The Brain Architecture Management System: User Manual

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1. What is the Brain Architecture Management System

The Brain Architecture Management System (BAMS; URL: <u>http://brancusi.usc.edu/bkms</u>) is an online knowledge management system designed to handle neurobiological information at different levels of organization of the vertebrate nervous system (NS).

BAMS handles data and metadata collated from original literature, or inserted by scientists that is associated to four levels of organization of the vertebrate NS: expressed molecules, neuron types and classes, brain regions, and networks of brain regions.

Structurally, BAMS consists of a relational MySQL database and several modules of middle-layer applications written in PHP for querying the backend database and web display of data and metadata.

1.1 BAMS: general structure

The structure of BAMS is modular (the general structure is shown in Figure 1), with the *Brain Parts* module as the center of the system. Brain parts are uniquely defined by a tuplet made of the name of the part, the nomenclature used to identify and name it, the nomenclature version, and species. A brain nomenclature is defined as an internally consistent set of terms used to name a part of the CNS. The number of terms included in a nomenclature is variable (at least one), and the nomenclature version uniquely specifies the set. Usually a brain nomenclature is associated with a brain atlas, but this does not constitute a constraint for inserting it. The constraints that are taken into account are the internal consistency of terms, whether the reference is original research, and the brain region names are associated with textual definitions, or at least depicted on a brain atlas.

The other modules of BAMS are Connections, Relations, Cell Types, and Molecules.

Connections module of BAMS holds data and metadata about macroscopic neuroanatomical projections between brain regions. Any neuroanatomical projection can be represented in BAMS by a set of more than 40 attributes. Details about this module can be found in Bota et al. 2005.

The *Relations* module stores qualitative spatial relations between brain regions, as well as cited references.

The *Cell Types* module allows insertion of names and definitions of neuron types and classes, as well as relations between them, as collated from references. The module also records neuron populations attributes, such as position within brain region, density and pattern of staining. It also includes a neurons classification schema, which allows specification of criteria used to hierarchically organize neuron nomenclatures. See Bota & Swanson, 2007 for details.

The *Molecules* module represents data and metadata as collated from the literature and pertaining to brain regions or neurons that are recorded in different physiological states: "normal" and "manipulated". Molecules are classified in two general classes: "cell associated" and "releasable by neurons". The "cell

associated" class is further divided in classes accepted by the IUPHAR nomenclature (http://www.iuphardb.org/index.jsp).



Figure 1. The relational structure of BAMS, emphasizing the *Molecules* and *Cell Types* modules. For detailed description of BAMS *Connections* and *Relations* modules see Bota et al. 2005.

The *Molecules* module allows insertion of quantitative and qualitative attributes as identified using radioactive tracers, immunohistochemistry, or gene expression. It also includes a comprehensive schema for metadata representation (see Figure 1). A full description of this module can be found in Bota & Swanson, 2006.

2. BAMS: web interface

BAMS interface was designed to handle data and metadata in different ways, and is organized in modules, matching the structure of the backend database of the system.

2.1 BAMS Menu - Main Features

The options for online search and manipulation of data and metadata can be found in the **Menu** of BAMS, which has the following structure:

Search Brain Parts by

Name Species Nomenclature

References

Cells

Molecules

Evaluate Connections Reports Outputs Inputs Nomenclatures Networks of Brain Regions

3. Searching for information in BAMS

3.1 Search Brain Parts by Name

The search of brain parts by name (direct link:

<u>http://brancusi.usc.edu/bkms/brain/search_bname_con.php</u>) can be performed in four different ways: search name of brain regions, search of abbreviations of brain regions, choosing an abbreviation from a scroll-down list and full text string search, as shown in Figure 2.

Search brain parts by name	Partial string match Search! Reset	
Search brain parts by abbreviation	Partial string match Search! Reset	Choose an abbreviation 6a 🔹
	Full text search Search! Reset	

Figure 2. The options of search brain regions by string match with their name, abbreviations, and full text search of their descriptions.

The general result of any search of brain regions by string match is similar to that shown in Figure 3. It includes the name, type (gray matter, fiber tract, or ventricle) and abbreviation of retrieved brain parts, the nomenclature and the version used to identify those, species (strain),

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	-	-	-				1
Brain Part	Type Abbreviation Nomenclature version Species General Description					General Description	BAMS associated information
Bed nuclei of the stria terminalis	of the stria gray matter BST Swanson Swanson-1998 Rat According to Ju and Swanson 1989.						projections molecules
Bed nuclei of the stria terminalis	f the stria gray matter BST Swanson Swanson-2004 Rat Based on extensive connectional data (see Dong et al. 2001; and Dong and Swanson, in preparation) we have simplified the nomenclature originally propo by Ju and Swanson (1989). In essence, the anterodorsal, anteroventral, and dorsolateral areas of the anterior division have been combined into an anterom area, and the subcommissural zone has been merged with the anterioral and of the anterior division. In addition, the rostral end of the principal nucleus the been added to the anteromedial race, and the principal nucleus the posterior division has been assigned to the interfascicular nucleus instead					Il projections	
Bed nuclei of the stria terminalis	gray matte	erBST	Swanson	Swanson-1992	Rat	None provided	
oed nucleus of the stria terminalis	gray matte	er BST	Paxinos	Paxinos/Watson-1998	Rat	No description provided. The nomenclature was adapted from atlas, pages 150- 159	-
bed nucleus of the stria terminalis	gray matte	er BST	Mai	Mai-1997	Human	No description provided. The nomenclature was adapted from the atlas, pages 313-328	
Bed nucleus of the stria terminalis	gray matte	er BST	Hof	Hofet al2000	Mouse	No description provided.	
Bed nuclei of the stria terminalis	gray matte	er BST	Dong	Dong-2007	Mouse	No description provided	
Bed nucleus of the stria terminalis	gray matte	er BST	Moga	Moga-1989	Rat	The bed nucleus of the stria terminalis (BST) is a rostral forebrain structure closely related to the amygdala, its major source of afferent input (Weller and Smith, 1982; De Olmos et al., 1985).	1
Bed nuclei of the stria terminalis	gray matte	er BST	de Olmos	de Olmos	Rat	generally classified as a member of the caudal group of septal nuclei. The BST forms the floor of the lateral ventricle and is bounded dorsomedially by the ventral aspect of the lateral septal nucleus, and laterally by the internal capsule which separates it from caudate-putamen and globus pallidus (Figs. 3A; 4A; 5A, B, C; 6A to E; 7F). Caudally, it is successively bounded by the stra medularis and in part by the columns of the fornix. Rostrally, it is bounded by the successive, with ventrally it merges with the preoptic area. Collator note: this term is not captured in a hierarchy; its subparts are components of the different amygdaloid nuclei.	
Partial matches:							
Brain Part	Туре	Abbreviation	Nomenclature	Nomenclature version	species	General Description	BAMS associated information
Bed nuclei of the stria terminalis oval nucleus	gray matter	STov	Swanson	Swanson-1998 F	Rat	According to Ju and Swanson 1989.	cells projections molecules
Bed nuclei of the stria terminalis	gray E	ISTju	Swanson	Swanson-1998 F	Rat	According to Ju and Swanson 1989.	cells projections

Figure 3. The result of search by brain parts by abbreviations. In this example, the searched string was "BST". The retrieved records of brain parts are associated to the part type, abbreviation, nomenclature and its version, species,

description that usually includes the definition of the brain part, according to the authors nomenclature. Additionally, this page includes a metadata field called "BAMS associated information" which summarizes the types of data and metadata that are registered in the system and are associated with the retrieved part.

The retrieved list of brain parts is organized according to two criteria. The first listed are those brain parts that match exactly the searched string. Inside of each of the two sets of records (exact matches and partial matches), the first listed are those regions that are associated to cell, molecules or connectivity information in BAMS.

The result of free text search is split in two steps. The first step retrieves those nomenclatures and nomenclatures versions that include brain parts with names partially matching or descriptions where searched text was found. An example is shown in Figure 4.



Figure 4. The list of nomenclatures and their versions (Atlas/Version), arranged by species, which include brain parts that have in the term "amygdala" in their description.

This additional step was introduced just to reduce the number of records, which can be big for strings like "amygdala", and thus increasing the processing and display time for each user. Once a nomenclature is chosen, the associated set of results will be posted as shown in Figure 5.

Name of Structure	Type of Structure	Abbreviation	Species	Atlas	Atlas version	Reference	General Description	Inserted On:
<u>Olfactory</u> amygdala	gray matter	Olfactory amygdala	Rat	de Olmos	de Olmos	The rat nervous system. Volume I Forebrain and Midbrain	The olfactory amygdala is characterized by direct inputs from the olfactory bulb and reciprocal connections with other areas receiving olfactory input. In addition to afferents from the main olfactory bulb, all the nuclei of the olfactory amygdala receive afferents from the piriform cortex, entorhnal octrex, horizontal limb of the diagonal band locus coursieus and raphe nuclei. No other extra-smygdaloid area appears to project to all the olfactory amygdala. Efferents from all the nuclei in the olfactory amygdala project to the piriform cortex and fundus striati.	2007- 11-28
Amygdala	gray matter	Amygdala	Rat	de Olmos	de Olmos	The rat nervous system. Volume I Forebrain and Midbrain	on the basis of histochemistry and connectivity the amygdala can be divided into an "olfactory amygdala", a "medial amygdaloid group", a "basolateral amygdaloid group", and a "central amygdaloid group".	2007- 11-28
Intra-amygdaloid portion of the BST	gray matter	BSTIA	Rat	de Olmos	de Olmos	The rat nervous system. Volume I Forebrain and Midbrain	is a relatively cell-poor area located lateral to the dorsal part of the medial nucleus [of amygdala] and traversed by fibers destined for the stria terminalis. The BSTIA cells are medium sized, but are larger and stain lighter than those in the medial amygdala. The BSTIA corresponds to the intra-amygdaloid division of the BST described by Krettek and Price (1978 a, b).	2007- 12-03
lucleus of the olfactory tract	gray matter	LOT	Rat	de Olmos	de Olmos	<u>The rat</u> <u>nervous</u> <u>system.</u> <u>Volume I</u> <u>Forebrain</u> and Midbrain	is a conspicuous ovoid collection of neurons creating an eminence on the surface of the rostromedial pole of the amygdala just at the caudomedial end of the main body of the lateral offactory tract (Attas, [Paxinos and Vlatson, 1982] Figs 17 and 18). It is surrounded by a superficial extension of the anterior amygdald which separates the LOT from the offactory tubercle rostrally, the anterior corrigation nucleus laterocaudally, and the bed nucleus of the accessory olfactory tract and medial amygdala caudomedially. In Niss1 sections, three layers can be recognised in the LOT: a molecular layer (1), a superficial dense cell layer (2), and a deep multiform cell layer (2). Layer 1 contains few scattered small to medium sized cells. Layer 2 consists of a circumscribed oval cell aggregate composed of tightly packed, deeply staining, medium sized pramidal neurons. Layer 3 is formed by slightly larger, more loosely arranged multiangular cells which cover the top of layer 2 like a cap. In Colgi preparations, the rounded apperaance of this nucleus separates the clearly from neighboring structures. Its neuronal population is made up in its greater part of pyramidal and modified pyramidal cells, but also include stellate cells.	2007- 11-28
Posteromedial sortical amyqdaloid tucleus	gray matter	РМСо	Rat	de Olmos	de Olmos	<u>The rat</u> <u>nervous</u> <u>system.</u> <u>Volume I</u> <u>Forebrain</u> <u>and Midbrain</u>	constitutes the caudal third of the superficial amygddla lying posterior to the Me and caudomedial to the PLCo (Fig. 3E, F). The posterior limb of the amygdaloid fissure signals superficially its separation from the caudomedial tail of the AHI and from the ventromedial transitional entork(NHEnL). Dorsally, its capped almost completely by the remainder of the AHI and the hippocampal formation. In cell preparations, the PMCo appears as a homogeneous, relatively well circumsribed ovoid mass of small and medium sized, palely staining cells which is separated from the pial surface by a molecular layer. The existence of an incipient stratification in the PMCo is consistent with the earlier neurogenesis of the superficial cells (E15-E16) as compared with the deeper lying ones (E16-E17) (Bayer, 1980). In Golgi preparations, the PMCo (Fig. 7E), like the other two cortical subnuclei, consists of amajority of modified pyramids, it is possible to find fusiform and polymorph (stellate) cells generally located in the depth of the nucleus. The PMCo corresponds to the amygdal superficial cells's superficial cells (e10-E40), and to the posterior cortical nucleus of Yu (1980), the posterior cortical nucleus of Krettek and Price (1978b), and to the posteromedial cortical nucleus of Turner and Zimmer (1984).	2007- 12-03
<u>Basolateral</u> amygdaloid group	gray matter	Basolateral amygdaloid group	Rat	de Olmos	de Olmos	<u>The rat</u> nervous system. Volume I Forebrain	On the basis of cytoarchitectural, fibroarchitectural and chemoarchitectural criteria, four major nuclei can be recognized as constituents of the basolateral amygdaloid group: lateral (La), basolateral (BL), ventral basolateral (BLV) and basomedial (BM). This heterogeneous assemblage of neurons occupies 48.8% of the total volume of the rat amygdala (Herzog, 1982).	2007- 12-03

Figure 5. The list brain parts that have in their description the term "amygdala", and are associated with "de Olmos" brain nomenclature. See text for details.

The table shown in Figure 5 includes two types of links: one that is associated with the retrieved brain parts, and one associated with the cited reference. The link associated with the cited reference leads to a page that displays details about it, which includes URL to the Pubmed abstract, if the reference is an article published in journal indexed by this database.

The link associated with the retrieved brain parts leads to a page that summarizes the data and metadata associated in BAMS. The example shown in Figure 6 represents a summary of the data and metadata associated with a nucleus of the rat paraventricular hypothalamic nucleus, identified in the Swanson-1998 nomenclature. The minimal displayed information is the list of identical terms identified in other species/nomenclatures and the definition, and the reference details of the brain part, which can be accessed by clicking on the button "More". An example of the metadata that can be accessed through the "More" button is shown in Figure 7. This includes the criteria used to include the associated brain part in an internally consistent hierarchy.

If the retrieved brain part is captured in a hierarchical tree, then the tree of super-parts (parents) including it and the set of substructures 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 the root (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. 6.

		Same term found in other nomenclatures	
Details about PVHmpd.	More <u>Tree</u>	Open list	Help?
Hierarchy level in atlas Swanson, vers	sion Swanson-1998 is 8: 7 superstructures include it.		
Tre	ee of Paraventricular nucleus of the hypothalamus	, parvicellular division, medial parvicellular part, dorsal zone	
Bra	in		
	Brainstem		
No other subparts of	Interbrain		
No other subparts of	Hypothalamus		
PVHmpa.	Periventri	cular zone of the	
	<u>nyp</u>	otnalamus Demostrationales estates	
		Paraventricular nucleus of the	
		Paraventricular nucleu	is of the
		hypothalamus, parvicellu	lar division
	Call acculations		
motor neuroen	decrine manageallular vasapressin neuron	Cnemoarchitecture	
motor neuroen	docrine magnocellular CDH neuron	releasable by neurons cell associated	
motor neuroen	docrine parvicellular TPH neuron	corticotropin-releasing hormone Enzymes	
motor neuroen	docrine parvicellular SOM neuron	enkephalin source and a second	
descending ne	euron sympathetic system	neurotensin	
descending ne	uron sympathetic/parasympathetic system		
		methionin enkenhalin	
		melanin-concentration hormone	
		hypocretin/orexin	
		angiotensin II	
	Complete ch	emoarchitecture profile	
1 2 2 2 1 1 1 2 2 2 2 2 2 2 2 2 2 2 2 2			
Efforcet projections of Dereventricula	s sucheus of the hypothelemus, pasylocillular division, me	lial Affarant projections to Dereventricular sucleus of the hypothelemus, particulated	livision modial
parvicellular part, dorsal zone	i nucleus of the hypothalamus, parvicellular division, me	Aneren projections to Paraventricular nucleus or the hypothalamus, parvicellular o parvicellular part, dorsal zone	invision, medial
	Afferent projections tra	nslated from other nomenclatures	

Figure 6. The output page that summarizes the data and metadata associated to a brain part in BAMS. See the text for detailed explanation of each displayed category.

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 catecho- laminergic cells in the hypothalamus of the mouse.	Mihail Bota
The hierarchy of the Bota is not endorse	e Hypothalam ed by the auth	us was construc for of the nomenc	ted partiall lature.	y from the information	found in the associate	d reference, as w	ell as using additional criteria.The approach used b	y the collator <u>Mihail</u>
Collator argument	The hier Watson 1	archy of this re 1998 and Simerly	gion was o 1995. See	constructed using the also Swanson 1992.	e rat atlas Paxinos an	d Reference	Same as for the associated structure s Anatomical substrates of hypothalamic integratio	n (1995) *
							*: the reference was used by b	oth collator and author

Figure 7. The details about a brain region of interest that can be accessed by clicking on the button "More" shown in Fig. 6. The displayed metadata include the description (definition) of the region, and the method of including it in a internally consistent hierarchy.

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 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. 6) also includes links to several BAMS inference engines associated with the *Cells* and *Molecules* modules. Each of these inference engines will be discussed below.

Search of brain parts can be performed in two additional ways (see the general structure of the Menu, page 4): search parts by species (direct link <u>http://brancusi.usc.edu/bkms/brain/search_bspecies.php</u>), and search by nomenclature (direct link <u>http://brancusi.usc.edu/bkms/brain/search-nomenclature.php</u>).

The interface for search brain parts by species lists the distinct species, or genera, which are recorded in BAMS. So far, there are five distinct species (genera) recorded in BAMS: human, macaque (general), Macaca fascicularis, cat, rat, and mouse. The various rat and mice strains are displayed in the output pages of different queries. As for the free text search option, the result of search by species is first limited by the nomenclature, and this type of encoding was made for the same reason: the reduction of time of processing of queries, which can become important if the computational load is big. Different of the free text search, the intermediary step of choosing a nomenclature includes graphically encoded metadata, that specify whether a nomenclature is hierarchically organized, and its brain parts are associated with connectivity reports. An example is shown in Fig.8, which is the display of nomenclatures associated in BAMS with species rat.



Figure 8. The intermediary step of choosing a nomenclature, which is a part of the query of search of brain regions by species. The nomenclatures that are hierarchically organized and include brain regions that are associated with connectivity reports, are graphically labeled (italics fonts, and font color green, respectively).

After a nomenclature is chosen, the system returns the brain parts included in it, alphabetically arranged. If the nomenclature includes more than 50 terms, then the returned page will include only the first 50 ones, an alphabetical index, and a search by name option. The structure of this output page was designed in such way that will be processed and displayed as fast as possible. An example of the output of search brain parts by species is shown in Figure 9.

Species: Rat, Atlas: S	wanson, Re	ference: Brain	n Maps: Structure of the Rat Brain
Your search	h will retriev	ve more than	50 names. You may want to narrow the search, or view the names of brain structures alphabetically.
Search by name of structure Sea	rch!		ABCDEFGHIJKLMNOPRSIUVZ
	-	The first 50 st	ructures retrieved by your query. Click on any below to see details about them
Name of Structure	Type of Structure	Abbreviation	General Description of Brain Part
Abducens nerve	fiber tract	VIn	According to Hebel and Stromberg 1986
Abducens nucleus	gray matter	VI	According to Glicksmann 1980.
Abducens nucleus proper	gray matter	VI_p	This is the remaining part of the abducens nucleus after eliminating the accesory abducens nucleus
Accesory abducens nucleus	gray matter	ACVI	According to Szekely and Matesz 1982.
Accessory facial nucleus	gray matter	ACVII	According to Szekeley and Matesz 1982.
Accessory olfactory bulb	gray matter	AOB	According to Gurdjian 1925, Shipley et al. 1996.
Accessory olfactory bulb, glomerular layer	gray matter	AOBgl	None provided
Accessory olfactory bulb, granular layer	gray matter	AOBgr	None provided



The result of search of brain regions by nomenclature is very similar to that of search by species (Fig. 9). The option of search is made of a pull-down list of available nomenclature versions, as shown in Figure 10.



Figure 10. The list of neuroanatomical nomenclatures included in BAMS, arranged in a pull-down list, which can used for brain parts searches.

3.2 Manipulation of neuroanatomical projections in BAMS

Neuroanatomical projections are modeled in BAMS by a complex backend database schema that includes more than 40 variables (Bota et. al. 2005). The interfaces that have been developed range from simple display of experimental data and metadata, to inference engines that construct possible brain regions networks, or qualitatively translate projection reports across different nomenclatures.

The simplest way to view the pattern of connectivity of a brain region is to search for it (see section 3.2), and the result of the search will be a page similar to Fig. 6. If the brain region is associated with projections reports in BAMS, then two links become available to the user: "Efferent projections to" and "Afferent projections from".

The link "Efferent projections to" becomes visible to the user whenever the brain region is associated with projections reports that originate from it and terminate in other regions. The output page of this link will list all brain regions that receive neuroanatomical projections from the region of interest, and are recorded in BAMS. If the associated brain nomenclature is hierarchically organized, then the list of inputs will be organized accordingly. An example of such output is shown in Fig. 11.

List of regions which receive projections from: PVHmpd	Target region	Number of reports	Collator(s)
Paraventricular nucleus of the thalamus (PVT)	PVT	1	Larry Swanson
Lateral hypothalamic area (LHA)	LHA	1	Larry Swanson
Medial preoptic nucleus (MPN)	MPN	2	Larry Swanson
Dorsomedial nucleus of the hypothalamus (DMH)			
Periaqueductal gray (PAG)	DMH	1	Larry Swanson
Dorsal motor nucleus of the vagus nerve (DMX)	PAG	1	Larry Swanson
Median eminence (<u>ME</u>)	DMX	1	Mihail Bota
	ME	1	Mihail Bota

Figure 11. The hierarchically organized list of brain regions that receive projections from the rat PVHmpd, identified in the Swanson-98 nomenclature, together with associated number reports in BAMS and collators.

The output page does not only display the list of regions that receive projections from the brain region of interest, but also the associated number of reports and collators. Clicking on the link associated with the target region abbreviation will lead the user to the summary page shown in Fig. 6. Clicking on the buttons included in the right-hand side table, under the field "Target region" will bring details about the target region, as shown in Fig. 7. The details of connectivity reports that are associated to each target region can be accessed by clicking on the buttons under the field "Number of reports". The details of the projection from the rat PVHmpd to the median eminence (ME) are shown in Figure 12.

	Details about	ut the neuro	anatomical p	projections f	from PVHmpd to I	ME	
Sending structure	Receiving structure	Projection strength	Type of connection	Technique	General description	Collator	Associated reference
Paraventricular nucleus of the hypothalamus, parvicellular division, medial parvicellular part, dorsal zone	Median eminence	light	not known	bisbenzimide	Collator note: see Figure 1 page 192.	Mihail Bota	Swanson L.W, Sawchenko P.E., Wiegand S.J. & Price J.L., 1980

Figure 12. Projection reports details that can be accessed by clicking on the buttons that display the numbers of reports, shown in Fig. 11. Displayed metadata include the assessed qualitative strength of the projection, the connection type (in terms of neurotransmitters), the used technique, an annotation which can be used to associate the text most relevant to the presence or absence of the projection, the collator's name, and the associated reference. If the reference is a published journal article, the URL to the PubMed abstract will also be displayed.

The link "Afferent projections from" shown in Figure 6 becomes available when the brain region of interest is associated in BAMS with reports of regions that send neuroanatomical connections to it. The display of sources that project to the brain region of interest and of the associated metadata is very similar to Figs. 11 and 12.

Whenever a brain region, captured in a hierarchy, is composed of subparts, and at least one of these is associated with connectivity reports in BAMS, then two additional links become available in the summary web page (Fig. 6): "Inferred efferent projections", and "Inferred afferent projections" (Fig. 13).

Details about PVH. More Tree	Same term found in other nomenclatures gOpen list <u>Help?</u>
Hierarchy level in atlas Swanson, version Swanson-1998 is 6: 5 superstructure	s include it.
Major Subparts	Tree of Paraventricular nucleus of the hypothalamus
Part Type Paraventricular nucleus of the hypothalamus, descending division gray matter Paraventricular nucleus of the hypothalamus, magnocellular division gray matter Paraventricular nucleus of the hypothalamus, parvicellular division gray matter	Brain Brainstem Interbrain Hypothalamus Periventricular zone of the hypothalamus
Inferre	d chemoarchitecture profile
Efferent projections of Paraventricular nucleus of the hypo	thalamus Afferent projections to Paraventricular nucleus of the hypothalamus
Inferred efferent projections of Paraventricular nucleus of the hyper	othalamus Inferred afferent projections to Paraventricular nucleus of the hypothalamus

Figure 13. The BAMS page that displays summary information about the paraventricular nucleus of the hypothalamus (PVH). If a brain regions, such as PVH, is made of a set of subregions, and at least one of these is associated with reports of efferent or afferent projections, then two additional links will become available to the user: "Inferred efferent projections" and "Inferred afferent projections". These links lead to pages that reconstruct the output, and input respectively", projections patterns of the brain region (PVH) from the projection reports associated to its subregions.

The output pages of either of these links reconstruct in tabular formats the connectivity patterns of the brain region of interest from the connection patterns of the component subparts. The inferred pattern of inputs to the rat PVH is shown in Figure 14.

Receiving Sending	PVHpv	PVHmpd	PVHap	PVHp	PVHpml	PVHpmm	PVHpm	PVHam	PVHf	PVHlp	PVHdp	PVHmpv	PVHd
BST	2	1	1		1	1		1	7	1	1	1	
BSTal	1	1	5		1	1		1	3	2	2	1	
BSTov	2	2	2		1	1		1	2	2	2	2	
BSTrh	2	1	1		1	1		1	1	1	1	1	
BSTdm	8	4	6		4	2		2	2	2	4	2	
BSTfu	5	5	3		1	1		1	2	2	3	2	
BSTv	8	6	4		2	2		2	2	2	4	2	
BSTmg	10	6	6		4	2		2	2	2	4	2	
BSTpr	10	4	5		1	1		2	1	1	1	1	
BSTif	1	1	1		1	1		1	1	1	1	1	
BSTtr	1	1	1		1	1	2000	1	1	1	1	1	
PSCH	2	1	1								1	1	
MEPO	2	3	2	-	2	2	1	2	1	2	2	3	
AVPV	2	2	2	1	1	1	2	1	1	2	2	2	
AAA													1
CEAI	1	1	2		1	1		1	1	1	1	1	1
MEAad			1						10000				1
MEApv			1										1
DMH	3	3	3	-	1	1	1	2	2	3	3	3	
MPN	2	1	1		1	1		1		1	1	1	
MPNI	1	1	1	1			1			1	1	1	
MPNm	1	1	1	1			1		1	1	1	1	
MPNc	1	1	1	1			1			1	1	1	
ADP	2	2	2	1	1	1	2	1	1	2	2	2	
AVP	2	2	2	1	1	1	2	1	1	2	2	2	
PS	2	2	2	1	1	1	2	1	1	2	2	2	
AHN	2	2	2	1	1	1	1	1		2	2	2	
AHNa	1	1	1	1	1	1		1	1	1	1	1	
AHNc	1	1	1	1	1	1		1	1	1	1	1	
AHNp	1	1 1	1	1	1	1		1	1	1	1 1	1	

The pattern of inferred afferent projections of the Paraventricular nucleus of the hypothalamus

Figure 14. The inferred afferent pattern of projections of the PVH, online reconstructed in BAMS. The pattern is displayed in a tabular format. Numbers in boxes represent reports about a specific projection (present or absent). The empty cells of the matrix represent lack of information about those particular projections.

3.3. Construction of brain regions networks in BAMS

The web interface of BAMS allows online construction of brain region networks from recorded connectivity reports.

The first way of creating brain regions networks is to use the "Outputs" option from the Menu (path: Menu \rightarrow Evaluate \rightarrow Connections \rightarrow Outputs). This option will first create the matrix of output connections of a set of brain regions that is chosen by the user. Therefore, users have to choose the set of brain regions of interest from the set of all regions that are recorded in BAMS with at least one projection. In order to do this,

they first have to choose the brain nomenclature they will be working with, from the list displayed by the system (Fig. 15).



Select from the table below a nomenclature used to identify neuroanatomical projections

Figure 15. The set of brain nomenclatures, from which the user has to chose in order to construct the connectivity matrix of interest.

Once the nomenclature is chosen, the system will display all the brain regions that are associated with efferent projections reports in BAMS, in a tabular checkboxes format as shown in Fig. 16.

	and the	Pl	ease cho	ose up t	to 100 re	gions def	fined in	nomencl	ature Swa	anson-19	98 and a	ssocia	ted with e	efferent p	rojectio	ons repo	orts:		
	ACA	ACAd	ACAv	АСВ	AD	ADP	АНА	AHN	AHNa	AHNc	AHNd	AHNp	Ald	Alp	Alv	AM	AMBd	AMd	AM∨ □
AOB		AP		ARH	AT Anter	odorsal preopti	ic nucleus	AV			в	BA	BLA	BLAa	BLAp	BMAa	BMAp	BST	BSTad
BSTal	BSTav	BSTdm	BSTfu	BSTif	B STju	BSTmg	BSTov	BSTpr	BSTrh	BSTsc	BSTtr	BSTV	CA1	CA1sp	CA2	САЗ	СВ	CEA	CEAc
CEAI	CEAm	CL	CLA	СМ	соа	СОАа	COApl	COApm	сом	СР	cs	C SI	CSm	CUN	DCO	DG	DGIb-po	DGIb-sg	омн
DMHa	омнр			DR		ЕСТ			ENTI1-6	ENTm	ENTm1-6	EP	EPd	EPv	FF	FN	FS	GP	GPI
GPm		HIP	HPF	нү		IC	IF	IGL					10	IOda	IOma	IOpr	IP		IPNa
IPNc			IPNr	isl	KF	LA	LAV	LC			LGd	LGv	LGvi	LGvm	LH		LM	LP	LPO
	LS	LSc	LSc.v	LSc.v.i	LSc.v.l.d	LSc.v.l.v	L Sr	LSr.dl	LSr.dl.l.d	LSr.m.d	LSr.m.v	LSr.vl	LSr.vl.d.l	LSr.vl.d.m	LSv	ма		мво	MD
MDc		MDm		MEA	MEAad	MEAav	MEApd	MEApd-a	MEApd-b	MEApd-c	MEApv	меро	MG	мм	мо	мов	МОр	MOs	moV
MPN	MPNc		MPNm	мро	мрт		M S	мт	MV	NB		NI	NIC	NId	NIS		NOT	NPC	NR
NTS	NTSm	OP			ORBm			от	ov	PA		PAG	PAGd	PAGdI	PAGm	PAGrm		PAR	РВ
PBG	РВІ	PBIc	PBId	PBle	PBIs		PBmm	PCG	PD		PF	PG		РН		PIR3	PL	PMd	PM∨
PO	POR	POST	PP	PPN	РРТ Г	PRC	PRE		PRNc	PRNr			PS	РЗСН	РТ	PVa	РVН □	PVHam	PVHap
PVHdp		PVHmpd	PVHmpv	PVHpm	PVHpv		PVp	PVpo	PVT	R	RA	RCH	RE	RER	RERd		RH	RL	RM
RN	RPO	RR	RSP	RSPagi	RSPd	RSPv	RSPv-a	RT	SBPV	sc	SCdg	sсн □	SCig	SCig-a	SCig-b	SCig-c	SCsg	SF	SFO
SG	sн □	sı	SLD	SMT	SN	SNc	SNr	so	SOr	SPF	SPFm	SPFp		SPVC	ss	SS-bfd	SS-II	SS-m	SS-tr
SS-ul	S Sp	STN	SUB	SUBd	SUBv	suм	suмі □	SUMm	suv		тн	тм	TR		πd2	TU		vi L	
vis	VISal	VISam	VISIm	VISp	VMH	VMHa	VМНс	VMHdm	VМН∨I	VNC	VP	VPLpc	VPMpc	VTA	VTN	×	y T	z	zı
					18. 19. 19				Submit	Reset									

Figure 16. Once users choose a brain nomenclature, the set of brain regions that are associated with efferent projections reports are displayed checkboxes labeled with the regions' abbreviations. The name of each brain region will be displayed if the mouse is over the abbreviation. Users can choose up to 100 regions, to create the matrix of interest.

Once the user chose the set of brain regions of interest, the system will display all the regions that receive connections, and are recorded in BAMS. The user can choose of subset from these targets, or all of them. Once these regions have been chosen, the system will create the corresponding matrix of projections in a tabular format. Figure 17 shows the connectivity matrix between several amygdalar nuclei and the components of the bed nuclei of the stria terminalis (BST), all of them identified in the rat nomenclature Swanson-1998.

										(Complete outp
			The r	econstr	ucted c	onnecti	vity ma	trix:			
Sending	AAA	BLAa	BLAp	BMAa	BMAp	CEAc	CEAI	CEAm	COAa	COApl	COApm
Receiving				1							
BSTad	1		1	2	2	1	3	1	1	2	1
BSTal	1		1	2	2	2	5	1	1	2	1
BSTav	1		1	2	2	2	2	1	1	2	1
BSTd	1		1	2	2	1	2	1	1	2	1
BSTdl	1		1	2	2	1	2	1	1	2	1
BSTdm	1		1	2	2	1	2	1	1	2	1
BSTfu	1		1	2	2	2	3	1	1	2	1
BSTif	1		1	2	2	1	2	1	1	2	2
BSTju	1		1	2	2	1	2	1	1	2	1
BSTov	1		1	2	2	1	3	1	1	2	1
BSTpr	1		1	2	2	1	2	1	1	2	1
BSTrh	1		1	2	2	2	2	1	1	2	1
BSTsc	1		1	2	2	2	2	1	1	2	1
BSTtr	1		1	2	3	1	2	1	1	2	2
BSTv	1		1	2	2	1	3	1	1	2	1
								2			
ne matrix	Exist	tence of	connec	tions	Maxin	num str	ength (color co	ded)	Extend	d this network
ill it		Eva	luate			E	valua	te		E	Extend

Figure 17. The user-created matrix of projections of several nuclei of the rat amygdala to the parts of the BST. Users have several options of further processing and organizing this matrix, trough the buttons displayed.

The reconstructed connectivity matrix shown in Figure 1 is similar with the matrix shown in Figure 14, with empty elements that mean lack of information about that particular connection. Details about each of connection (each element of the matrix) can be accessed by clicking on the corresponding buttons. As in Figure 14, the numbers displayed on each button mean the number of reports associated with a particular connection. This output display includes several options for further processing and display of projections

data. The button "Fill the data" becomes available whenever there is an empty cell in the reconstructed matrix. In this situation, the system will attempt to fill the "missing" information with connectivity data translated from other nomenclatures. The button "Existence of connections" will re-display the reconstructed connectivity matrix in a Boolean fashion: existent projections, absent projections and "missing" information. The "Maximum strength" button leads to a page that re-evaluates the matrix in terms of qualitative assessments of connections reports. This matrix will also be reordered if the brain regions are captured in a hierarchy. The color coded matrix from Fig. 17 is shown in Fig. 18

Color coded projections matrix (maximum strengths)



Source COAa COApl COApm BLAa BLAp BMAa BMAp CEAc CEAl CEAm AAA

Fig 18. The matrix of outputs of several amygdalar nuclei to BST, graphically displayed as qualitative assessments of projections strengths. The matrix is also rearranged according to the hierarchy of the rat brain nomenclature Swanson-98.

The button "Complete output", shown in Fig. 17, leads to the page that will display the output matrix of the chosen set of brain regions with all brain regions included in the associated nomenclature. The processing

time of this matrix can be significant, especially if the set of chosen output regions is large, and the computational of the server is high.

Finally, the button "Extend this network" shown in Figure 17 becomes visible whenever the set of target regions is associated in BAMS with reports of their efferents. Thus, this button allows users to create networks of brain regions from the inserted connectivity reports. Clicking on this button will retrieve those brain regions that receive projections from the targets shown in Figs. 17 and 18. Therefore, this set of targets becomes the second set of outputs for the brain regions shown in Fig. 19.

a any number etructures from the list of 201 targets

												-							
ACB		AD	ADP	AHA	AHN	AHNa	AHNc	AHNp	Ald	AMBd	AMBv	AMd	AONm	ARH	ASO	AV	AVP	First station	Seconstation
AVPV	В	BSTcc	BSTse	CA1	CA1spd	СЦ	СМ	сом	СР	CSm	DMH	DMHa	DMHp	DMHv	DMX	DR	ENTMV	AAA	BSTad
																		BLAa BLAp	BSTal
ENTI1- 6	EPd	EW	FS	GPI	GRN	IAM	IF	ILA	IMD	ISN	KF	LA	LC	LDT	LH	LHA	LPO	BMAa BMAp CEAc CEAI	BSTdl BSTdl BSTdm BSTfu
LSN	LSc.d.l	L.Sc.v.i	LSc.v.l.d	LSc.v.l.v	LSc.v.m.d	LSc.v.m.v	LSr	LSr.dl.l.d	LSr.dl.l.v	LSr.dl.m.d	LSr.dl.m.v	LSr.m	LSr.m.d	LSr.m.v.c	LSr.m.v.r	LSr.vl.v	LSv	CEAm	BSTif
																		COAa	BSTju
LTN	MA	MARN	MDRNd	MDRNv	MDm	MEA	MEAad	MEApd-a	MEApd- b	MEApd-c	MEApv	MEPO	MEV	MH	MM	MPN	MPNc	COApm	BSTov BSTpr BSTrh BSTsc
MPNI	MPNm	MPO	MRN	ND	NDB	NLL	NT Sce	NT Sco Nucleu	NT Sge	NT SI	NT Sm	NT Sm (c)	NT Sm (r)	OT1	OT2	OT3	ov		BSTV
PA	PAGd	PAGdi	PAGm	PAGrm	PAGvi	PARN	PBIc	PBId	PBle	PBlex	PBIi	PBIs	PBIv	PBme	PBmm	PBmv	PCG		
PD	PF	PGRNI	PH	PIR3	PL	PMd	PMv	PPN	PRC	PRN	PRNc	PS	PSCH	PT	PVHam	PVHap	PVHdp		
PVHf	PVHlp	PVHmpd	PVHmpv	PVHpml	PVHpmm	PVHpv	PVI	PVT	PVa	PVp	PVpo	RCH	RE	RECd	RECm	RECp	RERd		
RERI	RERm	RERv	RH	RL	RM	RO	RPA	RR	RS	SBPV	SCH	SCdg	SF	SFO	SI	SNc	SNr		
SO	SOr	SPFp	SPVI	S SN	STN	SUBv-m	SUMI	SUMm	SUT	TMv	TR	TTv3	TU	VMH	VMHc	VMHdm	VMHvi		
VTA	XII	ZI																	
			X		X			Sub	omit Re	set				Xa		X			

Figure 19. The screen that can be used to choose the third set of regions for creation of customized networks. This screen is very similar to the one shown in Fig. 16.

The network of regions that will be constructed by BAMS will be displayed in a tree-like format, with the first column made of the first station regions, the second made of the second station regions, listed for each of the first-order region. The third column, which is designed in the form of an expandable trees, called "Targets" in Figure 20. These trees are made of the third-order set of regions that receive projections from each of the second-order regions. Users have therefore the option of expanding only those trees with outputs of interest and view the associated details, which are provided through URL's. Figure 20 shows the example of the network constructed from regions used in Figs. 17-19, and a small set of motor output regions of the rat brain that are the targets of the BST nuclei.



Fig. 20. The network resultant from the matrix shown in Fig. 17 and the third set of regions chosen from the screen shown in Fig. 19. The first set of regions is made of several nuclei of the amygdala, the second from the BST nuclei, and the final from motor hypothalamic and brainstem regions that receive connections from the BST. The displayed links lead to pages that include details about retrieved projections.

This matrix organized in a tabular format as shown in Fig. 20 also includes a button called "Create graph" that will lead to a script which will construct the graphical version of it. The brain regions network shown in Figure 21 is thus the graphical version of the matrix constructed in Figure 20 and is constructed online.

This feature of BAMS, to construct online brain regions networks, from recorded in the backend database of the system, represents a unique feature it. BAMS is the first system that allows users to reconstruct the networks of the brain regions of interest.



Figure 21. The network displayed in Fig. 19, in a graphical format. This network can be saved by users in an image format (.png).

BAMS includes the options of creating user-customized projections matrices and networks, starting from the inputs of a set of regions of interest. The interface and method of constructing projection matrices and networks are very similar to those described above. The pathway of accessing "Inputs" is Menu→Evaluate→Connections→Inputs.

3.4. Inference of possible networks in BAMS.

A second way of creating online brain regions networks in BAMS is the "Networks" option of the Menu (pathway: Menu \rightarrow Evaluate \rightarrow Connections \rightarrow Networks). This method differs from the one described in the previous sections, in how the networks are created. A complete description of the employed inference engine and of the adopted formalism can be found in Bota et al., 2005.

The first step in creating possible networks of brain regions is to choose the brain nomenclature where the regions have been identified, or defined. Therefore, a screen very similar to Fig. 15 will ask the user to choose one of the nomenclatures associated in BAMS with projection reports.



Figure 22. Users have to choose the starting point of the inferred networks (a), the ending point of them (b), and the number of intermediary steps (brain regions) between them (c).

Once the nomenclature was chosen, users will have to choose the originating brain region (Fig. 22a), the final neuronal station of the network (Fig. 22b), and how many intermediary steps (layers of regions) will have the inferred networks (between 1 and 3; Fig. 22 c). After the originating and final stations, and the number of steps, were chosen, the system will display the inferred networks in a tabular format. If the connectivity data inserted in BAMS is not sufficient, the system will suggest the increase of the number of intermediary layers, or choosing another pair of brain regions. An example of the possible networks that can

Network	Originating Region	Intermediary Station 1	Intermediary Station 2	Final Station
1	R	AV	ACA	LHA
2	R	AV	RSP	LHA
3	R	AD	RSP	LHA
4	R	PVH	МРО	LHA
5	R	PVH	SCH	LHA
6	R	PVH	NDB	LHA
7	R	MEA	LSc	LHA
8	R	Medial nucleus of t	he BST	LHA
9	R	Amygdala MPO	ACB	LHA
10	R	МРО	MEPO	LHA
11	R	MPO	DMH	LHA
12	R	MPO	MPN	LHA
13	R	MPO PMd		LHA
14	R	МРО	MPO LPO	
15	R	MPO	LSr	LHA
16	R	МРО	LSv	LHA
17	R	MPO	SI	LHA
18	R	МРО	NDB	LHA
19	R	МРО	SN	LHA
20	R	МРО	VTA	LHA
21	R	МРО	PAG	LHA
22	R	МРО	PRC	LHA
23	R	MPN	BST	LHA
24	R	MPN	ACB	LHA
25	R	MPN	PVHmpd	LHA

be inferred between the retina (R) and the lateral hypothalamus (LHA), with two intermediary steps, is shown in Figure 23.

Figure 23. The first networks inferred between the rat retina and lateral hypothalamic area, with two intermediary layers. As with other displayed abbreviations, users can also view the CNS region name.

The projections reports associated with each of the inferred networks can be accessed by clicking on the buttons with the network numbers. An example of the data and metadata associated with each network is shown in Figure 24.

							Su	pport information for the inferred network				
R(Retina) — MPO(Media PRC(Precor	-→ MPO(M Il preoptic mmissura	edial pre area) — I nucleus	eoptic are → PRC(Pr s) —→ LH	a) ecomn A(Late	nissural ral hypo	nucle thalam	us) nic area)					
Support inf	ormation	about dir	ect proje	ctions	from Re	etina to	0 Medial	preoptic area:				
Sending structure	Receiving	Stre proj	ngth of jection	Type	e of ection	Techn	ique	General description	Collator	Associated reference		
Retina	Medial preoptic area	Medial preoptic exists i area		edial soptic exists rea		ts not kno		Cholera toxin conjugated to HRP		ase pg351,352, fig5a-f. Soma notes 36 female Sprague-Dawley rats weighing 00-350g. 10 microliters of CT-HRP(.20%40%) were injected into one eye ? ehind the lens into the vitreous chamber of the eye, pressure injection over min. Terminal notes in preoptic region ros. to SCN. lat. component of RHT abeled terminals and fibres within or lateral to the lateral haf of the medial recoptic area. Terminal label evident in ven. 1/2 of the lateral part of the edial preoptic area.	Gully Burns	Levine JD, Weiss ML, Rosenwasser AM, Miselis RR., 1991
Retina	Retina Medial preoptic area light/moderate not			not k	nown	Cholera onjuga HR	toxin b ted to 1 P d	ase pg348,349, fig5d-f. Soma notes 36 female Sprague-Dawley rats weighing 00-350g. 10 microliters of CT-HRP(.20%40%) were injected into one eye ? ehind the lens into the vitreous chamber of the eye. pressure injection over min. Terminal notes Medial component of the RHT included labeled fibres nd terminals found near the midline involved the medial half of the medial reoptic area?terminals evident in the anterior medial preoptic area Paper escribes a.m.p.a. as separate region .	Gully Burns	Levine JD, Weiss ML, Rosenwasser AM, Miselis RR., 1991		
Support inf	ormation	about dir	ect proje	ctions	from Me	edial p	reoptic a	area to Precommissural nucleus:				
Sending structure	Receiv	ving sure	Strengt project	h of tion	Type of connect	Type of Technique General description		General description	Collator	Associated reference		
Medial preoptic area	ial ptic nucleus ligh		light/mod	lerate	not kno	own	СТВ	In the preoptic regions, relatively sparse numbers of marked cells were observed in the median preoptic, anteroventral periventricular, medial preoptic, anterodorsal preoptic, anteroventral preoptic, and parastrial nuclei, as well as in the undifferentiated part of the medial preoptic area. In addition, a very few retrogradely labeled neurons were noted in the lateral preoptic area (Fig. 3C+F).	Mihail Bota	Canteras N.S.8 Goto M., 1999		
			5									
Support inf Sendin structu	ormation g re	about dir Receiving structure	ect proje Stren proje	ctions gth of ection	from Pr Type connec	of tion	missural Technique	nucleus to Lateral hypothalamic area: General description	Collator	Associated reference		
Precommis nucleu	sural hy	ral Lateral hypothalamic strong area		ong	not kno	own	PHAL	At the anterior hypothalamic level, ascending fibers coursing through the hypothalamus supply dense inputs to the anterior hypothalamic nucleus, subparaventricular zone, rostral retrochiasmatic area, and perifornical region of the lateral hypothalamic area in addition to a relatively sparse input to the other regions of the lateral hypothalamic area (Figs. 5D–G, 6B).	Mihail Bota	Canteras N.S. 8 Goto M., 1999		
Precommissural hy		al Lateral hypothalamic area light		nic light not known PHAL		PHAL	At the anterior hypothalamic level, ascending fibers coursing through the hypothalamus supply dense inputs to the anterior hypothalamic nucleus, subparaventricular zone, rostral retrochiasmatic area, and perifornical region of the lateral hypothalamic area in addition to a relatively sparse input to the other regions of the lateral hypothalamic area (Figs. SD-G, 6B).	Mihail Bota	Canteras N.S. 8 Goto M., 1999			
Precommis nucleu	sural s hy	Lateral pothalam area	ic lie	ht	not kno	own	PHAL	Proceeding rostrally, large numbers of fibers from the PRC reach the preoptic region, where they appear to provide a dense input to the lateral preoptic area in addition to a sparse input to the anteroventral preoptic nucleus (Fig. 5B,C).	Mihail Bota	Canteras N. S & Goto M., 1999		

Figure 24. Users can view details of each of the connections recorded in BAMS and used to infer networks. The
associated connections reports are listed for each component of the inferred network.

3.5 Handling molecule reports in BAMS

BAMS includes a fully developed *Molecules* module, which allows users to handle data and metadata in different ways. The knowledge representation schema of BAMS's *Molecules* module follows the general organization and presentation of experimental data in published neuroscience research articles. Any reference inserted in BAMS's *Molecules* module can be associated with multiple experiments. An experiment is defined as an experimental paradigm applied to a group of animals or human subjects. Each experiment may consist of several experimental series, which are defined by the specific procedures (for example, different antibodies or nucleic acid probes) that were applied. Each experimental series is associated with a set of experimental data that include mapped brain regions and measured variables. The conceptual design of BAMS's *Molecules* module completely separates experimental data from metadata collated from the reference, or inserted by collators. Metadata classes associated with data and experiments inserted in BAMS's *Molecules* module include: mapping, experimental series, experiment, data presentation, and physiological state. A complete description of this module can be found in Bota & Swanson, 2006.

The page that includes several ways of searching for information in molecules data and metadata is shown in Fig. 25, and can be accessed following the path Menu \rightarrow Molecules.

ecules releasable by neurons	Create reports from inserted experiment
acetylcholinesterase	
<u>angiotensin II</u>	
<u>aspartate</u>	Molecules comparison in brain regions
<u>corticotropin-releasing hormone</u>	Molecules comparison in brain regions
<u>dynorphin</u>	
<u>enkephalin</u>	
<u>GABA</u>	Search molecules presence by type of
<u>glycine</u>	manipulation
growth hormone-releasing hormone	
<u>hypocretin/orexin</u>	
<u>leucine-enkephalin</u>	
melanin-concentrating hormone	
<u>methionin-enkephalin</u>	
<u>neuropeptide Y</u>	
<u>neurotensin</u>	
<u>oxytocin</u>	
<u>somatostatin</u>	
<u>substance P</u>	
<u>vasopressin</u>	
Il associated molecules	
Receptors	
Enzymes	

Figure 25. The search options of molecules included in BAMS menu. Users can choose between the expandable tree constructed from the molecules registered in BAMS, in the left hand side of the screen, or any of the three options in the right hand of the screen.

Users can search for molecules either using the expandable tree on the left hand side in Fig. 25, or use one of the search options listed on the right hand half of the figure.

The expandable tree is created dynamically from the molecules classification schema included in the BAMS backend database. The links associated to each of the molecules captured in this tree leads to the list of central nervous system (CNS) regions that express it, and the corresponding physiological state of the animal. Clicking on the physiological state will retrieve the reports that state the presence of the molecule of interest in the brain region chosen by users. The list of brain regions (rat, Swanson-98 brain nomenclature) that express corticotrophin releasing hormone (CRH), the corresponding physiological states of the animals, and the data stating CRH presence in PVHmpd, manipulated state, are shown in Fig. 26.

Species: Rat																			
Parts where	Experimental	corticotropin-re	leasing horm	one in: PVHmp	d manipulate	d state								_					
CRH is present	condition manipulated state	Physiological condition	Cell pool position in region	Hemisphere	Qualitative density of CRH in PVHmpd	Labeled cells count	Percentage labeled cells	Average labeled cells	Standard deviation	Relative to basal	Annotation	Reference	Collator						
PVHmpd	basal state manipulated state	Chemical	everywhere	bilateral	not	808	40.50	0	not	not	Collator note: see Figure 2 page 168. The percentage of labeled cells was calculated using the numbers provided in the legend of Figure 2 and represents	<u>Swanson</u> LW, Sawchenko	Mihail Bota	Metadata 💙					
<u>PVHap</u>	manipulated state	colchicine Experiment I	CASE monit	29439 receiv	99429 monit	on all of	assigned				measured	measured	the ratio between the labeled cells in the associated region and the total number of labeled cells in this	PE, Rivier J, Vale WW, 1983					
<u>PVHm</u>	state	200 microgra	micrograms of colchicine		200 micrograms of colchici in the lateral ventricle 15								experiment.			123713			
PVHpm	manipulated state	hours befo	ore perfusion.								Collator note: experiment CRH/AVP, Table 3 page 506. Page 505: eighteen to twenty hours after an injection with	Watts, A.G.							
PVHmm	manipulated state	Chemical treatment: unclear colchicine	eatment: unclear pichicine	eatment: unclear olchicine	reatment: unclear colchicine	treatment: unclear colchicine		ient: unclear bilateral cine		not assigned	0	0.00	446	50.00	not measured	PEG, there was a significant 22% (P<0.01, Fig.1) increase of the CRH	& Sanchez- Watts, G.,	Mihail Bota	<u>Metadata</u>
<u>PVHam</u>	manipulated state										whicle-injected controls when measured using the 35S-cRNA probe.	1995		1					
	state manipulated state	Structural manipulation: ablation	not known	bilateral	exists	0	0.00	0	not	not	90% of the brightly labeled cells were found in the medial part of the parvocellular division. Collator note: see Figure 1b page 167. We assigned the	Swanson LW, Sawchenko	Mihail Bota	Metadata					
PVHdp	manipulated state	Manipulated structure: Adrenal gland		ulated ure: al oland					measured	measureu	CRH label as significantly higher than the normal state according to Swanson 1991 in Progress in Brain Research.	Vale WW. 1983		20					
<u>PVHmpv</u>	state	Chemical treatment:	everywhere	left hemisphere	very strong	0	0.00	0	not measured	significantly higher	Collator note: see Figure 2 page 6284 and Figure 3, page 6285.	Watts A.G. & Sanchez- Watts G., 2002	Mihail Bota	Metadata					
													immunohiste in situ hybri	ochemistry data idization data					

Figure 26. The result of search of CNS regions where CRH was identified. Users can view details of records associated with each retrieved CNS region, including qualitative density, cell counts, statistical measurements, spatial characteristics of cells expressing the molecule, and associated annotations by clicking on links associated with experimental conditions. For reports associated with manipulated state, users can also view type of manipulation, injected chemicals, and details about experimental procedure. Users may also access metadata associated with retrieved records. Records verified by original authors of collated references will also have a check mark associated with them.

The information that can accessed through the "Metadata" link, which is associated in Fig. 26 with each retrieved record includes all three major classes described in Bota and Swanson, 2006. The table with experimental method, anatomy and mapping metadata is shown in Fig. 27.

Experiment acronym	Annotation	Collator	Author checked
PS439	Mapping of CRH neurons in the ardrenalectomized rat brain.	Mihail Bota	no

Animals (subjects)	Experimental method
Sex: M	Experiment type: immunohistochemistry
Number of animals: 3	Neuron/glia identification method: not specified
Age: not specified	Staining frequency: 1:4 or 1:8
Mass: not specified	
Unit of mass: not specified	Experimental details:
Housing conditions: normal	Antigen: CRF
housing	Antigen species: sheep
Annotation: The third group	Source (producer): not specified
was bilaterally	Primary antibody: 24 ([Try22. Gly23]-CRF (1-23)
adrenalectomized and allowed	Primary antibody species: rabbit
to survive for 3 days, 1 month	Antibody type (monoclonal, polyclonal): polyclonal
and 2 months before perfusion	Secondary antibody: not specified
(n=3).	Secondary antibody species: not specified
* *	Immunoglobulin class: Alpha globulin
	Control: not specified
	Visualization method: fluorescence
	Visualization medium: slide
	Annotation: Seven different antisera to synthetic ovine CRF (or to a fragment
	of CRF), which were raised in rabbits [7], were tested and all but one were
	found to stain cells and fibers in the rat. Since antiserum 24 ([Try ²² . Gly ²³]-
	CRF (1-23) conjugated to human alpha-globulin with bis-diazetized
	benzidine] has been found to interact with rat CRF particularly well in
	radioimmunoassays [Vale, unpublished observations], it was used
	extensively for the mapping studies reported here.

Anatomy and histology

Section plane: coronal	Angle: not specified	Cutting method: Not specified	Preservation: freezing	Thickness: 30 micrometer						
Staining type: thionin	Sampling: 1:4 or 1:8	Annotation: In general, 1-in-4 or 1-in-8 serios of sections through the brain were stained for immunofluorescence. In addition, an adjacent series of sections from each brain was cut and stained with thionine.								

Mapping details

	Data presentation:								
	text								
Coordinates:	representative labeled	Mapping approach: brain region is captured in a BAMS							
none	images	nomenclature other than that used in the original publication							
	drawings or template								
	mappings of all sections								

Figure 27. Users can access experimental method, anatomy and mapping metadata, associated with retrieved experimental data.

The option "Create reports from inserted experiments" can be used to create composite tables with data from several references. This option will bring to the user the list of the molecules experiments that are registered in BAMS and are associated with the collated references. Users can choose any number of these, to create a composite table of the presence or absence of reported molecules. The interface that allows users to choose the experiments of interest is shown in Figure 28.

Create reports from inserted experiments		
Choose at least two experiments	Experiment acronym	
Sawchenko, P.E. & Swanson, L.W.: Immunohistochemical identification of neurons in the paraventricular nucleus of the hypothalamus that project to the medulla or to the spinal cord in the rat	Sawchenko-Swanson-1982	•
Watts A.G. & Sanchez-Watts G.: Interactions between helerotypic stressors and corticosterone reveal integrative mechanisms for controlling corticotropin-releasing hormone gene expression in the	Watts-normal	•
paraventricular nucleus	Watts-CRH (PEG)	
	Watts-CRH/AVP	
	Watts-CRH/NT	•
	Watts-CRH/pENK	
& Sanchez-Watts, G.: Physiological regulation of peptide messenger RNA colocalization in rat hypothalamic paraventricular medial parvicellular neurons	Watts-CRH/AVP(PEG)	
	Watts-CRH/pENK(PEG)	
	Watts-NT/pENK (PEG)	
	Swanson-1983(CRH)	
Iswanson LW, Sawchenko PE, Rivier J, Vale VWV: Urganization of ovine corticotropin-releasing factor immunoreactive cells and fibers in the rat brain: an immunonistochemical study	PS439	
Lind W.R., Swanson L.W. & Ganten D.: Organization of angiotensin II immunoreactive cells and fibers in the rat central nervous system	Swanson-All	
Wada, E., Wada, K., Boulter, J., Deneris, E., Heinemann, S., Patrick, J. & Swanson, L.W.: Distribution of alpha2, alpha3, alpha4, and beta2 neuronal nicotinic receptor sununit mRNAs in the central nervous system: a hybridization histochemical study in the rat	Wada-nAChR	

Figure 28. A subset of the molecules experiments recorded in BAMS. The experiments are grouped by reference, and users can choose any number of them, to create reports of presence/absence of molecules in different CNS regions (*see* text below and Fig. 29)

Once a set of experiments was chosen by users, the system will display data from all of them in a composite tabular format, together with reference information, as shown in Figure 29.

Selected experiments:												
Acronym: Sawchenko- in Sawchenko, P.E. & Swanson, L.W.: Immunohistochemical identification of neurons in the paravent							n the paraventricular					
Swanson-1982	reference	nucleu	s of the hyp	othalamu	us that pro	oject to th	ne medull	a or to th	e spinal	cord in the	rat Pubmed	
Acronym: Watts- normal	in reference	Watts A integra parave	latts A.G. & Sanchez-Watts G.: Interactions between heterotypic stressors and corticosterone reveal ntegrative mechanisms for controlling corticotropin-releasing hormone gene expression in the araventricular nucleus Pubmed									
Acronym: Watts-CRH (PEG)	in reference	Watts A integra parave	Vatts A.G. & Sanchez-Watts G.: Interactions between heterotypic stressors and corticosterone reveal ntegrative mechanisms for controlling corticotropin-releasing hormone gene expression in the paraventricular nucleus Pubmed									
Acronym: Watts- CRH/AVP	Watts, hypoth	Watts, A.G. & Sanchez-Watts, G.: Physiological regulation of peptide messenger RNA colocalization in rat hypothalamic paraventricular medial parvicellular neurons Pubmed										
Acronym: Watts- CRH/NT	in reference	Watts, hypoth	A.G. & Sancl alamic para	nez-Watts ventricula	s, G.: Phys ar medial	siological parvicelli	regulatio ular neuro	n of pept ons Put	tide mess omed	senger RNA	colocalization in rat	
					Compo	site data						
		PVHp	v PVHmpd	PVHap	PVHpm	PVHmm	PVHam	PVHf	PVHdp	PVHmpv		
	Оху	+	+	+	+	+	+	+	+			
	VAS	. +	+	+	+	+	+	+	+	+		
	SON	+	+	+	+	+		+	+			
	met ENk leu-El		+	+	+	+	+	+	+			
			+	+	+	+		+		1		
	CRH		+				-4.5%					

			the second se						
SOM	+	+	+	+	+	-	+	+	
met- ENK	+	+	+	+	+	+	+	+	
leu-ENK	+	+	+	+	+		+		1
CRH		+							
NT	24				12		£	2 - 12	
:	click on sy molecule (molecule) molecule (ymbols to v present in present in absent in n	view assoc basal phys manipulate ormal phys	ciated expe iological st d physiolog siological s	erimental d ate gical state tate	ata			

Figure 29. The result of combining data and metadata from several experiments. First, the experiments, together with the associated reference information are listed. Below, the composite table shows graphically the presence or absence of molecules in both normal and manipulated experimental conditions. Users can view details of the associated reports by clicking on the symbols in each cell. Empty cells represent absence of information.

The option "Molecule comparison in brain regions" processes the query type "What are the CNS parts where all the molecules of interest have been identified?" This engine returns a list of CNS parts where all the chosen molecules have been identified, and the associated physiological states. This engine also returns records of coexpression data for any pair of molecules in the chosen set. The interface for choosing the molecules is shown in Fig. 30, and an example of the reconstruction of the molecular composition of CNS parts is shown in Fig. 31.

AChE	alpha1 GABA	alpha1 GlyR	alpha2 nAChR	alpha3 GlyR	alpha3 nAChR	alpha4-1 nAChR	alpha4-2 nAChR	alpha5 GABA	alpha6 GABA	alpha7	GluR1	GluR2	GluR3	GluR4	AR		Asp	beta GlyR	beta1 GABA
beta2 GABA	beta2 nAChR	beta3 GABA	СаВ		CRF-R1	CRH Celts	delta GABA GABA rece	D1 ptor subun	D2 it	D3	DYN		ER	GABA	GAD65	GAD67	gamma2 GABA-R	Gephyrin	GAD
Gly	GlyR		нз	н/о	GluR5	GluR6	KA1	КА2	leu-ENK	мсн	mGluR1	mGluR3	met- ENK	MR	M2		NT	nAChR	NR1
NR2A	NR2B	NR2C	NR2D	Оху	PaV	PKC- alpha	PKC- beta	PKC- delta	PKC- epsilon	som	SP	SPR	QSOX	TH		VAS			
100			1			32.20		S	ubmit	Reset	1208			100	1				

Fig. 30. The user interface that allows users to choose any number of molecules to be compared in terms of presence/absence in CNS regions. As with the other checklist interfaces, users can view the name of the molecules by going with mouse over the corresponding abbreviation.

Compared	molecules	corticotropin-rele vasopressin (VA oxytocin (Oxy)	asing hormone (C S)	(RH)											
Brain	Physiologi	ical condition	Data about pres	sence of CRH	in PVHmpd ma	anipulated sta	ate:								
regions	CRH	basal state	Physiological condition	Cell pool position in region	Hemisphere	Qualitative density of CRH in PVHmpd	Labeled cells count	Percentage labeled cells	Average labeled cells	Standard deviatior	Relative to basal	Annotation	Reference	Collator	
<u>PVHmpd</u>	VAS Oxy	basal state manipulated state basal state	Chemical treatment: colchicine	everywhere	bilateral	not assigned	808	40.50	0	not measured	not measured	Collator note: see Figure 2 page 168. The percentage of labeled cells was calculated using the numbers provided in the legend of Figure 2 and represents the ratio between the labeled cells in the associated region and the total number of labeled cells in this experiment.	<u>Swanson</u> LVV, Sawchenko PE, Rivier J, Vale VWV, 1983	Mihail Bota	Metadata 💙 ord checked by aut
	CRH/VAS CRH/Oxy	manipulated state basal state manipulated state manipulated state	Chemical treatment: colchicine	unclear	bilateral	not assigned	0	0.00	446	50.00	not measured	Collator note: experiment CRH/AVP, Table 3 page 506. Page 505: eighteen to twenty hours after an injection with PEG, there was a significant 22% (P<0.01, Fig.1) increase of the CRH mRNA in the PVHmpd compared to vehicle-injected controls when measured using the 355-CRNA probe.	Watts, A.G. & Sanchez- Watts, G., 1995	Mihail Bota	Metadata
<u>PVHam</u>	CRH VAS Oxy	manipulated state basal state manipulated state basal state	Structural manipulation: ablation Manipulated structure: Adrenal gland	not known	bilateral	exists	0	0.00	0	not measured	not measured	90% of the brightly labeled cells were found in themedial part of the parvocellular division. Collator note: see Figure 1b page 167. We assigned the CRH label as significantly higher than the normal state according to Swanson 1991 in Progress in Brain Research.	<u>Swanson</u> LW, Sawchenko PE, Rivier J, Vale VWV, 1983	Mihail Bota	<u>Metadata</u>
37.5	CRHIVAS CRHIOXy	manipulated state manipulated state manipulated state	Chemical treatment:	everywhere	left hemisphere	very strong	o	0.00	o	not measured	significantly higher	Collator note: see Figure 2 page 6284 and Figure 3, page 6285.	Watts A.G. & Sanchez- Watts G., 2002	Mihail Bota	Metadata
<u>PVHap</u>	CRH VAS Oxy CRH/VAS CRH/Oxy	manipulated state basal state manipulated state basal state manipulated state manipulated state												inmunohisti in situ hybri	ochemistry data dization data

Fig 31. Users may compare the existence of particular molecules in different CNS regions (in this example, the rat PVHmpd). The result is a list of regions that are associated in BAMS with reports of all the searched molecules (corticotrophin releasing hormone [CRH], oxytocin [Oxy], and vasopressin [VAS]), in either basal physiological state or manipulated state. Coexpression data is also returned for all pairs of molecules in the set of interest. Users can access reports of molecule presence in the retrieved CNS regions.

The third option shown in the right half of Fig. 25, called "Search by type of manipulation," processes the query type "Show identified molecules and CNS parts that are associated with a specific molecule or structural manipulation." This engine returns the list of CNS parts and molecules associated with the searched type of manipulation, as well as basal state data for each retrieved molecule. If any retrieved experimental data is associated with statistical information, it also will be displayed in graphical format. An example of the online retrieval of chemoarchitectonic data associated with systemic injection of polyethylene glycol is shown in Fig. 32.

Region where PEG was injected	Brain region	Molecule	Manipulated state data	Basal state data
3ystemio	Paraventricular nucleus of the hypothalamus, parvicellular division, medial parvicellular part, dorsal zone (PVHpmd)	enkephalin	Watts, A.G. & Sanchez-Watts, G., 1995, Average number of labeled cells: 201 Standard error: 25.00	Watts, A.G. & Sanchez- Watts, G. 1995, Average number of labeled cells: 105 Standard error: 15.00
		neurotensin	Watts, A.G. & Sanchez-Watts, G., 1395, Average number of labeled cells: 104 Standard error: 15.00	no basal state data
		corticotropin-releasing hormone	Watts A.G. & Sanchez-Watts G., 2002, Relative absorbance: 125 +	Watts, A.G. & Sanchez- Watts, G., 1995, Average number of labeled cells: 489 Standard error: 70.00
			Standard error: 42 00 Relative absorbance, basal state: 100 Collator note: see Figu	produe: 0.0200. Amotation: re 2 page 6284. Tabeled cells: 488 Standard error: 69.00
				Watts, C., 1995, Average number of labeled cells: 390 Standard error: 76.00
				<u>Swanson, L.W.,</u> <u>Sawchenko, P.E., Lind,</u> <u>R.W. & Rho, JH., 1987,</u> Qualitative strength: exists
	BURBUR			Watts A.G. & Sanchez- Watts G., 2002, Relative absorbance: 100 Standard error: 5.00
		coexpression: neurotensin and corticotropin-releasing hormone	Watts, A.G. & Sanchez-Watts, G., 1995, Percentage expression NT/CRH: 54.50 Standard error percentage expression NT/CRH:	no basal state data

Fig. 32. Users can retrieve chemoarchitectonic data associated with a chemical or structural manipulation and compare the presence of molecules in basal and manipulated states. Additional data and metadata can be viewed by going with the mouse over the graphical symbols that represent statistical changes relative to the basal state.

Molecules that are expressed in CNS regions or neurons, as well as several other inference engines, can be accessed by users from the page that displays the summary of regions (Figs 6 and 13). Another example is shown in Fig.33, the summary information about the rat cerebellar cortex identified in the Swanson-98 nomenclature.



Figure 33. The summary page of the rat cerebellar cortex, Swanson-98 nomenclature. The chemoarchitecture profile of the CNS region is divided in the molecules classes implemented in BAMS.

The molecules that are expressed in the CNS region of interest are displayed according to the molecules schema implemented in BAMS. Clicking on the links associated with each of the retrieved molecules will display the data and metadata inserted in BAMS, which are related to the CNS region, and with the molecule (Fig. 34).

Reports of presence of	CRH in PVHmpd.						Time dependence of CRH					
		<u>Watt</u> horm	s A.G. & Sanchez-Watts G., 201 none gene expression in the par-	02: Interactions be aventricular nucle	etween heterotypic stre: eus <u>Data</u>	ssors and cortic	osterone reveal integrative mechanisms for controlling corticot	opin-releasing	1			
Reports of CRH presenc physiological state	e in PVHmpd, normal	<u>Watt</u> Data	s, A.G. & Sanchez-Watts, G., 1	995: Physiological	I regulation of peptide me	essenger RNA o	olocalization in rat hypothalamic paraventricular medial parvicel	lular neurons	<u>Methods</u> comparison			
		<u>Swa</u> endo	Swanson, L.W., Sawchenko, P.E., Lind, R.W. & Rho, JH., 1987: The CRH Motoneuron: differential peptide regulation in neurons with possible synaptic, paracrine, and endocrine outputs <u>Data</u>									
		<u>Watt</u> horm	s A.G. & Sanchez-Watts G., 201 none gene expression in the par	02: Interactions be aventricular nucle	etween heterotypic stre eus <u>Data</u>	ssors and cortic	osterone reveal integrative mechanisms for controlling corticot	opin-releasing				
Reports of CRH presence in PVHmpd, manipulated ohysiological state			Vatts, A.G. & Sanchez-Watts, G., 1995: Physiological regulation of peptide messenger RNA colocalization in rat hypothalamic paraventricular medial parvicellular neurons Meth									
		<u>Swa</u> immu	nson LW, Sawchenko PE, Rivie Inohistochemical study <u>Data</u>	r J, Vale WW, 198	33: Organization of ovine	e corticotropin-re	eleasing factor immunoreactive cells and fibers in the rat brain:	an				
CRH coexpression repor physiological state	ts in PVHmpd, normal	Watt Data	Watts, A.G. & Sanchez-Watts, G., 1995: Physiological regulation of peptide messenger RNA colocalization in rat hypothalamic paraventricular medial parvicellular neurons Data									
CRH coexpression report CRH coexpression report CRH coexpression report	ts in PVHmpd, manipu	lated Saw	s, A.G. & Sanchez-Watts, G., 19 chenko, P.E., Swanson, L.W. & inoreactive neurons in the hypo	995: Physiological Vale W.W., 1984 thalamus of the m	regulation of peptide me : Corticotropin-releasing ale rat Data	essenger RNA o factor: co-expr	olocalization in rat hypothalamic paraventricular medial parvicel ession within distinct subsets of oxytocin-, vasopressin-, and r	lular neurons eurotensin-	<u>Methods</u> comparison			
Physiological condition	Cell pool position in region	Hemisphere	Qualitative density of CRH in PVHmpd	Labeled cells count	Percentage labeled cells	Relative to basal	Annotation	Collator				
Chemical treatment: colchicine	everywhere	bilateral	not assigned	808	40.50	not measured	Collator note: see Figure 2 page 168. The percentage of labeled cells was calculated using the numbers provided in the legend of Figure 2 and represents the ratio between the labeled cells in the associated region and the total number of labeled cells in this experiment.	Mihail Bota	Metadata 🛛			
Structural manipulation: ablation	not known	bilateral	exists	0	0.00	not measured	90% of the brightly labeled cells were found in the medial part of the parvocellular division. Collator note: see Figure 1b page 167. We assigned the CRH label as significantly higher	Mihail Bota	Metadata			
lanipulated structure: Adrenal gland							than the normal state according to Swanson 1991 in Progress in Brain Research					

Figure 34. Users can view detailed reports about the presence of a molecule in a particular CNS region. Experimental data is grouped in four categories, which depend on the physiological state of the animal, and coexpression data. Records verified by original authors are indicated with a green checkmark.

Records associated with the molecule of interest are grouped in four categories (molecule presence in normal and manipulated physiological state, and coexpression of other molecules in normal and manipulated state; *see* Fig. 34, by experimental condition, and by coexpression of other molecules in the same CNS region). The system first retrieves references corresponding to each category. Every reference is associated with a "Data" link that retrieves corresponding experimental records. If at least two experiments from different references are retrieved in the same category and have metadata associated with them, a new link called "Methods comparison" becomes available. Users can therefore compare methods used in all experiments associated with metadata retrieved in one of the four categories. An example of methods comparison is shown in Fig. 35.

Experiments comparison			
Reference: Watts A.G. & Sanchez-Watts G., 2002:	Reference: Watts, A.G. & Sanchez-Watts, G., 1995:	Reference: Swanson LW, Sawchenko PE, Rivier J,	Vale WW, 1983:
Experiment acronym: Watts-CRH (PEG) Data types: qualitative Mapping approach: brain region in a BAMS nomenclature Mapping details Coordinates: none Anatomical data presentation: text representative labeled images	Experiment acronym: Watts-CRH/AVP(PEG) Data types: quantitative qualitative Mapping approach: brain region in a BAMS nomenclature Mapping details Coordinates: none Anatomical data presentation: text representative labeled images representative drawings/mappings onto templates	Experiment acronym: Swanson-1983(CRH) Data types: quanitative qualitative Mapping approach: brain region in a BAMS nomenclature, constructed ulterior to the experiment Mapping details Coordinates: none Anatomical data presentation: text representative labeled images drawings/template mappings of all sections	Experiment acronym: PS439 Data types: quantitative qualitative Mapping approach: brain region in a BAMS nomenclature, constructed ulterior to the experiment Mapping details Coordinates: none Anatomical data presentation: text representative labeled images drawings/template mappings of all sections
Animals (subjects): Number: not specified Sex: M Weight: 225-250g Housing conditions: normal housing Annotation: Adult male Sprague Dawley rats (225-250 gm body weight at the beginning of the experiment) were maintained on a 12 hr light/dark photoperiod (lights on at 6:00 AM) with ad libitum access to water and rat chow and were allowed at least 5d of acclimation to the animal quarters.	Animals (subjects): Number: 6 Sex: M Weight: 280-320g Housing conditions: normal housing Annotation: Adult male Sprague-Dawley rats (280-320 g BW at injection) were maintained on a 12 hour light/ 12 hour dark photoperiod (lights on 0700 hours) with water and rat chow available ad libitum. They were allowed 7 days' acclimatization to the animal quarters before we proceeded with the experiment.	Animals (subjects): Number: 10 Sex: M Weight: 0 Housing conditions: normal housing Annotation: The second group consisted of animals that received a single injection of colchine (4-8 microgram/microliter) saline into either the lateral ventricle (100-200 micrograms; n=8) or the fourth ventricle (50 micrograms; n=2) the day before perfusion	Animals (subjects): Number: 3 Sex: M Weight: 0 Housing conditions: normal housing Annotation: The third group was bilaterally adrenalectomized and allowed to survive for 3 days, 1 month and 2 months before perfusion (n=3).
Method: Neuron/glia identification method: not specified Staining frequency: 1:8 Technique: in situ hybridization Measurement 1: Measured nucleic acid: not specified Source (producer): not specified Probe sequence: not specified Sequence species: not specified Probe sequence orientation: not specified Control: not specified Labelling method: not specified Visualization method: autoradiogram Visualization method: not specified Annotation: not specified	Method: Neuron/glia identification method: not specified Staining frequency: 1:8 Technique: in situ hybridization Measurement 1: Measured nucleic acid: not specified Source (producer): not specified Probe sequence: 700 bp Rsal-Rsal CRH Sequence species: not specified Probe sequence orientation: not specified Control: not specified Visualization method: DIG Visualization medium: not specified Annotation: not specified Measurement 2:	Method: Neuron/glia identification method: not specified Staining frequency: 1:4 or 1:8 Technique: immunohistochemistry Measurement 1: Antigen: not specified Antigen: species: not specified Source (producer): not specified Primary antibody: not specified Primary antibody species: not specified Antigedy type (monoclonal, polyclonal): not specified Secondary antibody species: not specified Immunoglobulin class: not specified Control: not specified	Method: Neuron/glia identification method: not specified Staining frequency: 1:4 or 1:8 Technique: immunohistochemistry Measurement 1: Antigen: not specified Antigen species: not specified Source (producer): not specified Primary antibody: 24 ([Try22. Gly23]-CRF (1-23) antiserum Primary antibody species: not specified Antibody type (monoclonal, polyclonal): not specified Secondary antibody not specified Secondary antibody species: not specified Immunoglobulin class: not specified
	Measured nucleic acid: not specified Source (producer): not specified	Visualization method: fluorescence Visualization medium: not specified Annotation: not specified	Control: not specified Visualization method: fluorescence Visualization medium: not specified

Figure 35. Users may compare metadata associated with experimental data and experiments for the presence of a molecule in a CNS region of interest.

BAMS's *Molecules* module includes an inference engine for reconstructing the chemoarchitectonic profile of a CNS region from the molecular data associated with its substructure. This engine can be accessed from the page describing CNS parts in BAMS, shown in Figs. 6 and 13. It is similar to the projections profile inference engine described above (section 3.3) and in Bota et al. (2005), and it displays gene expression data as a function of experimental conditions (normal and manipulated states). An example of chemoarchitectonic profile reconstruction of the rat PVH is shown in Fig. 36.

Inferred chemoarchitecture pattern of the Paraventricular nucleus of the hypothalamus (PVH)

Click on symbols to access detailed reports

	P∨Hp	P∨Hm	PVHd	PVHpv	PVHmpd	PVHap	PVHpm	P∨Hmm	P∨Ham	PVHf	PVHlp	PVHdp	PVHmpv	P∨Hpml	P∨Hpmm
beta2 nAChR	+	+	+		1										
CRH		+	- 50	+	+	+	+	+	+	+	+	+	+	-	1
alpha4-2 nAChR	-	+	+					32			33			25	
alpha4-1 nAChR	-	-	+												
Оху	2	1	12	+	+	+	+	+	+	+	1	+			
VAS				+	+	+	+	+	+	+		+	+		
SS				+	+	+	+	+		+	1	+			
met-ENK		13.2		+	+	+	+	+	+	+	2.2	+			
leu-ENK		3199		+	+	+	+	+		+	1994				
QSOX	1.18	1	10	+	+	+		5	+	+	+	+	+	+	+
ENK					+++++++++++++++++++++++++++++++++++++++							X			
NT				+	+	+			-					1.00	
MCH					+										
H/O					+					110013	+				

Figure 36. The result of a BAMS gene expression pattern reconstruction dealing with the various subdivisions of the rat paraventricular nucleus of the hypothalamus (PVH). The reconstructed chemoarchitecture profile is similar with the matrix displayed in Fig. 29, and includes presence or absence of molecules in both normal and manipulated experimental conditions. Users can view details of the associated reports by clicking on the symbols in each cell.

Molecules reports inserted in BAMS are also associated with neuron types, if those were experimentally identified and recorded in the system. Therefore, BAMS also reconstructs the chemical phenotypes of neurons, in either of the physiological states. Thus, the neuron types records are associated in BAMS with reports of molecules presence or absence, and these are further dissociated by the physiological state. An example of the chemical phenotype reconstruction of a neuron type is shown in Figure 37. For details of the *Cells* module, *see* the next section of the manual.

Molecules expressed in cerebellar granule cell			Molecules not expressed in cerebellar granule cell	2 9 9
Molecule	Physiological condition	-	Molecule	Physiological condition
AMPA-GluR2 subunit (GluR2)	basal		AMPA-GluR1 subunit (GluR1)	basal
AMPA-GluR4 subunit (GluR4)	basal		AMPA-GluR3 subunit (GluR3)	basal
KA-GluR6 subunit (GluR6)	basal		KA-GluR5 subunit (GluR5)	basal
KA-KA2 subunit (KA2)	basal		KA-GluR7 subunit (GluR7)	basal
NR1 NMDA receptor subunit (NR1)	basal		KA-KA1 subunit (KA1)	basal
NR2A NMDA receptor subunit (NR2A)	basal	2	NR2B NMDA receptor subunit (NR2B)	basal
NR2C NMDA receptor subunit (NR2C)	basal		NR2D NMDA receptor subunit (NR2D)	basal
alpha6 GABA receptor subunit (alpha6 GABA)	basal		alpha2 GABA receptor subunit (alpha2 GABA)	basal
beta2 GABA receptor subunit (beta2 GABA)	basal		alpha3 GABA receptor subunit (alpha3 GABA)	basal
delta GABA receptor subunit (delta GABA)	basal		gamma1 GABA receptor subunit (gamma1 GABA-R)	basal
alpha5 GABA receptor subunit (alpha5 GABA)	basal	-	histamine H3 receptor (H3)	basal
calretinin (CART)	basal		choline acetyltransferase (CHAT)	basal
metabotropic glutamate receptor 1 (mGluR1)	basal		alpha7 subunit nicotinic receptor (alpha7)	basal
			enkephalin (ENK)	basal
			metabotropic glutamate receptor 3 (mGluR3)	basal
			calbindin D28K (CaB)	basal
		0	parvalbumin (PaV)	basal
		1	protein kinase C alpha (PKC-alpha)	basal
		1	protein kinase C beta (PKC-beta)	basal
			protein kinase C gamma (PKC-gamma)	basal
			protein kinase C delta (PKC-delta)	basal
		- 1	protein kinase C epsilon (PKC-epsilon)	basal
			GABA (GABA)	basal
			glycine (Gly)	basal

Figure 37. BAMS's web interface reconstructs automatically the chemical phenotype of recorded neuron types. Users can also access details about each of the expressed molecules, as well as those that are not expressed, in the corresponding physiological state.

3.6 Searching for neurons in BAMS

The menu for searching neurons in BAMS can be found following the path: Menu \rightarrow Cells. The webpage that includes three ways of searching neurons and neuron populations identified in different brain regions is shown in Fig. 38. The first two options of search are complementary, therefore, they will described together.

As with brain nomenclatures, neurons are grouped in BAMS in neuron nomenclatures. Neuron nomenclatures are internally consistent sets of terms that describe different neuron populations (neuron types and classes) in a specific part of the CNS. Neuron nomenclatures are defined by an author or group of authors, and are associated with a set of references in the literature. Since the populations that make up a specific part of the CNS can be named differently by different authors, those nomenclatures that are the most complete to our knowledge are called "BAMS reference" and used to construct BAMS ontology (Bota &

	Choose a neuron name (BAMS Reference)	
	Name 360 nm-cone 👻	
	Search	
2 23		
	Choose a neuron name (other nomenclatures)	
	Name 1CA amacrine retinal cell	
	Search	
2		
	Choose a brain part	
Name Abdu	ucens nucleus	-
	Search	

Figure 38. The search options of the Cell module interface of BAMS.

Swanson, 2008). Details about the criteria for constructing a "BAMS Reference" nomenclature can be found in Bota & Swanson 2007, and 2008.

Users can choose either the "BAMS Reference" or "Other nomenclature" drop-down lists to look for a neuron name. This action will return details about that neuron type or class, which include its definition, subclasses, CNS regions where it was identified, and terms defined in other nomenclatures and related to it. An example is shown in Fig. 39.

1 record(s) assoc	ciated with retinal gangl	ion cell A1:							
1. retinal ganglior	n cell A1, nomenclature	(acronym): Huxlin & Goodchild (HG)							
Definition:	Subgroup RGA1 cells (Figs. 2A, 3-5, Table 1) have a morphology similar to that of the giant cells of Bunt (1976). They have large somata, often polygonal in shape, from which a medium- to large-gauge axon emerges (Figs. 2A, 3). In one instance, a bifucarting axon was seen to exit the soma (see Fig. 3A). The large dendring to fields of RGA1 cells consist of three to seven stout dendrites that emerge radially from a certrally placed soma. The dendrites are smooth and overlap infrequently (Figs. 2A), SRGA1 cells are found across the retinar (Figs. 5), 6) and, on average, have the largest dendritic fields of RGA1 cells are found across the retinar (Figs. 5). A start for the retinar (Figs. 5), 6) and, on average, have the largest dendritic fields are smooth and overlap exhibited tracer coupling. They were strongly coupled to at least ten neurons (large-bodied gnalgion cells and some presumed amacrine cells-the latter gad very small somata and were found both the GCL and the INL; Fig.5).								
	We classified cells as RGB, and cells v average soma diam Perry's type I cells (with a large soma and a large dendritic field as RGA, cells with tith a small-to medium-sized soma but a medium-to-large dend eter of 23.4 micrometers, an average dendritic-field diameter o Perry, 1979).	a small- to medium-sized soma itic field RGC. Seventy five RG f 300.0 micrometers, and a radi	a and a small- to medium-sized dendritic field A cells were identified. RGA cells had an al pattern of branching. They are similar to	in: <u>Large-scale</u> <u>morphological survey of</u> <u>rat retinal ganglion cells</u> , Sun W., Li N. & He S.	collated by: Mihail Bota			
Cell	Brain regions where is identified								
retinal ganglion o	cell A1	Retina, ganglion cell layer (R	<u>acl)</u>						
Related terms (su	immary):								
cell populations	identical with retinal ga	nglion cell A1:	giant ganglion	n cell (Bunt)					
Related terms (de	etails)								
Term	Nomenclature (Acronym)	Definition	Relation of retinal ganglion cell A1	Annotation	Reference	Collator			
<u>giant ganglion</u> cell	Bunt (Bunt)	Several examples have been found of giant cells similar to those described by Polyak in the primate retina as having large somata [20 micrometers or greater] and relatively thick dendritic branches which were smooth and spine-free, radiating outward from the soma to extend throughout the inner plexiform layer. The diameter of the dendritic spread reached 260 micrometers.	synonym	Subgroup RGA1 cells (Figs. 2A, 3–5, Table 1) have a morphology similar to that of the "giant" cells of Bunt (1976).	Huxlin K.R & Goodchild A.K., 1997	Mihail Bota			

Figure 39. The details about the neuron term of interest, which include its definition, the associated reference, collators, brain regions where it was identified, terms defined in other neuron nomenclatures and related to it, the semantical relations, and associated annotations.

Additional details about a "BAMS Reference" neuron type or class can be accessed from the page that provides the summary information about a CNS region (Figs.6, 13, and 33). Whenever a CNS region is associated with neuron types or classes, these will be listed in a tabular format in the summary web page. Clicking on links associated with the retrieved neuron names will retrieve the chemical phenotypes, distributions in the CNS region, and related terms. If the neuron type of interest is captured in the BAMS ontology, thus in the "is a" hierarchy, the classification criteria and its parents will also be displayed. The example of the cerebellar basket neuron is shown in Figure 40.

			Cell details			
ree of the basket neuron, nomencl	ature (acronym): Chan-Pala	iy (Chan-Palay)				
neuron interneu	iron <u>local in</u>	terneuron cerebellar molecular layer	r interneuron	Definition		
criteria	<u>criteria</u>	a <u>criteria</u>				
Molecules expressed in basket ne	euron	Molecules not expressed in basket neuron				
Molecule	Physiological condition	Molecule	Physiological condition	RING REAL PROVIDENCE		
GAD67 (GAD67)	basal	AMPA-GluR1 subunit (GluR1)	basal			
GAD65 (GAD65)	basal	choline acetyltransferase (CHAT)	basal			
NR1 NMDA receptor subunit (NR1) basal	alpha7 subunit nicotinic receptor (alpha7)	basal			
GABA (GABA)	basal	calretinin (CART)	basal			
		enkephalin (ENK)	basal			
		calbindin D28K (CaB)	basal			
		glycine (Gly)	basal			
I CARLY N.	Contraction of the second					
Related concepts						
Cell type (class)	Nomenclature (Acronym)	Definition	Relation of basket neuron	Annotation	Reference	Collator
cerebellar molecular layer interneuron	Sultan & Bower (SB)	the data support the view that the molecular layer interneurons represent one population of cells, which vary continuously in their morphology depending on the depth of the soma in the molecular layer.	is included	The standard division of these cells into basket and stellate cells, for example, depends principally on two features, their different depths (basket cells are desper than stellate cells) and, importantly, whether their axons contribute basket endings onto somata of nearby Purkinje cells (Eccles et al., 1967; Palay and Chan- Palay, 1974)Consistent with previous classification schemes (Eccles et al., 1967; Palay and Chan-Palay, 1974) the particular feature that is most striking is the dependence on depth for the generation of the baskethype ending (Fig. 8). However, our analysis shows that this property actually varies smoothly with depth (Fig. 9). Collator note: see also Table, page 369.	Sultan F. & Bower J.M.	Mihail Bota

Figure 40. Information that can be retrieved in BAMS and is related neuron concepts include to the chemical phenotype, related terms, their semantic relations, annotations, references and collators, as well as the set of parents with links to the associated classification criteria

Any parent-child relationship between "BAMS Reference" terms can be associated in BAMS *Cell* module with criteria for classification that are collated from associated references. These are the major criteria used by various authors to classify neurons: morphology, specialized parts, input and output regions or neurons types, regions where the neurons were identified, expressed molecules, and physiology. The database classification criteria schema was constructed to comply with measurements performed by a broad range of research groups, and with the most recent efforts to create a unified terminology of neuron types. All variables included in the classification criteria are in text format, and are associated with annotations and references. Details about the database schema implemented in BAMS can be found in Bota and Swanson 2007, and 2008.

Thus, if a "BAMS Reference" term is associated with classification criteria, these can be viewed by clicking on the "criteria" links shown in Fig. 40. The page that will be returned will display the classification criteria used with all the intermediary classes, up to the class of interest. An example is shown in Fig. 41: the criteria used to classify the retinal ganglion cell A2 inner as a projection interneuron will displayed step-wise, passing through all intermediary classes.

	Criterion: neuron morphology
	Subcriterion 1: morphology-dendrite, branching pattern Annotation:the dendrites of RGA2 cells branched moderately frequently in a shallow Y-shaped pattern. Reference: <u>Huxlin K.R & Goodchild A.K.</u> Collator: Mihail Bota
Cell type retinal ganglion cell A2 inner is in class retinal ganglion cell A2	Subcriterion 2: morphology-soma, size (general) Annotation: At all eccentricities, RGA1 cells were larger than inner- and outer-stratifying RGA2 ganglion cells. Reference: <u>Huxlin K.R & Goodchild A.K.</u> Collator: Mihail Bota
	Subcriterion 3: morphology-dendrite, dendrite thickness Annotation: The dendrites of RGA1 cells were thicker than those of RGA2 cells. Reference: <u>Huxlin K.R & Goodchild A.K.</u> Collator: Mihail Bota
	Criterion: neuron morphology Subcriterion 1: morphology-soma, size (general) Annotation:Group RGA cellshave large somata (15-39 micrometers in diameter) Reference: <u>Huxlin K.R & Goodchild A.K.</u> Collator: Mihail Bota
Cell type retinal ganglion cell A2 is in class retinal ganglion cell A	Subcriterion 2: morphology-dendrite, dendritic field radius Annotation: Group RGA cellshavelarge, radially branching dendritic fields (235-748 micrometers) Reference: <u>Huxlin K.R & Goodchild A.K.</u> Collator: Mihail Bota
Cell type retinal ganglion cell A is in class retinal ganglion cell	Criterion: region where it was identified Region where retinal ganglion cell A is identified: Retina, ganglion cell layer (Rgcl) Annotation:cell bodies are in the ganglion cell layer (GCL) Reference: <u>Huxlin K.R & Goodchild A.K.</u>
Cell type retinal ganglion cell is in class projection interneuron	Criterion: target region Axons of retinal ganglion cell are part of a major fiber tract: Optic nerve (IIn) Annotation: A retinal ganglion cell is defined as a neuron whose perikaryon lies in the retina and which has an axon that becomes a fiber of the optic nerve. Reference: <u>Rodieck R.W</u> Collator: Mihail Bota

Figure 41. Users can access classification criteria associated with each "is a" relationship. Retrieved criteria are organized as ordered lists of variables used to define and classify the neuron concepts. Associated information includes textual annotations, references, and collator names. The list of variables shown in this Figure is used to classify rat retinal ganglion cells A2 inner as projection interneurons, passing through the intermediary classes.

Clicking on the classes displayed in Figure 40 will return the subclasses of each of them displayed in a tree like format. Thus, the tree of the class "interneuron" will be more general than that of the "local interneuron" and it will include it. Users can therefore access other neuron classes through this dynamically created tree. An example of such tree is shown in Fig. 42.



Figure 42. A "is a" hierarchical tree dynamically reconstructed in BAMS. Users can easily navigate across cell classes and types, and from here to the brain regions that contain those.

3.7 Searching for references in BAMS

Searching for information by reference (path: Menu \rightarrow References) can be performed using any combination of three attributes: author, book or journal, and year of publication. The screen that allows users to search by authors, journal and year is shown in Figure 43. The database schema for handling reference information is described in detail in Bota et al. 2005.

Sear	ch of informat	tion by refer	rence
Any jo	urnal		•
0.5	An	y year 💌	1 200
	Search	Reset	
	Sear Any jo	Search of informat	Search of information by refer

Figure 43. The interface for searching references in BAMS. Users can choose any combination of the three fields: author, journal, and year.

If users would like to see the entire set of publications of a certain author, then the journal and year fields of the form shown in Fig. 43 should be left blank. In this case, the system will return all references published by the author of interest, organized in several categories: books, book chapters, published articles, theses, etc. An example of such search is shown in Figure 44.

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 qualitative strength.

-	Search of	information by reference														
Author	Swanson															
Inumat	Anviourne	J	-													
Journal 17	Any journa															
Year		Any year 💌														
	Se	earch Reset														
Books																
Author	Title of	Book	-	Volume S	erle	Year	Pages	Edition	Publ	lisher		Editor	URL	Type of info	omation	
Swanson L	L.W. Brain N	laps: Structure of the Rat Brain		N/A N	/A	1992	198-212	first	Else	vier		N/A	Not availab	brain structu	ures	
Swanson L	LW Brain N	laps: Structure of the Rat Brain		N/A N	/A	1998	196-213	second	Else	vier		N/A	Not availab	brain structu	ures	
Swanson L	L.W. Brain N	laps: Structure of the Rat Brain. 1	Third Edition	N/A N	A	2004	188-179	third	Else	vier		N/A	Not availab	brain structu	ines	
Swanson L	L.W. Brain A	rchitecture: Understanding the bi	isic plan	-	1	2004	_		Oxfo	rd Univ	ersity Pres	6	Not availab	ple	1	
Book Chapt	ters															
Author	Title of ch	apter	Title of Bo	ok		Volume	Seriez		Year	Page	Edition	Publis	her Editor	1.0.35	URL	Type of information
Swanson L.W.	Biochemi circuits me	hemical switching in hypothalamic Progress in the research		n brain		87 Progress in brain rese		in Jearch	1 1991 18 arch 1991 20		-	Elsevie	er Holsteg	Holstege G.		
Swanson L.W.	The hypothalamus		Handbook of chemical neuroanatomy			5				1-124	First	Elsevie	er & Swan	Bjorklund A., Hokfelt T. & Swanson L.W.	Not available	chemoarchitecture
		1					-							1919		
Journal art	icles	Title of Article		_	- [4	oumal	-	Vear	Volu	melles	Pane	IIRI	Time o	Linformation		
Autora		Projections from bed nuclei of t	he stria term	inalis	-	Jumar		rear	1000	nie paa	re reye	- Onc	Type o			
Dong HW Swanson L	/. & L.W.	anteromedial area: cerebral he neuroendocrine, autonomic, an energy balance	misphere int d behavioral	egration of aspects of	L	Comp N	eurol	2006	494	1	142- 148	Abstra	ict fiber tr	acts reports		
Dong H. & L.W.	Swanson	Projections from bed nuclei of t dorsomedial nucleus: implication hemipshere integration for neur and drinking responses	he stria term ons for cereb coendocrine,	inalis, ral autonomic	J	Comp N	eurol	2005	N/A	N/A	N/A	Abstra	ict fiber tr	acts reports		
Dong H. & L.W.	Swanson	Projections from bed nuclei of t msgnocellular nucleus: implica hemisphere regulation of mictu penile erection	he stria term tions for cere rition, defect	inalis, ebral ation, and	J	Comp N	eurol	2005	N/A	N/A	N/A	Abstra	ict fiber tr	acts reports		
Cenquizca Swanson L	LA&	An Analysis of direct hippocam axonal projections to dienceph	al cortical fi alon in the ra	eld CA1	J	J Comp Neurol		2005	N/A	N /	A N/A	Abstra	tet fiber tr	acts reports		
Dong H.W. L.W.	I.W., Swanson posterior division: Implications for orrebral i regulation of defensive and reproductive be		inalis, emisphere haviors.	J	J Comp Neurol		2004	471	4	396- 433	Abstra	ict fiber tr	acts reports			
Dong H-W. L.W.	., Swanson	Projections from the rhomboid nucleus of the bed nuclei of stris terminalis: implications for œrebral hemipshere regulation of Ingestive behaviors		L	Comp N	eurol	2004	463	4	434- 472	Abstra	ict fiber tr	acts reports			
Thompson Swanson L	R.H., L.W.	Structural characterization of a visceromotor pattern generator	hypothalami network	ic .	BR	rain Res ev	Brain Re	^s 2003	N/A	M/4	A N/A	Not availa	ible fiber tr	acts reports		
Dong H-W L.W.	& Swanson	Organization of axonal projecti area of the bed nuclei of the str	ons from the	anterolatera	L le	Comp N	eurol	2003	N/A	N/A	N/A	Abstra	tot fiber tr	acts reports		
Dong HW, GD, Watts Swanson L	Petrovich AG, LW	Basic organization of projection fusiform nuclei of the bed nucle adult rat brain	is from the o i of the stria	val and terminalis in	n J	Comp N	eurol	2001	5	43	430-5	5 Abstra	ict fiber tr	acts reports		

Fig 44. The output of a search for references, by author (*see* inset) in BAMS. Users can inspect details of each retrieved reference, and the types of neurobiological information found in it are also listed.

The interface that allows 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. 45, the retrieved reference (Dong and Swanson, 2003) is associated with the reconstructed matrix of projections, and with tract tracing data for each of four individual experiments. Additionally the interface allows combination of all experiments in a single composite table (the link "Cases, composite" in Fig. 45).

			Associated cases
			Cases, composite
			Individual case (Injection sit
			BST178(BSTal)
			BST19(BSTal)
			BST124(BSTal)
			BST74(BSTsc)
Efferent	BSTsc	BSTal	
Afferent			
ACB	4	11	
ОТЗ	4	7	
SI	11	39	
FS	8	16	
LSr.vl.d.m	1	1	
OT1	1	1	
OT2		1	
LSr.m.v.r	3	6	
BSTad	4	15	
BSTal	6	13	
BSTav		15	
BETde			
barum			
LPO	4	13	
LSc.d.d	1	1	
LSr.m.d	1	1	

Figure 45. 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. 44.

4. Saving queries results in the Personal Workspace

The functionality of BAMS's web interface has with two additional features: registered users may now add comments to data reports, and they can also save their activity in a personal workspace. Registered users are allowed to attach comments to brain region, projection, and molecule reports inserted in the public part of BAMS. These comments may be accessed and viewed at any time by the registered user who inserted them.

The BAMS Personal Workspace becomes the place where registered users can save and view reports of interest concerning CNS regions, their input and output axonal connections, customized connection matrices, molecules, and groups of gene expression pattern experiments. The number of reports and matrices that can be used by registered users is unlimited.

The process of registration in BAMS is very simple: just click on the link "Register" (path: Menu \rightarrow Register) and the form with the first name, last name, and email address. The username of the newly registered user is his or her last name and the email address becomes the password.

Once the registration is completed, users can start using the workspace (path: Menu \rightarrow Workspace). The system will display login interface, as shown in Fig. 46.

	a he used to save and view reports of brain	
This workspace ca	n be used to save and view reports of brain	
regions, neuroanato	omical projections, molecules presence in brain	
regions, customized	d projection matrices, and groups of gene	
expression experim	ients.	
To Login, enter you	r Username (your last name) and Password (your	
email address) into	the boxes below, then click "Login".	
If you are unsure al	bout whether you have an account, or have	
forgotten your pass	word, please contact the System Administrator.	
If you do not have a	in account, please <u>register</u> , or contact the <u>System</u>	
lf you do not have a Administrator.	in account, please <u>register</u> , or contact the <u>System</u>	
lf you do not have a <u>Administrator</u> .	in account, please <u>register</u> , or contact the <u>System</u>	
lf you do not have a <u>Administrator</u> .	in account, please <u>register</u> , or contact the <u>System</u> Login to your workspace	
lf you do not have a <u>Administrator</u> .	In account, please <u>register</u> , or contact the <u>System</u> Login to your workspace Username (last name):	
If you do not have a <u>Administrator</u> .	In account, please <u>register</u> , or contact the <u>System</u> Login to your workspace Username (last name):	

Figure 46. The login interface to the BAMS Personal Workspace.

Once users are logged to the Personal Workspace, they can use BAMS as before. The differences that will appear are related to the possibility of associating personal notes to results of queries, and saving these in the workspace. An example is shown in Figure 47: the summary page of the rat PVHmpd is almost identical with Figure 6, except the link that allows users to associate annotations with this region, and the link necessary to save it in the personal workspace.



Figure 47. The summary page of the rat PVHmpd in BAMS, for a registered user who logged to the Personal Workspace. This page includes two additional links: "Save in workspace" that allows users to save this region, and "Add comment", which users to associate any number of text annotations.

This approach was also implemented in the other modules of the BAMS web interface. Therefore, users can save CNS parts reports, projections patterns (both inputs and outputs), and molecules presence/absence reports, and gene expression experiments. A typical Personal Workspace, with several queries saved from each category is shown in Figure 48.

Workspace of Mihail Bota

Menu

Saved brain parts	Saved on		Saved output patterns	Saved on]	Saved input patterns	Saved on		Molecules presence	Saved on]
AAA	2006-05-04 21:00:05	Delete	<u>CEAm</u>	2006-05-04 18:31:43	Delete	<u>PVHmpv</u>	2006-05-04 18:00:24	Delete	reports	2006-05-05	Delet
<u>so</u>	2006-05-08 11:44:01	<u>Delete</u>	<u>BSTrh</u>	2006-05-04 18:31:25	<u>Delete</u>	<u>BSTrh</u>	2006-05-04 18:31:35	<u>Delete</u>		12:51:07 2006-05-05	Delet
HPF	2006-05-05 21:16:10	<u>Delete</u>	TR	2006-05-05 19:50:18	Delete	<u>CEAm</u>	2006-05-04 18:31:52	Delete	ENV.	12:54:20 2006-05-08	Delet
RHP	2006-05-08 10:20:57	Delete	ENT	2006-05-08 10:21:46	Delete	AAA	2006-05-04 20:44:36	Delete		10:22:24 2006-05-08	Delet
				1		<u>so</u>	2006-05-08	Delete		11:45:16	Delet
							11.44.04		All	18:51:00	Delet

Saved projections matrices & gene expression experiments

Saved projections matrices	Saved on		Saved gene expression experiments	Saved on	
<u>PVH-output</u>	2006-05-07 14:18:46	<u>Delete</u>	<u>watts-2</u>	2006-05-05 19:33:30	<u>Delete</u>
<u>BST-input</u>	2006-05-07 16:07:46	<u>Delete</u>	Swanson-group	2006-05-05 21:23:49	<u>Delete</u>
AHN-outputs	2006-05-08 10:23:40	<u>Delete</u>	<u>Watts-Swanson</u>	2006-05-08 10:25:10	<u>Delete</u>
Arshad	2006-05-08 11:45:59	<u>Delete</u>	watts-all	2006-05-08 11:46:29	<u>Delete</u>

Figure 48. BAMS Personal Workspace allows registered users to store and view reports of interest concerning CNS parts and cell types, input and output axonal connections, and a wide variety of molecules-as well as complex, axonal connection matrices and groups of gene expression patterns. The number of saved reports in any category is unlimited.

5. Web services and downloadable forms.

Besides having a complex web interface and being open to the neuroscience community, BAMS is also is a data and knowledge provider. This is accomplished in several ways, which include backend MySql connections with other neuroinformatics groups (Senselab; http://senselab.med.yale.edu; LONI; http://www.loni.ucla.edu, etc.), and XML pages with the data and the metadata stored in BAMS. The access to the page that includes the XML pages is via the path: Menu \rightarrow XML. Here, users will find XML pages organized by brain nomenclatures. The general structure of any XML page is exemplified by the snippet below:

Log out

<part id="p524" name="Abducens nucleus" abbreviation="VI" is_part_of_idrefs="p519"
url_base_ref="u1" url_param="aidi=524">

<sources>

<source id="s835" name="Flocculus" abbreviation="FL" url_base_ref="u2"</pre>

url_param="eff=835&aff=524" />

</sources>

<molecules_in_region>

<molecule_in_region id="m17" name="beta2 subunit nicotinic receptor" abbreviation="beta2

nAChR" url_base_ref="u3" url_param="aidi=524&chem=17&type=1&what=0" />

<molecule_in_region id="m15" name="alpha4-1 subunit nicotinic receptor" abbreviation="alpha4-

1 nAChR" url_base_ref="u3" url_param="aidi=524&chem=15&type=1&what=0" />

<molecule_in_region id="m16" name="alpha4-2 subunit nicotinic receptor" abbreviation="alpha4-

```
2 nAChR" url_base_ref="u3" url_param="aidi=524&chem=16&type=1&what=0" />
```

<molecule_in_region id="m19" name="sulfhydryl oxidase" abbreviation="QSOX"

url_base_ref="u3" url_param="aidi=524&chem=19&type=1&what=0" />

</molecules_in_region>

<cells>

<cell id="c241" name="motor neuron, extraocular muscles" url_base_ref="u4"

```
url_param="aidi=524&id2=241" />
```

</cells>

</part>

Since XML pages tend to become large, the loading time may become a problem, especially to those that use Internet Explorer. In this situation, we encourage the users to contact us, to either send the XML pages by email, or create custom (and smaller) XML scripts.

Any XML page can be saved in users' computers and later used as base for searching BAMS for additional information, or run different inference engines.

BAMS interface also includes a growing set of downloadable forms, written in Excel, which can be used to either construct "in house" small databases, or populate it. These forms can be found under the "Forms" category of the Menu (path: Menu \rightarrow Forms). So far, this category has only one downloadable Excel form, for populating the *Connections* module of the system. Here, we will add Excel forms for molecules and neuron types records.

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