W462–W469 Nucleic Acids Research, 2011, Vol. 39, Web Server issue Published online 9 May 2011
doi:10.1093/nar/gkr285

BeeSpace Navigator: exploratory analysis of gene function using semantic indexing of biological literature

Moushumi Sen Sarma[1], David Arcoleo[1], Radhika S. Khetani[1], Brant Chee[1], Xu Ling[2], Xin He[2], Jing Jiang[2], Qiaozhu Mei[2], ChengXiang Zhai[2] and Bruce Schatz[1,2,*]

[1]Institute for Genomic Biology and [2]Department of Computer Science, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA

Received January 28, 2011; Revised March 19, 2011; Accepted April 12, 2011

ABSTRACT

With the rapid decrease in cost of genome sequencing, the classification of gene function is becoming a primary problem. Such classification has been performed by human curators who read biological literature to extract evidence. BeeSpace Navigator is a prototype software for exploratory analysis of gene function using biological literature. The software supports an automatic analogue of the curator process to extract functions, with a simple interface intended for all biologists. Since extraction is done on selected collections that are semantically indexed into conceptual spaces, the curation can be task specific. Biological literature containing references to gene lists from expression experiments can be analyzed to extract concepts that are computational equivalents of a classification such as Gene Ontology, yielding discriminating concepts that differentiate gene mentions from other mentions. The functions of individual genes can be summarized from sentences in biological literature, to produce results resembling a model organism database entry that is automatically computed. Statistical frequency analysis based on literature phrase extraction generates offline semantic indexes to support these gene function services. The website with BeeSpace Navigator is free and open to all; there is no login requirement at www.beespace.illinois.edu for version 4. Materials from the 2010 BeeSpace Software Training Workshop are available at www.beespace.illinois.edu/bstwmaterials.php.

INTRODUCTION

Automatic classification of gene function enables computers to complement curators for new genomes, by developing new pipelines for annotating genomes. As sequencing becomes cheaper, task-oriented genome analysis will become common, studying dynamic expression of differential genes for particular tasks for particular organisms. Fixed microarrays are already being replaced for expression experiments by high-throughput sequencing using RNA-seq methodologies. The source of functional information still primarily resides in the biological literature, but automatic extraction is necessary due to the range of experimental tasks now feasible on organisms with unknown genetics. The original proposal for the BeeSpace project stated testing on honey bees the goal of 'biotechnology enables routine expression analysis and bioinformatics enables functional analysis unconstrained by pre-existing categories'.

The BeeSpace Navigator is a prototype software for interactive analysis of gene function, via semantic indexing of biological literature. The software enables users to create spaces, which are literature collections targeted toward the gene functions of a particular task. Available services analyze gene lists from expression experiments and summarize gene functions using descriptions extracted within specified spaces. These services support automatic analogues of curator processes of reading literature for creating databases, with accuracy high enough for practical utility. Using the analysis environment enables biologists to interactively transform unknown genes into known functions.

The semantic indexing enables interactive sessions to discover gene functions, using statistical operations on user-specified collections task specific for the user's experiments. Indexing details are discussed in separate papers

*To whom correspondence should be addressed. Tel: +1 217 244 0651; Fax: +1 217 244 1781; Email: schatz@illinois.edu for the individual components as described below; this article focuses on their integration into an interactive system for functional analysis on community spaces. See Figure 1 for schematic of the services interacting with the spaces for BeeSpace Navigator. All services uniformly revolve around spaces, which represent a specific point of view for the specific task at hand. The paradigm of space manipulation is explicitly embedded into the user model of creating spaces, with Filter and Cluster, then navigating them to support the functional analysis, with Summarize and Analyze.

COMMUNITY SPACES

The BeeSpace Navigator is an analysis system for creating and traversing spaces. It represents the first fully fledged implementation of the Interspace, the next-generation information infrastructure for the Internet, where the fundamental paradigm is concept navigation of community spaces rather than document search of scientific literature (1). The technologies of the Interspace promise a new level of functionality in building analysis environments for functional genomics (2).

In the BeeSpace system, a '*space*' is a collection that is semantically indexed. Every service operates on spaces. Every collection of documents generated in any way can be saved as a space. The spaces are automatically named for user convenience, but can be renamed for special purposes. For example, a search query generates a space for the user with the search string as name. The spaces are used as the input to the services, for example, the Genelist Analyzer and the Gene Summarizer operates on the selected space.

The easy selection of the underlying space is a major difference between manual and automatic curation processes, between 'base' systems such as FlyBase and 'space' systems such as BeeSpace. This has to do with the underlying collection from which the function facts are extracted. With manual curation, there is a single static collection. In the FlyBase case, this collection is a selected subset of the MEDLINE articles that mention *Drosophila melanogaster*.

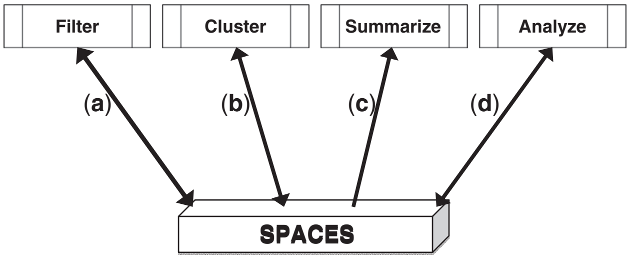


Figure 1. Interaction schematic of system usage, services interacting with spaces. A 'space' is set of scientific documents for a particular task. (**a**) Search (or filter) any system or user space and make new smaller spaces. (**b**) Use terms of interest as seeds to cluster together related terms, in a space; save the documents associated with a given cluster of terms as a smaller space. (**c**) Summarize functional information about a gene, in the context of a space. (**d**) Analyze gene lists in the context of a space to reveal significant 'concepts' and genes present; and select concepts and/or genes to make new smaller spaces.

With automatic curation, there can be multiple dynamic collections. That is, different collections can be used for extraction for different tasks. For example, a gene can be described with the Gene Summarizer using a genetic model (*Drosophila melanogaster*), the organism being studied (*Apis mellifera*) or the behavior being studied (early foraging). The gene will match different sentences and different functions may result. Thus, task-dependent curation can be achieved, using the automatic extraction from different collections.

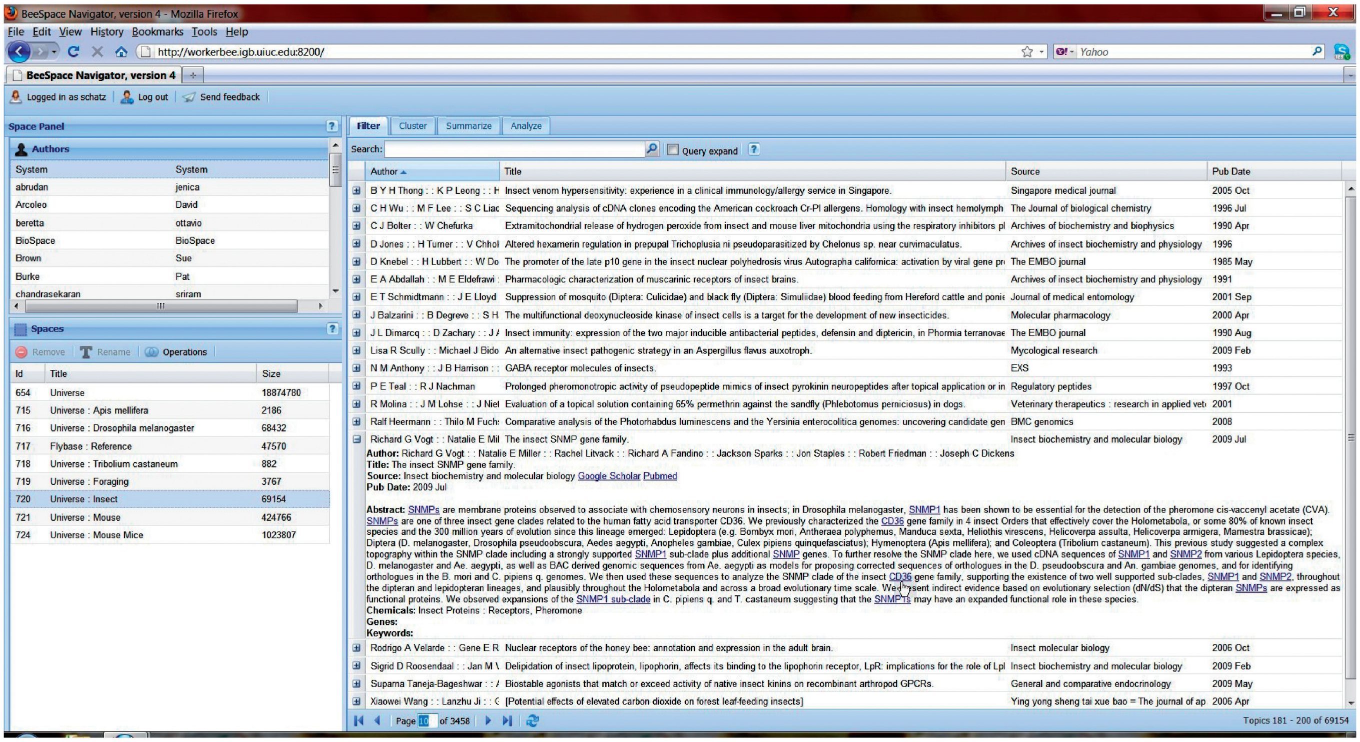
The current master database is all MEDLINE abstracts, but other biological or scientific literature would work equally well. For example, previous versions of BeeSpace Navigator had substantial collections from Biological Abstracts and from beekeeping books. The statistical technologies for semantic indexing have been utilized across a variety of subjects over many years with good results (3,4); they rely upon consistent terminology for contextual redundancy.

Figure 2 illustrates the nascent BioSpace within the system, with spaces across all of biology. There are spaces derived from the Universe, which is currently all of MEDLINE. Some of these spaces focus on organisms, such as *Apis mellifera* or *Tribolium castaneum*, whose gene expression is being analyzed. Some of these spaces focus on behaviors, such as foraging, which represent specific tasks being studied. Note the foraging space includes this behavior within both insects and mammals. Finally, some of these spaces are broad categories, such as insect or mouse, primarily useful as standard platforms to leverage new spaces. These spaces are moderated by the administrator; user spaces can be migrated into system spaces as appropriate.

All system services utilize spaces, which are collections of documents generated by internal operations. This concept is a more general research version of the currently popular commercial concept of smart folders automatically generated with simple searches. The basic operations enable users to create spaces in various ways, and then use these spaces to analyze gene functions. A common user session is thus to generate an appropriate space describing the task at hand and then operate on this space with appropriate services. For example, search for foraging within insect collection then cluster to find the set of documents relating to foraging within social insects. After saving this set as a space, use that space to analyze the functions of genes from an expression experiment concerning honey bee foraging.

SPACE CREATION

Building new spaces from old is an important part of the new paradigm. As mentioned, users can subsearch within their previous spaces to create smaller spaces or utilize space arithmetic to merge together several spaces into a combined one. But users can also leverage the spaces found by other users. This feature represents a powerful form of information sharing. No login is required, since spaces are default to the guest account, but users can login to create spaces that are categorized within their own


BeeSpace Navigator, version 4 - Mozilla Firefox
File Edit View History Bookmarks Tools Help
http://workerbee.igb.uiuc.edu:8200/
Yahoo
BeeSpace Navigator, version 4
Logged in as schatz
Log out
Send feedback
Space Panel
Authors
Spaces
Remove
Rename
Operations
Filter
Cluster
Summarize
Analyze
Search:
□ Query expand

System	System
abrudan	jenica
Arcoleo	David
beretta	ottavio
BioSpace	BioSpace
Brown	Sue
Burke	Pat
chandrasekaran	sriram

Id	Title	Size
654	Universe	18874780
715	Universe : Apis mellifera	2186
716	Universe : Drosophila melanogaster	68432
717	Flybase : Reference	47570
718	Universe : Tribolium castaneum	882
719	Universe : Foraging	3767
720	Universe : Insect	69154
721	Universe : Mouse	424766
724	Universe : Mouse Mice	1023807

Author ▲	Title	Source	Pub Date
B Y H Thong : : K P Leong : : H	Insect venom hypersensitivity: experience in a clinical immunology/allergy service in Singapore.	Singapore medical journal	2005 Oct
C H Wu : : M F Lee : : S C Liac	Sequencing analysis of cDNA clones encoding the American cockroach Cr-PI allergens. Homology with insect hemolymph	The Journal of biological chemistry	1996 Jul
C J Bolter : : W Chefurka	Extramitochondrial release of hydrogen peroxide from insect and mouse liver mitochondria using the respiratory inhibitors pl	Archives of biochemistry and biophysics	1990 Apr
D Jones : : H Turner : : V Chhol	Altered hexamerin regulation in prepupal Trichoplusia ni pseudoparasitized by Chelonus sp. near curvimaculatus.	Archives of insect biochemistry and physiology	1996
D Knebel : : H Lubbert : : W Do	The promoter of the late p10 gene in the insect nuclear polyhedrosis virus Autographa californica: activation by viral gene pr	The EMBO journal	1985 May
E A Abdallah : : M E Eldefrawi :	Pharmacologic characterization of muscarinic receptors of insect brains.	Archives of insect biochemistry and physiology	1991
E T Schmidtmann : : J E Lloyd	Suppression of mosquito (Diptera: Culicidae) and black fly (Diptera: Simuliidae) blood feeding from Hereford cattle and ponie	Journal of medical entomology	2001 Sep
J Balzarini : : B Degreve : : S H	The multifunctional deoxynucleoside kinase of insect cells is a target for the development of new insecticides.	Molecular pharmacology	2000 Apr
J L Dimarcq : : D Zachary : : J /	Insect immunity: expression of the two major inducible antibacterial peptides, defensin and diptericin, in Phormia terranovae	The EMBO journal	1990 Aug
Lisa R Scully : : Michael J Bido	An alternative insect pathogenic strategy in an Aspergillus flavus auxotroph.	Mycological research	2009 Feb
N M Anthony : : J B Harrison : :	GABA receptor molecules of insects.	EXS	1993
P E Teal : : R J Nachman	Prolonged pheromonotropic activity of pseudopeptide mimics of insect pyrokinin neuropeptides after topical application or in	Regulatory peptides	1997 Oct
R Molina : : J M Lohse : : J Niet	Evaluation of a topical solution containing 65% permethrin against the sandfly (Phlebotomus perniciosus) in dogs.	Veterinary therapeutics : research in applied vet	2001
Ralf Heermann : : Thilo M Fuch:	Comparative analysis of the Photorhabdus luminescens and the Yersinia enterocolitica genomes: uncovering candidate gen	BMC genomics	2008
Richard G Vogt : : Natalie E Mil	The insect SNMP gene family.	Insect biochemistry and molecular biology	2009 Jul

Author: Richard G Vogt : : Natalie E Miller : : Rachel Litvack : : Richard A Fandino : : Jackson Sparks : : Jon Staples : : Robert Friedman : : Joseph C Dickens
Title: The insect SNMP gene family.
Source: Insect biochemistry and molecular biology Google Scholar Pubmed
Pub Date: 2009 Jul

Abstract: SNMPs are membrane proteins observed to associate with chemosensory neurons in insects; in Drosophila melanogaster, SNMP1 has been shown to be essential for the detection of the pheromone cis-vaccenyl acetate (CVA). SNMPs are one of three insect gene clades related to the human fatty acid transporter CD36. We previously characterized the CD36 gene family in 4 insect Orders that effectively cover the Holometabola, or some 80% of known insect species and the 300 million years of evolution since this lineage emerged: Lepidoptera (e.g. Bombyx mori, Antheraea polyphemus, Manduca sexta, Heliothis virescens, Helicoverpa assulta, Helicoverpa armigera, Mamestra brassicae); Diptera (D. melanogaster, Drosophila pseudoobscura, Aedes aegypti, Anopheles gambiae, Culex pipiens quinquefasciatus); Hymenoptera (Apis mellifera); and Coleoptera (Tribolium castaneum). This previous study suggested a complex topography within the SNMP clade including a strongly supported SNMP1 sub-clade plus additional SNMP genes. To further resolve the SNMP clade here, we used cDNA sequences of SNMP1 and SNMP2 from various Lepidoptera species, D. melanogaster and Ae. aegypti, as well as BAC derived genomic sequences from Ae. aegypti as models for proposing corrected sequences of orthologues in the D. pseudoobscura and An. gambiae genomes, and for identifying orthologues in the B. mori and C. pipiens q. genomes. We then used these sequences to analyze the SNMP clade of the insect CD36 gene family, supporting the existence of two well supported sub-clades, SNMP1 and SNMP2, throughout the dipteran and lepidopteran lineages, and plausibly throughout the Holometabola and across a broad evolutionary time scale. We present indirect evidence based on evolutionary selection (dN/dS) that the dipteran SNMPs are expressed as functional proteins. We observed expansions of the SNMP1 sub-clade in C. pipiens q. and T. castaneum suggesting that the SNMP1s may have an expanded functional role in these species.
Chemicals: Insect Proteins : Receptors, Pheromone
Genes:
Keywords:

Author	Title	Source	Pub Date
Rodrigo A Velarde : : Gene E R	Nuclear receptors of the honey bee: annotation and expression in the adult brain.	Insect molecular biology	2006 Oct
Sigrid D Roosendaal : : Jan M \	Delipidation of insect lipoprotein, lipophorin, affects its binding to the lipophorin receptor, LpR: implications for the role of Lpl	Insect biochemistry and molecular biology	2009 Feb
Suparna Taneja-Bageshwar : : /	Biostable agonists that match or exceed activity of native insect kinins on recombinant arthropod GPCRs.	General and comparative endocrinology	2009 May
Xiaowei Wang : : Lanzhu Ji : : C	[Potential effects of elevated carbon dioxide on forest leaf-feeding insects]	Ying yong sheng tai xue bao = The journal of ap	2006 Apr

Page 10 of 3458

Topics 181 - 200 of 69154

Figure 2. System spaces provide standard starting collections for new task spaces within the BioSpace.

accounts, enabling them to save and manage their spaces. The privacy settings permit spaces to be hidden, but encourage openness for scientific progress. Indeed, building new research upon old research is the paradigm of science; this is directly represented within the space paradigm using community spaces as the knowledge unit.

The system services for space creation are general. Searching is a mechanism for partitioning spaces via the Filter service, there are also powerful features for clustering via the Cluster service. These have been optimized via parallel computation on shared memory servers, to operate interactively with appropriate-sized collections. The Natural Clusterer works from the bottom-up, partitioning on the basis of phrases occurring in the documents. Using small worlds algorithms, it operates interactively on collections in the range of 50–100 K documents (5). The Steerable Clusterer works from the top-down, partitioning on the basis of phrases weighted by words specified by the user for each cluster. Using language models algorithms, it operates interactively on collections in the 5–10 K document range (6). Individual clusters can be saved as spaces by the user to feed into other services for functional analysis.

The real-time interactive clustering is possible only because of modern computing technology. Clustering involves computing distance in an *n*-dimensional space, so speed is proportional to size of the memory. The production system for BeeSpace Navigator is hosted on a $70 K parallel computer with 128GB memory at http://workerbee.igb.uiuc.edu. This is double the memory of the $7 M super computer that hosted Interspace Prototype for the first semantic indexing of MEDLINE a decade ago (7). The project server has fewer processors than the supercomputer did, 16 versus 128, but the software is largely memory bound on the shared-memory machine. The implementation gains its interactive speed by locking the pre-computed indexes into memory.

GENE LIST ANALYSIS

Genomics has progressed from single genes to multiple genes, as the wet lab technologies have improved with microarrays and next-generation sequencing. The dry lab technologies have to correspondingly progress from single genes to multiple genes, to support functional analysis. The Genelist Analyzer is the automatic computational analogue of a genetic classification database, just as the Gene Summarizer discussed next is the automatic computational analogue of a model organism database.

The Gene Ontology (GO) is a hierarchical classification for biological topics used by human curators to specify the functions of genes (8). The major model organism databases are committed to GO and use the GO categories to specify additional functions for the curated genes. Functional analysis for microarray experiments is commonly supported using GO, by translating differentially expressed genes into the closest model organism using ortholog computations and then looking up the major classifications of the corresponding genes in the classification.

The Gene Ontology has the same limitations as other biomedical classifications, being dependent on the literature curated by the model organism database projects. For example, the BeeSpace project performed large-scale microarray experiments on social behavior in honey bee. There was thus difficulty in obtaining good results from GO, since the closest model organism was fruit fly, an insect but one with little social behavior. Recent analyses of GO nodes have also shown that annotation quality varies across model organisms (9) and that functional coherence of hierarchical terms is not uniform (10).

In contrast, the BeeSpace Navigator uses a computational approach to gene classification based upon current terminology contained in biological literature. Just as full-text search can extract the most specific and most current documents, automatic curation can extract the most specific and most current categories. Since discriminating concepts are uniformly extracted from whatever terms are represented within the specified literature, there is no bias from existing classifications. The Genelist Analyzer thus trades accuracy for currency: it uses the free text of specified documents to extract concepts that frequently appear with genes.

The Analyzer transforms gene names into concept names (11). The concepts identified are those with differential expression against the background, just as the statistical model for differential expression in microarray experiments. But concepts are identified, rather than genes, and the background is the specified space that describes the current task being analyzed. The ability in BeeSpace for space-oriented computations enables some of the accuracy loss in automatic extraction to be overcome, since the concepts are extracted only from the documents within that space. Just as different backgrounds produce different expressions with microarray experiments, different spaces produce different lists of concepts given the same lists of genes.

BeeSpace Navigator is an interactive system with selectable spaces, where the background for differential expression can be rapidly changed, providing support for dry lab experiments. Since every document collection created within the system can be transformed into a space, sets of concepts can be sweep selected and the documents associated with these concepts saved into a space. The saved space is then fully usable within the system and can be filtered or clustered to produce relevant subsets. For example, the most frequent concepts or the most frequent genes that are differentially expressed from a microarray experiment can be saved into a space, and then this space clustered using Steerable Cluster to find the documents most relevant to the behavior task. This dynamically created space can then be used as background for gene list analysis.

GENE SUMMARIZATION

Once a gene list is analyzed within a space, individual genes can be described using functional information contained within the articles of that space. BeeSpace began with automatic reproduction of FlyBase summarization (12). In FlyBase, gene descriptions are generated from database entries specified manually by human curators, who read literature articles to extract facts. The automatic curation process in BeeSpace Navigator was developed into a production service called the Gene Summarizer (13). This takes a gene name as input and produces relevant sentences describing the gene's functions as output.

During early system usage, it became clear that within an interactive system, showing the sentences from which the facts were extracted was more useful than simple summaries, since it enabled the biologist users to fully interpret the document context. The context for utility for biologists is necessarily more detailed than that for curators since they are generating hypotheses rather than extracting facts; the language processing is necessarily deeper than interactive support for FlyBase curators (14).

The categorization for the summarizer relied upon a semi-structured machine learning algorithm, derived in part from those for newspaper summarization. Development required new algorithms for deriving and training to classify sentences into functional categories (15). These categories were initially taken from FlyBase summaries, later refined by the curators themselves through our collaboration with the FlyBase project. The categories of gene function are: Protein Domain/Structure, Homologs/Orthologs, Expression Patterns, Regulatory Elements, Phenotype/Function, Genetic/Physical Interactions and Population Genetics.

The original plan was to have FlyBase curators provide training sets through our collaboration. But in comparing the recognitions of the professional curators to those of the practicing biologists who were working closely with us on developing the analysis system, we discovered that they differed substantively. Curators wanted only unambiguous facts, whereas biologists wanted useful observations. For example, a sentence speculating about a function was eliminated by the curators as uncertain but marked by the biologists as interesting.

We chose those biologists closest to our projected user population, graduate students and postdocs in entomology and neuroscience, as trainers to judge the categories of sentences. Semantic indexing using the trained recognizers was performed during 8 hour batch jobs on the National Science Foundation Cloud Computing Testbed hosted at the University of Illinois at Urbana-Champaign, making BeeSpace its largest internal user. Later, we were able to develop separate software for question answering (4), not included in version 4, which extracted entities and relations to generate biological facts, so closer in semantics to human biologist curators.

EXPLORATORY ANALYSIS OF GENE FUNCTION

The software has gone through four versions over 6 years and has been used by over 100 biologists, including local researchers, workshop trainees and meeting attendees at Arthropod Genomics Symposia. The production Version 4 was early released in January 2010 and fully released in June 2010.

Training materials are available at www.beespace.uiuc.edu/bstwmaterials.php, including overview talks and sample sessions from the Training Workshop held in April 2010. The software itself is a mix of C, Python and Java. The user interface runs within a web browser using ExtJS javascript, an AJAX toolkit. A recent version of Mozilla Firefox or Google Chrome is recommended for best performance. No login is required for usage as guest, but if the user logs in, then generated spaces are saved under their login for future utilization.

This interface enables all the services to be used in concert with each other, demonstrating the utility of a space-based system. Every service can create a new space during the interactive session, whenever a relevant collection of documents is created. Thus the whole of the system is greater than the sum of the parts. In particular, community sharing of discovered knowledge about gene function is an integral part of the system, since biologists can reuse existing spaces.

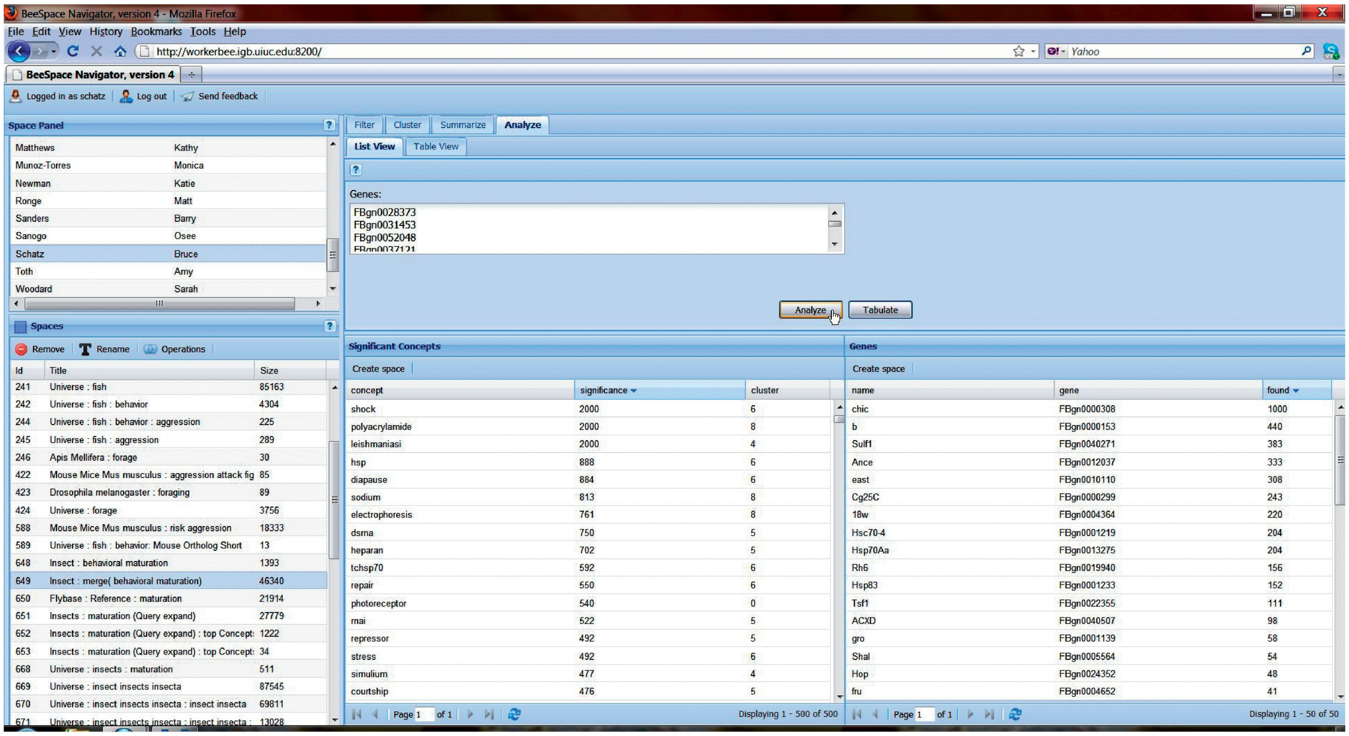
As an example session, following are representative screendumps of the analysis performed by the first author, a BeeSpace biologist postdoc, for her gene expressions on behavioral maturation in honey bee (16). Only a few key screens are shown; for a full step-by-step usage, see the sample sessions in the Supplementary Data, with each step annotated.

The gene list extracted from these experiments and used below in the session can be found at www.canis.uiuc.edu/~schatz/GAtest.txt. The gene list must consist of record numbers from model organism databases, here FlyBase (FB), but also including Mouse Genome Informatics (MGI) and Saccharomyces Genome Database (SGD).

In the session, the biologist did multiple Filter operations with space arithmetic to build a task space on behavior maturation containing 46 340 of the 69 154 documents for insect. She created separate spaces for social insects (sociality within insect space) and for behavioral maturation (maturation within animal space), then intersected these custom spaces into a task space.

Now that the background is selected, the exploratory analysis of gene function can commence. Figure 3 shows the Analyze service where the gene list from the expression experiment has been entered into the box and the concepts within the background space analyzed. The most discriminating concepts are rank ordered in the left lower pane. These are the terms that differentially occur most often in documents with genes from the list mentioned as opposed to terms in other documents. The genes themselves are rank ordered in the right pane, with names translated from the FlyBase ortholog numbers specified as input, as described elsewhere (11).

To examine the results, the top genes are selected, taking the 10 most frequent after skipping the first two as artifacts. A save is then issued, to create a space of the documents containing these genes within the background space. The new space resulting from the top genes differentiating the gene expressions within the maturation task can now be used for further exploration. Figure 4 shows the *Cluster* service operating on the 2314 documents. At this scale, the biologist can partition semantically along desired lines using the Steerable Clusterer. Here the user partitions along the lines of the top concepts discovered during analysis, namely 'shock', 'diapause', 'repair', and adding the important 'hormone'. Note diapause was discovered automatically, and is relevant to behavioral maturation in response to environmental conditions. Within the 'hormone' cluster, underlined terms such as JH for Juvenile Hormone were



Matthews	Kathy
Munoz-Torres	Monica
Newman	Katie
Ronge	Matt
Sanders	Barry
Sanogo	Osee
Schatz	Bruce
Toth	Amy
Woodard	Sarah

Id	Title	Size
241	Universe : fish	85163
242	Universe : fish : behavior	4304
244	Universe : fish : behavior : aggression	225
245	Universe : fish : aggression	289
246	Apis Mellifera : forage	30
422	Mouse Mice Mus musculus : aggression attack fig	85
423	Drosophila melanogaster : foraging	89
424	Universe : forage	3756
588	Mouse Mice Mus musculus : risk aggression	18333
589	Universe : fish : behavior: Mouse Ortholog Short	13
648	Insect : behavioral maturation	1393
649	Insect : merge(behavioral maturation)	46340
650	Flybase : Reference : maturation	21914
651	Insects : maturation (Query expand)	27779
652	Insects : maturation (Query expand) : top Concept:	1222
653	Insects : maturation (Query expand) : top Concept:	34
668	Universe : insects : maturation	511
669	Universe : insect insects insecta	87545
670	Universe : insect insects insecta : insect insecta	69811
671	Universe : insect insects insecta : insect insecta :	13028

Genes:
FBgn0028373
FBgn0031453
FBgn0052048
FBgn0037121

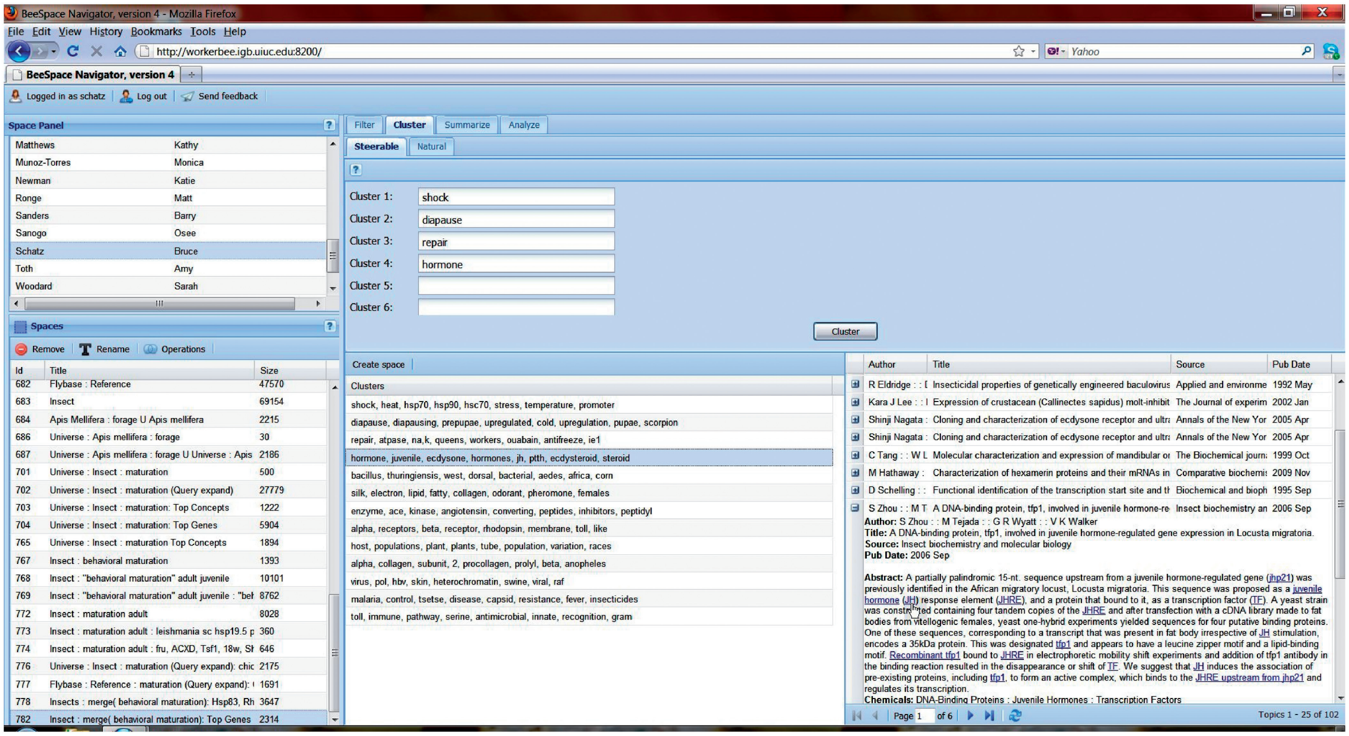
concept	significance	cluster
shock	2000	6
polyacrylamide	2000	8
leishmaniasi	2000	4
hsp	888	6
diapause	884	6
sodium	813	8
electrophoresis	761	8
dsrna	750	5
heparan	702	5
tchsp70	592	6
repair	550	6
photoreceptor	540	0
rnai	522	5
repressor	492	5
stress	492	6
simulium	477	4
courtship	476	5

Page 1 of 1 Displaying 1 - 500 of 500

name	gene	found
chic	FBgn0000308	1000
b	FBgn0000153	440
Sulf1	FBgn0040271	383
Ance	FBgn0012037	333
east	FBgn0010110	308
Cg25C	FBgn0000299	243
18w	FBgn0004364	220
Hsc70-4	FBgn0001219	204
Hsp70Aa	FBgn0013275	204
Rh6	FBgn0019940	156
Hsp83	FBgn0001233	152
Tsf1	FBgn0022355	111
ACXD	FBgn0040507	98
gro	FBgn0001139	58
Shal	FBgn0005564	54
Hop	FBgn0024352	48
fru	FBgn0004652	41

Page 1 of 1 Displaying 1 - 50 of 50

Figure 3. Analyze transforms a gene list into a list of discriminating concepts within a space.



Matthews	Kathy
Munoz-Torres	Monica
Newman	Katie
Ronge	Matt
Sanders	Barry
Sanogo	Osee
Schatz	Bruce
Toth	Amy
Woodard	Sarah

Id	Title	Size
682	Flybase : Reference	47570
683	Insect	69154
684	Apis Mellifera : forage U Apis mellifera	2215
686	Universe : Apis mellifera : forage	30
687	Universe : Apis mellifera : forage U Universe : Apis	2186
701	Universe : Insect : maturation	500
702	Universe : Insect : maturation (Query expand)	27779
703	Universe : Insect : maturation: Top Concepts	1222
704	Universe : Insect : maturation: Top Genes	5904
765	Universe : Insect : maturation Top Concepts	1894
767	Insect : behavioral maturation	1393
768	Insect : "behavioral maturation" adult juvenile	10101
769	Insect : "behavioral maturation" adult juvenile : "bel	8762
772	Insect : maturation adult	8028
773	Insect : maturation adult : leishmania sc hsp19.5 p	360
774	Insect : maturation adult : fru, ACXD, Tsf1, 18w, Sl	646
776	Universe : Insect : maturation (Query expand): chic	2175
777	Flybase : Reference : maturation (Query expand): (	1691
778	Insects : merge(behavioral maturation): Hsp83, Rh	3647
782	Insect : merge(behavioral maturation): Top Genes	2314

Cluster 1: shock
Cluster 2: diapause
Cluster 3: repair
Cluster 4: hormone
Cluster 5:
Cluster 6:

Clusters
shock, heat, hsp70, hsp90, hsc70, stress, temperature, promoter
diapause, diapausing, prepupae, upregulated, cold, upregulation, pupae, scorpion
repair, atpase, na,k, queens, workers, ouabain, antifreeze, ie1
hormone, juvenile, ecdysone, hormones, jh, ptth, ecdysteroid, steroid
bacillus, thuringiensis, west, dorsal, bacterial, aedes, africa, corn
silk, electron, lipid, fatty, collagen, odorant, pheromone, females
enzyme, ace, kinase, angiotensin, converting, peptides, inhibitors, peptidyl
alpha, receptors, beta, receptor, rhodopsin, membrane, toll, like
host, populations, plant, plants, tube, population, variation, races
alpha, collagen, subunit, 2, procollagen, prolyl, beta, anopheles
virus, pol, hbv, skin, heterochromatin, swine, viral, raf
malaria, control, tsetse, disease, capsid, resistance, fever, insecticides
toll, immune, pathway, serine, antimicrobial, innate, recognition, gram

Author	Title	Source	Pub Date
R Eldridge : : [	Insecticidal properties of genetically engineered baculovirus	Applied and environme	1992 May
Kara J Lee : : I	Expression of crustacean (Callinectes sapidus) molt-inhibit	The Journal of experim	2002 Jan
Shinji Nagata :	Cloning and characterization of ecdysone receptor and ultr:	Annals of the New Yor	2005 Apr
Shinji Nagata :	Cloning and characterization of ecdysone receptor and ultr:	Annals of the New Yor	2005 Apr
C Tang : : W L	Molecular characterization and expression of mandibular or	The Biochemical journ:	1999 Oct
M Hathaway :	Characterization of hexamerin proteins and their mRNAs in	Comparative biochemi:	2009 Nov
D Schelling : :	Functional identification of the transcription start site and tl	Biochemical and bioph	1995 Sep
S Zhou : : M T	A DNA-binding protein, tfp1, involved in juvenile hormone-re	Insect biochemistry an	2006 Sep

Author: S Zhou : : M Tejada : : G R Wyatt : : V K Walker
Title: A DNA-binding protein, tfp1, involved in juvenile hormone-regulated gene expression in Locusta migratoria.
Source: Insect biochemistry and molecular biology
Pub Date: 2006 Sep

Abstract: A partially palindromic 15-nt. sequence upstream from a juvenile hormone-regulated gene (jhp21) was previously identified in the African migratory locust, Locusta migratoria. This sequence was proposed as a juvenile hormone (JH) response element (JHRE), and a protein that bound to it, as a transcription factor (TF). A yeast strain was constructed containing four tandem copies of the JHRE and after transfection with a cDNA library made to fat bodies from vitellogenic females, yeast one-hybrid experiments yielded sequences for four putative binding proteins. One of these sequences, corresponding to a transcript that was present in fat body irrespective of JH stimulation, encodes a 35kDa protein. This was designated tfp1 and appears to have a leucine zipper motif and a lipid-binding motif. Recombinant tfp1 bound to JHRE in electrophoretic mobility shift experiments and addition of tfp1 antibody in the binding reaction resulted in the disappearance or shift of TF. We suggest that JH induces the association of pre-existing proteins, including tfp1, to form an active complex, which binds to the JHRE upstream from jhp21 and regulates its transcription.
Chemicals: DNA-Binding Proteins : Juvenile Hormones : Transcription Factors

Figure 4. Cluster partitions a space into groups of related documents that each can become a space.

automatically recognized as genes during the semantic indexing (17).

If the biologist wishes to discover the function of genes discovered during the exploratory analysis, she can summarize what knowledge is known within the literature. Figure 5 shows the Summarize service, where it has been implicitly invoked by clicking on the gene name underlined as juvenile hormone. The Gene Summarizer then simulates the curation process for the specified gene on the specified collection. In this case, the specified collection was the task space that resulted from exploratory analysis of the experiment for gene expression. The computed categories of gene function include gene phenotypes and gene interactions. The automatic curation enables a task-centered analysis of gene function rather than an organism-centered, which fits better with experiments such as this on dynamic expression for animal behavior.

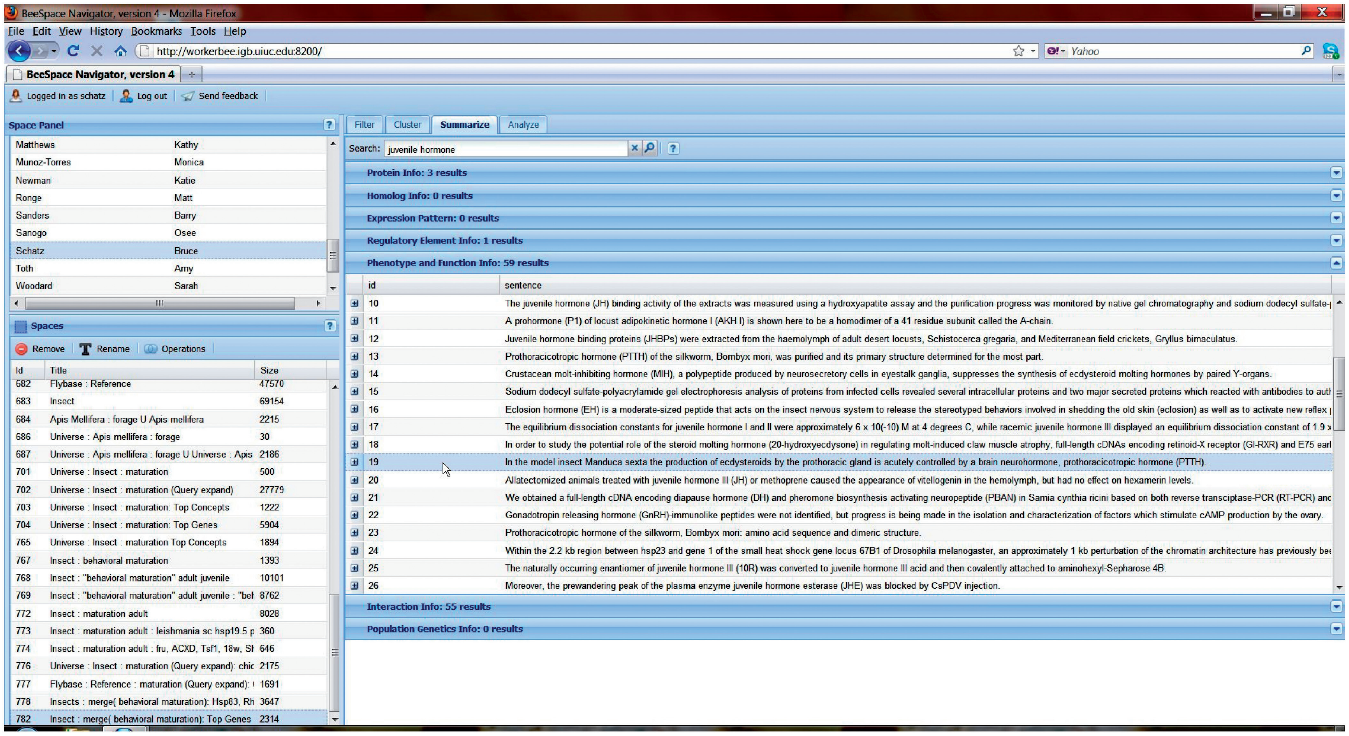
The process of concept navigation can be continued by opening a document such as highlighted one on *Manduca sexta* and clicking on an underlined gene name, such as EcR for Ecdysteroid Receptor. Now that the biologist has explored from bees to moths, she could re-analyze the expression gene list within the new context of ecdysteroid receptors by simply creating a space from the summarizer results and clicking the Analyze tab to reinvoke the Analyze service with the same gene list but on the new space. Exploratory analysis of gene function is an iterative process of concept navigation through biological literature.

As another example, another BeeSpace postdoc was investigating gene expression of maternal behavior in paper wasp (18). Maternal behavior is little studied in insects so running Analyze against *Drosophila* space was little help. After trying analysis with fly orthologs from the wasp genes, she instead generated mouse orthologs from the same wasp genes. A task-oriented space was created from the mouse literature relevant to maternal behavior using Filter of 'maternal' query against mouse space. Then Cluster was done on the 9618 documents within Mouse Maternal space, using the Natural Clusterer this time since the functional category was not known. The 33 resulting documents from one relevant cluster included an article dealing with regulation by a heat shock factor gene of maternal expression in the oocyte (19).

The postdoc insect biologist found this article in the mouse literature of significant interest. Her GO analysis did not identify heat shock as discriminating term for her gene list, possibly due to the wide distribution of heat shock entries across their conceptual hierarchy. The more focused automatic analysis discovered this concept relation. Typically, navigations with appropriate orthologs against task-oriented spaces produce novel documents of interest to the biologist. Besides insects, the BeeSpace Navigator has helped biologists working on fish, pigs and plants.

CONCLUSION

As the examples above show, the effective process of exploring function via concept navigation leverages existing manual classifications and existing biologist descriptions. The model organism databases are essential


BeeSpace Navigator, version 4 - Mozilla Firefox
File Edit View History Bookmarks Tools Help
http://workerbee.igb.uiuc.edu:8200/
Yahoo
BeeSpace Navigator, version 4
Logged in as schatz
Log out
Send feedback
Space Panel
Spaces
Remove
Rename
Operations
Filter
Cluster
Summarize
Analyze

Search: juvenile hormone

Matthews	Kathy
Munoz-Torres	Monica
Newman	Katie
Ronge	Matt
Sanders	Barry
Sanogo	Osee
Schatz	Bruce
Toth	Amy
Woodard	Sarah

Id	Title	Size
682	Flybase : Reference	47570
683	Insect	69154
684	Apis Mellifera : forage U Apis mellifera	2215
686	Universe : Apis mellifera : forage	30
687	Universe : Apis mellifera : forage U Universe : Apis	2186
701	Universe : Insect : maturation	500
702	Universe : Insect : maturation (Query expand)	27779
703	Universe : Insect : maturation: Top Concepts	1222
704	Universe : Insect : maturation: Top Genes	5904
765	Universe : Insect : maturation Top Concepts	1894
767	Insect : behavioral maturation	1393
768	Insect : "behavioral maturation" adult juvenile	10101
769	Insect : "behavioral maturation" adult juvenile : "bel	8762
772	Insect : maturation adult	8028
773	Insect : maturation adult : leishmania sc hsp19.5 p	360
774	Insect : maturation adult : fru, ACXD, Tsf1, 18w, Sl	646
776	Universe : Insect : maturation (Query expand): chic	2175
777	Flybase : Reference : maturation (Query expand): (	1691
778	Insects : merge(behavioral maturation): Hsp83, Rh	3647
782	Insect : merge(behavioral maturation): Top Genes	2314

Protein Info: 3 results

Homolog Info: 0 results

Expression Pattern: 0 results

Regulatory Element Info: 1 results

Phenotype and Function Info: 59 results

id	sentence
10	The juvenile hormone (JH) binding activity of the extracts was measured using a hydroxyapatite assay and the purification progress was monitored by native gel chromatography and sodium dodecyl sulfate-
11	A prohormone (P1) of locust adipokinetic hormone I (AKH I) is shown here to be a homodimer of a 41 residue subunit called the A-chain.
12	Juvenile hormone binding proteins (JHBPs) were extracted from the haemolymph of adult desert locusts, Schistocerca gregaria, and Mediterranean field crickets, Gryllus bimaculatus.
13	Prothoracicotropic hormone (PTTH) of the silkworm, Bombyx mori, was purified and its primary structure determined for the most part.
14	Crustacean molt-inhibiting hormone (MIH), a polypeptide produced by neurosecretory cells in eyestalk ganglia, suppresses the synthesis of ecdysteroid molting hormones by paired Y-organs.
15	Sodium dodecyl sulfate-polyacrylamide gel electrophoresis analysis of proteins from infected cells revealed several intracellular proteins and two major secreted proteins which reacted with antibodies to aut
16	Eclosion hormone (EH) is a moderate-sized peptide that acts on the insect nervous system to release the stereotyped behaviors involved in shedding the old skin (eclosion) as well as to activate new reflex
17	The equilibrium dissociation constants for juvenile hormone I and II were approximately 6 x 10(-10) M at 4 degrees C, while racemic juvenile hormone III displayed an equilibrium dissociation constant of 1.9 x
18	In order to study the potential role of the steroid molting hormone (20-hydroxyecdysone) in regulating molt-induced claw muscle atrophy, full-length cDNAs encoding retinoid-X receptor (Gl-RXR) and E75 earl
19	In the model insect Manduca sexta the production of ecdysteroids by the prothoracic gland is acutely controlled by a brain neurohormone, prothoracicotropic hormone (PTTH).
20	Allatectomized animals treated with juvenile hormone III (JH) or methoprene caused the appearance of vitellogenin in the hemolymph, but had no effect on hexamerin levels.
21	We obtained a full-length cDNA encoding diapause hormone (DH) and pheromone biosynthesis activating neuropeptide (PBAN) in Samia cynthia ricini based on both reverse transciptase-PCR (RT-PCR) and
22	Gonadotropin releasing hormone (GnRH)-immunolike peptides were not identified, but progress is being made in the isolation and characterization of factors which stimulate cAMP production by the ovary.
23	Prothoracicotropic hormone of the silkworm, Bombyx mori: amino acid sequence and dimeric structure.
24	Within the 2.2 kb region between hsp23 and gene 1 of the small heat shock gene locus 67B1 of Drosophila melanogaster, an approximately 1 kb perturbation of the chromatin architecture has previously bee
25	The naturally occurring enantiomer of juvenile hormone III (10R) was converted to juvenile hormone III acid and then covalently attached to aminohexyl-Sepharose 4B.
26	Moreover, the prewandering peak of the plasma enzyme juvenile hormone esterase (JHE) was blocked by CsPDV injection.

Interaction Info: 55 results

Population Genetics Info: 0 results

Figure 5. Summarize describes the gene functions of specified gene within a task-specific.

to turn expressed genes into gene names, which can then be correlated within the biological literature to extract gene functions. BeeSpace is the first major system to build spaces upon bases, to utilize scalable semantic indexing to automatically extract functional concepts and categories. Space creation is a uniform operation, enabling community sharing to build new collections of related documents from old.

Such systems will be used to support hypothesis generation to rapidly compare gene function using different spaces to discover new classifications. Currently, most gene lists are generated via microarrays specialized to particular organisms. But the rapid increase in sequencing power is changing this paradigm to one where gene lists for specific tasks can be generated with general RNA-seq (20). Even an early system such as BeeSpace is just as effective for RNA-seq as for microarray, since it deals only with gene names and gene lists. Exploratory analysis by knowledgeable biologists leveraging existing databases is the viable path towards understanding gene function in the new era of dynamic expression of organism behavior. The interconnected space of biological knowledge will be created by functional analysis from insects such as fly and bee, beetle and wasp, then move to InsectSpace and ArthropodSpace then AnimalSpace and PlantSpace en route to creating the BioSpace.

The future system will change its name to BioSpace Navigator, reflecting this more general mission. As noted, the software has no embedded knowledge of bees or insects, merely general text mining. Future plans are to integrate the navigator functionality described in this production version into a fully fledged gene function discovery environment. Enhancements will include enhanced speed for services and periodic updating of sources, importing gene lists and exporting document sets, computing orthologs and linking to genome browsers.

SUPPLEMENTARY DATA

Supplementary Data are available at NAR Online, giving a step by step interactive session with BeeSpace Navigator.

ACKNOWLEDGEMENTS

The Informatics team thanks the Biology team, especially leader Gene Robinson and his laboratory including Amy Toth and Nyla Ismail. Other Computer Science graduate students who contributed include Yuanhua Lv, Yanen Li and Yue Lu. Other Institute for Genomic Biology (IGB) professional staff on the project contributed include Matt Ronge, Chris Fields and Jim Buell. We thank the administration at IGB especially the computer support led by Dan Davidson. We thank the Cloud Computing Testbed in the Department of Computer Science, especially lead faculty Indranil Gupta. The administrators of the insect databases provided expertise and support in many ways, and we especially thank William Gelbart of FlyBase at Harvard, Susan Brown of BeetleBase at Kansas State, Christine Elsik of BeeBase at Georgetown. Creating this new system with new research and development would have been impossible without all these people and many others.

FUNDING

National Science Foundation (0425852) in the Frontiers Integrative Biological Research (FIBR) program from September 2004 to August 2010, entitled 'BeeSpace: An Interactive Environment for Analyzing Nature and Nurture in Societal Roles'. Additional funding for software development and open access provided by United States Department of Agriculture National Research Initiative Arthropod Biology Tools (2009-35302-05285, to B.S. PI as with NSF FIBR grant).

Conflict of interest statement. None declared.

REFERENCES

1. Schatz,B. (2002) The Interspace: concept navigation across distributed communities. *IEEE Comp*., **35**, 54–62.
2. Schatz,B. (2002) Building analysis environments: beyond the genome and the web. Special Issue on Mining Information for Functional Genomics. *IEEE Intel. Sys*., **17**, 70–73.
3. Chen,H., Martinez,J., Ng,T. and Schatz,B. (1997) A concept space approach to addressing the vocabulary problem in scientific information retrieval: an experiment on the worm community system. *J. Am. Soc. Inform. Sci*., **48**, 17–31.
4. He,X., Li,Y., Khetani,R., Sanders,B., Lu,Y., Ling,X., Zhai,C. and Schatz,B. (2010) BSQA: integrated text mining using entity relation semantics extracted from biological literature of insects. *Nucleic Acids Res*., **38**, W175–W181.
5. Chee,B. and Schatz,B. (2007) Document clustering using small worlds communities. *Proc 7th ACM/IEEE Jt. Conf. Digit. Lib*., 53–62.
6. Ling,X., Mei,Q., Zhai,C. and Schatz,B. (2008) Mining multi-faceted overviews of arbitrary topics in text collections. *Proc 17th ACM Conf. Knowl. Disc. Data Mining*, 497–505.
7. Chung,Y., He,Q., Powell,K. and Schatz,B. (1999) Semantic indexing for a complete subject discipline. *Proc 4th Int. ACM Conf. Digit. Lib*., 39–48.
8. Harris,M., Clark,J., Ireland,A., Lomax,J., Ashburner,M., Foulger,R., Eilbeck,K., Lewis,S., Marshall,B., Mungall,C. *et al*. (2004) The Gene Ontology (GO) database. *Nucleic Acids Res*., **32**, D258–D261.
9. Buza,T., McCarthy,F., Wang,N., Bridges,S. and Burgess,S. (2008) Gene Ontology annotation quality analysis in model eukaryotes. *Nucleic Acids Res*., **36**, e12.
10. Chagoyen,M. and Pazos,F. (2010) Quantifying the biological significance of gene ontology biological processes—implications for the analysis of systems-wide data. *Bioinformatics*, **26**, 378–384.
11. He,X., Chee,B., Sen Sarma,M., Zhai,C. and Schatz,B. (2010) Identifying overrepresented concepts in gene lists from literature: a statistical approach based on Poisson mixture model. *BMC Bioinformatics*, **11**, 272–284.
12. Drysdale,R., Crosby,M. and FlyBase Consortium. (2005) FlyBase: genes and gene models. *Nucleic Acids Res*., **33**, D390–D395.
13. Ling,X., Jiang,J., He,X., Mei,Q., Zhai,C. and Schatz,B. (2006) Automatically generating gene summaries from biological literature. *Pac. Symp. Biocomput*., **11**, 40–51.
14. Karamanis,N., Lewin,I., Seal,R., Drysdale,R. and Briscoe,E. (2007) Integrating natural language processing with FlyBase Curation. *Pac. Symp. Biocomput*., **12**, 245–256.
15. Ling,X., Jiang,J., Mei,Q., He,X., Zhai,C. and Schatz,B. (2007) A study of semi-structured summarization: generating gene summaries from biological literature. *Inform. Process. Manage*., **43**, 1777–1791.
16. Sen Sarma,M., Whitfield,C. and Robinson,G. (2007) Species differences in brain gene expression profiles associated with adult behavioral maturation in honey bees. *BMC Genomics*, **8**, 202.
17. Jiang,J. and Zhai,C. (2007) An empirical study of tokenization strategies for biomedical information retrieval. *Inform. Retriev*., **10**, 341–363.
18. Toth,A., Varala,K., Newman,T., Miguez,F., Hutchison,S., Willoughby,D., Simons,J., Egholm,M., Hunt,J., Hudson,M. *et al*. (2007) Wasp gene expression supports an evolutionary link between maternal behavior and eusociality. *Science*, **318**, 441–444.
19. Christians,E., Davis,A., Thomas,S. and Benjamin,I. (2000) Embryonic development: maternal effect of Hsf1 on reproductive success. *Nature*, **407**, 693–694.
20. Wang,Z., Gerstein,M. and Snyder,M. (2009) RNA-seq: a revolutionary tool for transcriptomics. *Nat. Rev. Genet*., **10**, 57–63.