’s menu under the name “Networks.”

## Discussion

In this article we have described the structure and major features of the BAMS knowledge management system, which has been designed for the online searching and processing of neurobiological information focused on brain circuitry.

This is part of an expanding effort in the field of neuroinformatics. Several research groups

have developed online systems that handle data pertaining to various levels of nervous system organization: brain region nomenclatures (Stephan et al., 2001; Bowden and Dubach, 2003; Bota and Arbib, 2004; Kotter, 2004), connectivity data (Burns, 1997; Burns et al., 2001; Stephan et al., 2002; Bota and Arbib, 2004; Kotter, 2004), and cytology (Marenco et al., 1999; Bota and Arbib, 2004). Two online systems that share similar features with BAMS are

Support information for the inferred network							
CEAI(Central nucleus of amygdala lateral part) → LHA(Lateral hypothalamic area)							
LHA(Lateral hypothalamic area) → BST(Bed nuclei of the stria terminalis)							
BST(Bed nuclei of the stria terminalis) → PVH(Paraventricular nucleus of the hypothalamus)							
<b>Support information about direct projections from Central nucleus of amygdala lateral part to Lateral hypothalamic area:</b>							
Sending structure	Receiving structure	Strength of projection	Type of connection	Technique	General description	Collator	Associated reference
Central nucleus of amygdala lateral part	Lateral hypothalamic area	exists	not known	PHAL	light parasubthalamic nucleus region...	Larry Swanson	Petrovich G.D., Canteras N.S., Swanson L.W., 2001
<b>Support information about direct projections from Lateral hypothalamic area to Bed nuclei of the stria terminalis:</b>							
Sending structure	Receiving structure	Strength of projection	Type of connection	Technique	General description	Collator	Associated reference
Lateral hypothalamic area	Bed nuclei of the stria terminalis	moderate	not known	PHAL	Case pg 430, fig 7C. Soma notes PHA-L pressor site inj, dense group of filled cells dorsal, medial and ventral to fomix. Terminal notes not specified..	Gully Burns	Allen G.V., Cechetto D.F., 1993
Lateral hypothalamic area	Bed nuclei of the stria terminalis	exists	not known	autoradiography	anterior part of LHA; anterior part of LHA; from rostromedial, at anterior level; Fig. 7 in Swanson JCN 167:227-256, 1976	Larry Swanson	Saper C.B., Swanson L.W., Cowan W.M., 1979
<b>Support information about direct projections from Bed nuclei of the stria terminalis to Paraventricular nucleus of the hypothalamus:</b>							
Sending structure	Receiving structure	Strength of projection	Type of connection	Technique	General description	Collator	Associated reference
Bed nuclei of the stria terminalis	Paraventricular nucleus of the hypothalamus	exists	not known	autoradiography	Collator note: Experiment R77; in addition to those described in Swanson JCN 167:227-256, 1976.	Larry Swanson	Swanson L.W., Cowan W.M., 1979

Fig. 16. Support information for each inferred network of brain regions includes the set of reports of direct projections between related brain regions that are used to construct the network. Support information shown in this figure corresponds to the second network shown in Fig. 15.

NeuroNames (Bowden and Dubach, 2003; <http://braininfo.rprc.washington.edu>) and CoCoMac (Stephan et al., 2002; Kotter, 2004; <http://cocomac.org>).

The present status of BAMS is “in progress” because we continue to add new data and extend its functionality. New features of BAMS will include a method for evaluating the reliability of connectivity information, based on the algorithm implemented in NHDB (Bota and Arbib, 2004), a schema for representing chemoarchitectural data at the levels of brain regions and molecules expression patterns in particular cell types, and a cell type classification schema. These schemas will allow BAMS to include chemical data in descriptions of brain

regions and cell types and to run complex queries, such as extracting gene expression patterns in specific cell types under certain experimental conditions.

We invite members of the neuroscience community to search for information in BAMS, to participate in our efforts to populate it with more neurobiological data, and to suggest functionality extensions.

## Acknowledgments

This work was supported by NIH/NIMH Grant MH61223 and by NINDS Grant NS-16668, and the NINDS/NIMH/NIBIB/NLM Grant NS050792-01.

Please select the experiment you want to evaluate from the table below

BST74	BST19	BST178	BST124	BST110	BST117	BST167	BST91	BST116
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Receiving Structures	Strength of connections	Levels	Evaluation options
AAA	very light, fibers of passage	24, 24	<input type="button" value="Maximal"/> <input type="button" value="Mode"/> <input type="button" value="Your choice"/>
ACB	very light, fibers of passage	15, 15	
ADP	fibers of passage	18	
AHA	strong, strong, fibers of passage, fibers of passage	22, 23, 22, 23	
AHNa	fibers of passage, fibers of passage, fibers of passage	22, 24, 25	
AHNc	very strong, strong, strong, fibers of passage, fibers of passage, fibers of passage	24, 25, 26, 24, 25, 26	
AHNp	very light, fibers of passage	27, 27	
AVP	fibers of passage	20	
BMAa	moderate, fibers of passage, fibers of passage, fibers of passage	28, 26, 27, 28	
BMAp	moderate, moderate, moderate, moderate, fibers of passage, fibers of passage, fibers of passage, fibers of passage, fibers of passage	31, 32, 33, 34, 29, 30, 31, 32, 33, 34	
BSTad	strong, moderate, very light, fibers of passage, fibers of passage, fibers of passage, fibers of passage, fibers of passage	19, 17, 16, 16, 17, 19, 19, 20	

Fig. S1. BAMS registered users have three different ways to process the results of pathway tracing experiments: maximal strength, mode, and personal assessment of qualitative staining strength across different Atlas Levels.

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Please select the experiment you want to evaluate from the table below

BST74	BST19	BST178	BST124	BST110	BST117	BST167	BST91	BST116
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Submit Reset

**Experiment: BST110**

Receiving Structures	Evaluated Strength (Frequency)	Levels		
AAA	± (1/1), fp	24		
ACB	± (1/1), fp	15		
ADP	fp			
AHA	+++ (2/2), fp	22, 23		
AHNa	fp			
AHNc	+++ (2/3), fp	25, 26		
AHNp	± (1/1), fp	27		
AVP	fp			
BMAa	++ (1/1), fp	28		
BMAp	++ (4/4), fp	31, 32, 33, 34		
BSTad	± (1/3), ++ (1/3), +++ (1/3), fp	16	17	19
BSTav	++ (2/3), fp	20, 21		
BSTcc	++ (1/1), fp	18		
BSTdl	fp			
BSTif	+++ (1/2), ++++ (1/2), fp	23	22	
BSTmg	++ (1/1), fp	21		
BSTpr	fp			
BSTtr	+++ (1/1), fp	22		
BSTv	± (1/2), ++ (1/2), fp	21	22	

Fig. S2. Processing the results of pathway tracing experiments by mode, identified as unimodal, bimodal, or multimodal distributions of qualitative strengths across Atlas Levels. The processed experiment is BST110 shown in the inset.

- hemisphere regulation of ingestive behaviors, *J. Comp. Neurol.* 3(4), 434–472.
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**The reconstructed and arranged connectivity matrix:**

Case (Injection Site) Terminal field	BST74 (BSTsc)	BST19 (BSTal)	BST124 (BSTal)
	<b>PIR3</b>	+	-
<b>TR</b>	-	-	±
<b>COApI</b>	-	+	-
<b>COApm</b>	-	+ --> ++	-
<b>SUBv-m</b>	-	+ --> ++	-
<b>BLAp</b>	-	+	++
<b>BMAa</b>	-	-	++
<b>BMAp</b>	±	+	±
<b>CP</b>	-	+	-
<b>ACB</b>	+++	+++	+++
<b>OT3</b>	±	++	+
<b>OT2</b>	fp	-	-
<b>OT1</b>	±	-	-
<b>FS</b>	++	+	+
<b>LSv</b>	-	±	-
<b>LSr.dI.lv</b>	fp	-	±
<b>LSr.vI.v</b>	±	±	+
<b>LSr.vI.d.m</b>	±	-	-
<b>LSr.m.v.c</b>	-	-	+

Fig. S3. Registered users have the option of creating composite tables from previously processed experiments.

- nuclei of the stria terminalis in the rat: II. Chemoarchitecture. *J. Comp. Neurol.* 280(5), 603–621.
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