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PathBinderH: a Tool for Sentence-Focused, Plant Taxonomy-Sensitive Access to the Biological Literature

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Access to the Biological Literature

ABSTRACT

Mining the biological “literaturome” promises significant advancements in genome annotation, literature access, curation support, and other applications. Standard tools allow users to identify scientific abstracts containing one or more query terms. In contrast, PathBinderH is a Web-served text mining tool that allows users to search PubMed (including MEDLINE) for sentences with co-occurring terms and their containing abstracts. The most novel and distinguishing feature of PathBinderH, however, is that the set of abstracts to be searched can be constrained by user-specified plant taxa. This enables (1) screening out abstracts dealing with species of less interest while retrieving sentences from abstracts about any of the potentially many species within the specified taxa, and (2) identifying abstracts that are more likely to prove relevant to a user than abstracts that contain the query terms in different sentences, because the query terms are more likely to be used in a coordinated way.

PathBinderH may be run over the Web at www.plantgenomics.iastate.edu/PathBinderH. By making it easier to access relevant literature, PathBinderH not only enables the plant community to efficiently zero in on existing works, enhancing their dissemination and hence their contributions, it also demonstrates a literature access model that can be directly applied to the literatures of other biological research communities.

INTRODUCTION

Automated text mining in biology has grown dramatically in importance and activity since the late 1990s, motivated by the expectation that this will enhance efforts to understand and control biological processes (Barnes, 2002; Blagosklonny and Pardee, 2002; Dickman, 2003). Mined information can then be used for applications such as gene annotation and streamlined literature access.

The goal of mining the biological literature for interactions has inspired several efforts to generate public resources. Prominent among these are MedMiner at the National Library of Medicine (Tanabe et al., 1999), PreBIND (Donaldson et al., 2003), a project feeding the curated BIND (Bader et al., 2002) system at the University of Toronto, Arrowsmith at the University of Chicago (Swanson, 2004), and iHOP (2004). The scale of such mined resources is much greater than that of on-line interaction database projects that rely on manual input of interactions such as MINT (Zanzoni et al., 2002), DIP (Marcotte et al., 2001; Xenarios et al., 2002), and HPRD (Peri et al., 2003). This attests to the present and potential future value of automatically mining the scientific literature.

However, mining-based works do not usually integrate information from the biological taxonomy into the resources they provide. Species relatedness as expressed by the biological taxonomy promises significant improvement in gene annotation and literature access. The lack of taxonomy sensitivity unnecessarily hinders access to the scientific literature by systems biologists, students, and many others. It also renders unavailable the ready annotation of genes with relevant passages from the literature, thus hindering full use of existing knowledge.

PathBinderH is designed to demonstrate incorporation of the plant taxonomy into literature access. Users can view sentences and their containing abstracts relevant to specified plant taxa even when the taxon in the query is not the one mentioned in the abstract. For example, specifying poaceae as the taxon will enable an abstract mentioning maize or corn to be retrieved.

This is significantly more powerful than requiring users to state all of the species and other taxa names that are of interest explicitly.

The system we have built to demonstrate this is described next. The account here significantly expands the material presented by Ding et al. (2005).

THE PATHBINDERH SYSTEM

PathBinderH is a Web-based tool that allows biologists enhanced access to an important segment of the scientific literature, PubMed, an on-line literature search service provided by the U.S. National Library of Medicine that contains MEDLINE and some smaller resources. PathBinderH itself consists of five modules: a dictionary, PubMed crawler, sentence database, taxonomy filter, and Web-based user interface (Figure 1). The *dictionary* contains terms collected from the Enzyme Nomenclature Database (ENZYME, 2004), The Gene Ontology (GO, 2004), the Plant Ontology (PO, 2004), and MeSH (2004). The *crawler* populates the sentence database by pulling in each sentence containing two (or more) different terms in the dictionary from each PubMed entry. A PubMed entry usually consists of a title, an abstract, and some ancillary information. Often, multiple terms exist for the same or very similar concepts. Thus, PathBinderH returns sentences containing either the terms specified by the user or their synonyms. The Web interface provides a convenient interface for retrieving and presenting sentences. Each presented sentence is accompanied by a clickable link pointing to its containing on-line PubMed entry. The interface also provides an easy way to set up taxonomy filters, so that sentences are retrieved only from PubMed entries that concern the plant species or other taxa of interest.

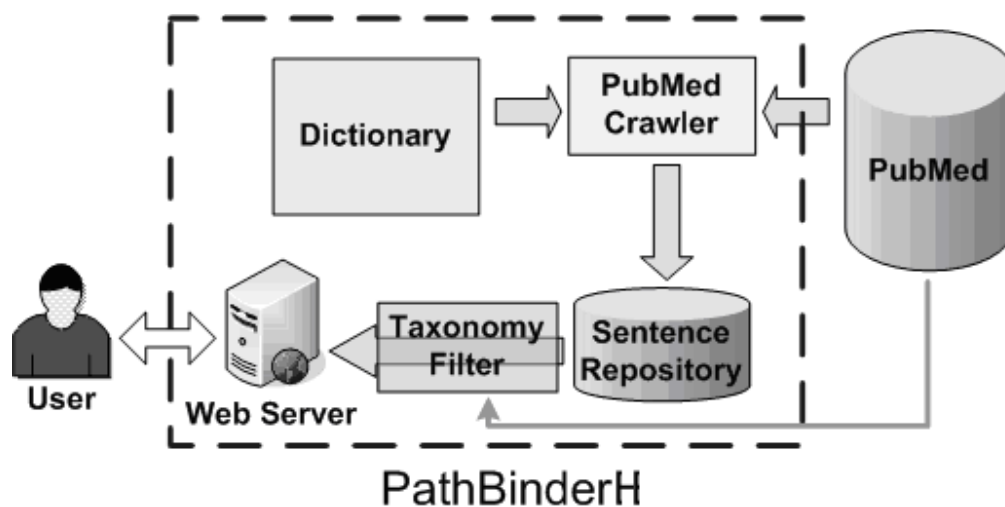


Figure 1. Architectural overview of PathBinderH.

The Taxonomy Filter

This useful capability is apparently not currently available in other biomedical text retrieval systems with the exception of PubMedCentral (<http://www.pubmedcentral.nih.gov/>), which does not support the sentence-focused retrieval approach of PathBinderH. Thus, a user is unable to search only those PubMed entries relevant to grasses (including maize, wheat, rice, etc.), or to green plants in general (thus also considering *Arabidopsis* and many other species). To address this important challenge, PathBinderH uses of a synonym database and the Linnaean taxonomy database available via the NCBI Entrez Taxonomy Homepage (2004). This database contains the names of organisms represented in the genetic databases in a hierarchical format. For every taxon in the plant portion of the tree, a list of PubMed entries that mention the taxon was automatically created by querying PubMed with the entry's scientific name plus its common names. Each PubMed entry indexed in PathBinderH is classified according to any plant taxa it explicitly mentions, as well as all plant taxa above it in the NCBI taxonomy. Consequently if a user sets the taxonomy filter when querying, sentences from PubMed entries in lists associated with the same or lower taxa are retrieved. Hence, a PubMed entry mentioning maize (or *Zea mays*, or corn) will

also be flagged as being associated with *Zea*, Andropogoneae, Panicoideae, Poaceae, etc. This feature allows users to search, for example, all PubMed entries that mention a species or other taxon below Poaceae in the taxonomy (which will cover those that mention maize, wheat and rice, but not Arabidopsis) or below Magnoliophyta (which will additionally cover Arabidopsis and many other plants).

The Dictionary

This database of concepts and terms was built from a variety of sources (Table I). For the current system, terms from the Gene Ontology (GO, 2004), the Plant Ontology (PO, 2004), the Enzyme Nomenclature Database (ENZYME, 2004), and MeSH (2004) are included. In the future, additional terms from the Unified Medical Language System (UMLS, 2004), may be added. The **Gene Ontology** is provided by the Gene Ontology Consortium to help annotate gene products based on molecular function, biological process and cellular component. The **Plant Ontology** from the Plant Ontology Consortium (POC) gives a controlled vocabulary for plant anatomy and growth stages. Both the plant and gene ontology updates for PathBinderH are through Gramene (2004), the Comparative Mapping Resource for Grains. The **Enzyme Nomenclature** was obtained from ExPASy Enzyme. This includes the Enzyme number (EC#) and enzyme names. **MeSH** gives a lexicon of concepts and synonyms which is continually updated by subject specialists in various bioscience areas.

Source	# of concepts	# of terms
Enzyme Nomenclature Database	3,978	12,944
Gene Ontology	15,959	20,128
Plant Ontology	551	551
Medical Subject Headings	22,584	79,873
Total	43,072	113,496

Table I. Sources of the concepts and terms in the PathBinderH dictionary.

PubMed

The source of all the text mined by PathBinderH is the U.S. National Library of Medicine's PubMed (2004) service, which provides all of the information including titles and abstracts available from the MEDLINE database at NLM, in addition to lesser amounts of other texts. PubMed includes over 14 million citations to articles in the bioscience literature. The most recent update of the PathBinderH database was based on PubMed as of June 22, 2004.

ANALYSIS

The value of the sentence-based, taxonomy-sensitive literature access provided by PathBinderH may be illustrated by an example comparing it to the access provided by PubMed. The topic of interest in this example is embryo development in plants. The queries to PubMed that were tested were as follows.

1. Embryo AND development, internally converted by PubMed into ("embryo" [MeSH Terms] OR embryo[Text Word]) AND ("growth and development" [Subheading] OR "human development" [MeSH Terms] OR development [Text Word]). (The internal conversion is easily viewed by clicking the "Details" menu item on the PubMed results page.) This query returned 63,606 hits, mostly about animals. For clarification, a variant of this query with a simpler internal representation was typed into the input box directly, shown next.

2. Embryo[Text Word] AND development[Text Word]. This returned 55,863 hits. Because this and the previous query had such low precisions, simple taxonomic filtering was included in the next query.
3. Embryo AND development AND plants. This query filtered out many irrelevant PubMed entries, resulting 1,731 hits. A variant query containing plant in singular form was also tried, described next.
4. Embryo AND development AND plant. After internal conversion this returned 1,838 hits. To try a simple internal expansion directly, the following query specifying the internal representation was typed directly into the query input window.
5. Embryo[Text Word] AND development[Text Word] AND plant[Text Word]. This query returned 890 PubMed entries. This and the preceding two queries have the similar problems of returning hits which are about development of things other than embryos, and not returning hits on specific kinds of plants when the term “plant” is not present. These problems help motivate the new tool we have developed, PathBinderH.

To use PathBinderH for the embryo development in plants example, the taxon of interest was specified as Viridiplantae (green plants, Figure 2). PathBinderH, which is available at www.plantgenomics.iastate.edu/PathBinderH, provides *sentence-focused, taxonomy-sensitive* searches in contrast to the abstract-focused, taxonomy-insensitive search provided by PubMed. This restricts results to sentences in those PubMed entries that contain the name of a species or other taxon at or below green plants in the biological taxonomy. Next, two terms were chosen to request retrieval of sentences (defined to include titles) from PubMed entries in which those two terms or their synonyms co-occur (Figure 3), resulting in 651 such sentences contained within 542 PubMed entries.

PathBinderH

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Hierarchical taxonomy filter

NCBI : Lineage > Eukaryota ->

- **Viridiplantae** (Green plants) ▾ <- Click funnel icon to add filter
 - **Chlorophyta** ▾
 - Chlorophyceae ▾
 - Chlorophyta incertae sedis ▾
 - Pedinophyceae ▾
 - Picocystophyceae ▾
 - Prasinophyceae ▾
 - Trebouxiophyceae ▾
 - Ulvophyceae ▾
 - unclassified Chlorophyta ▾
 - **Streptophyta** ▾
 - Charophyta/Embryophyta group ▾
 - Chlorokybophyceae ▾
 - Klebsormidiophyceae ▾
 - Mesostigmatophyceae ▾
 - Zygnemophyceae ▾
 - unclassified Viridiplantae ▾
 - environmental samples ▾

To add filter click funnel (▾) icon next to taxonomy term in the tree at left.

Filter List

Viridiplantae (Green plants)

Note: Applying filter process might take few minutes depending on the taxonomy terms in the filter list, please be patient

Figure 2. Selecting green plants (and therefore its constituent species and other sub-taxa).

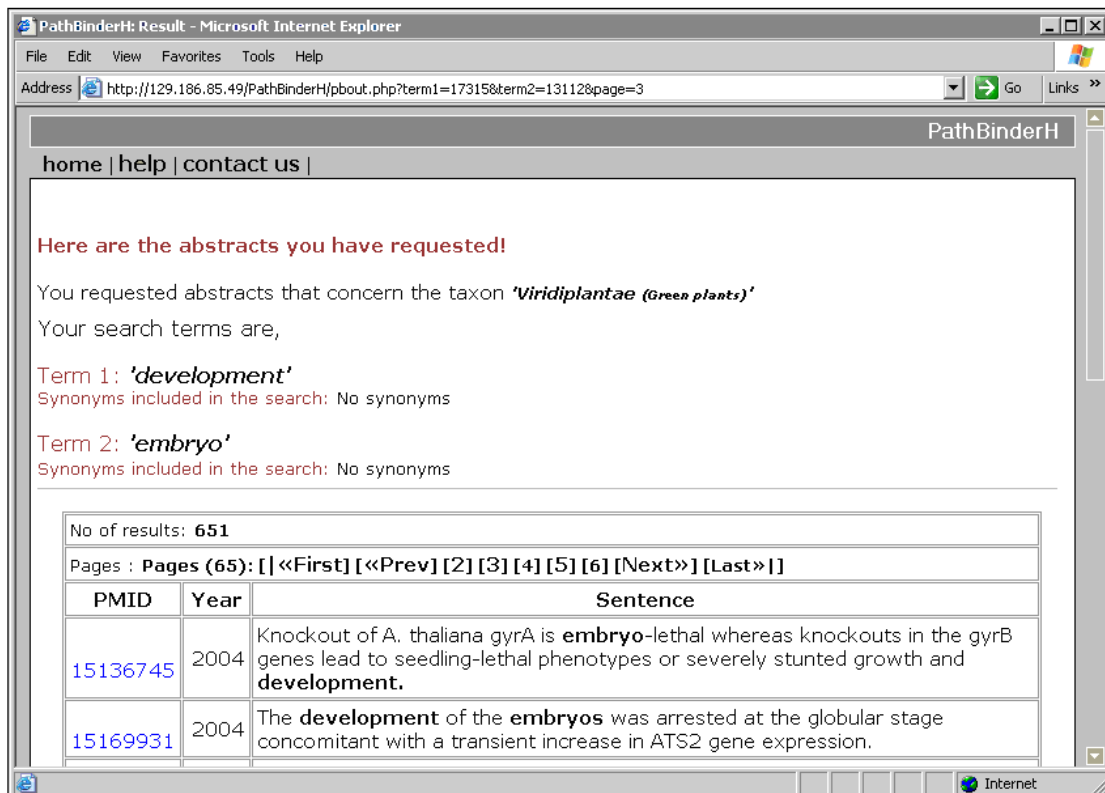


Figure 3. Sentences (including titles) containing two specified terms, and that are found in PubMed entries containing the name of a green plant species or other taxon. Clicking the PMID displays the full entry.

A revealing contrast exists between the 651 PubMed entries returned by this query, and the 890 returned by query 5 above using the standard PubMed interface: only 159 PubMed entries were returned by both queries.

The numbers just given for the query example are summarized in Table II. These numbers have some notable characteristics, discussed next.

Query terms:	PubMed entries containing→	“plant” or “plants”	another plant taxon name
“embryo”	...when query terms are↓		
and	in one sentence	159	383
“development”	not in one sentence	731	undetermined

Table II. Numbers of PubMed entries retrieved by three categories of query. The numbers refer to the quantity of PubMed abstracts in each category.

- The numerical contrast between the cells containing 159 and 383 shows that most (383) plant-related entries do not actually contain the term “plant.” This illustrates the advantage of retrieval that is sensitive to the biological taxonomy, thereby enabling retrieval of material about groups of related organisms. In this example entries about individual crop species, about grain plants in general, about the well-studied plant *Arabidopsis*, etc., are retrieved, while those about humans, animals in general, specific animal species, and so on are filtered out.
- The numerical contrast between the cells containing 159 and 731 shows that most (731) collocations of “embryo” with “development” are not in the same sentence. This is significant because Ding et al. (2002) showed that a large majority of relationships, at least between biomolecule names, are described within single sentences. Therefore single-sentence collocations will often be a significantly richer source of information on the relationships between the co-occurring terms than more widely spaced collocations.
- The lower right cell does not contain a number. This is because of limitations in both PubMed and PathBinderH. PubMed does not currently provide taxonomy-sensitive retrieval (although as the present report shows, this would certainly be feasible), and

PathBinderH does not retrieve PubMed entries containing the query terms but not in the same sentence.

Further analysis of PubMed queries

To obtain a more detailed understanding of PubMed's automated query system and the relationship of its results to those of PathBinderH, six different permutations of the terms *development*, *embryo*, and *plant* were each applied to the PubMed search interface, which automatically expanded them to produce more complex queries. The first permutation was the query "**development embryo plant**". The following is the automatic expansion resulting from giving PubMed that query:

("growth and development"[Subheading] OR ("human development"[TIAB] NOT Medline[SB]) OR "human development"[MeSH Terms] OR development[Text Word]) AND ("embryo"[MeSH Terms] OR embryo[Text Word]) AND (("plants"[TIAB] NOT Medline[SB]) OR "plants"[MeSH Terms] OR plant[Text Word])

This query resulted in 1877 different abstracts. Compared to the more restricted unexpanded version of the query (which was run by typing **embryo [Text Word] and development [Text Word] and plant [Text Word]** into the PubMed query type-in window), more of the abstracts found by PathBinderH were returned. More quantitatively, of a sample set of 99 abstracts found by PathBinderH that were not found by PubMed in response to the unexpanded query, the expansion found 37 (so 62 were not found). Of a sample of 249 abstracts determined by manual examination to be relevant, 187 were found by this query, while 62 were not.

The second permutation was "**development plant embryo**" which was expanded by PubMed into:

("growth and development"[Subheading] OR ("human development"[TIAB] NOT Medline[SB]) OR "human development"[MeSH Terms] OR development[Text Word]) AND ("embryo"[MeSH Terms] OR embryo[Text Word]) AND (("plants"[TIAB] NOT Medline[SB]) OR "plants"[MeSH Terms] OR plant[Text Word])

This expansion retrieved 3374 abstracts. Of the sample set of 99 abstracts that PathBinderH found but the unexpanded query PubMed query did not, 47 were found by this query, so 52 were not. Of the sample of 249 relevant abstracts, 146 were found by this query while 103 were not.

The third permutation was “**embryo development plant**”. PubMed expanded that into

("embryo"[MeSH Terms] OR embryo[Text Word]) AND (("plants"[TIAB] NOT Medline[SB]) OR "plants"[MeSH Terms] OR plant[Text Word]) AND ("growth and development"[Subheading] OR ("human development"[TIAB] NOT Medline[SB]) OR "human development"[MeSH Terms] OR development[Text Word])

This query resulted in 868 different abstracts. Of the 99 sample PathBinder abstracts not found by the unexpanded query, 8 were found by this query so 91 were not. Of the sample of 249 relevant abstracts, 46 were found by this query so 203 were not.

The fourth permutation was “**embryo plant development**” which resulted in the following expanded query:

("embryo"[MeSH Terms] OR embryo[Text Word]) AND (("plants"[TIAB] NOT Medline[SB]) OR "plants"[MeSH Terms] OR plant[Text Word]) AND ("growth and development"[Subheading] OR ("human development"[TIAB] NOT Medline[SB]) OR "human development"[MeSH Terms] OR development[Text Word])

This query resulted in 1877 different abstracts. Of the 99 sample PathBinderH abstracts not found by the unexpanded query, 37 were found by this expansion while 62 were not. Of the sample of 249 relevant abstracts, 187 were found by this query while 62 were not.

The fifth permutation was “**plant development embryo**” which was expanded into

((("plants"[TIAB] NOT Medline[SB]) OR "plants"[MeSH Terms] OR plant[Text Word]) AND ("growth and development"[Subheading] OR ("human development"[TIAB] NOT Medline[SB]) OR "human development"[MeSH Terms] OR development[Text Word]) AND ("embryo"[MeSH Terms] OR embryo[Text Word])

This expansion resulted in 1877 different abstracts. Of the 99 sample PathBinderH abstracts not found by the unexpanded query, 37 were found by this query while 62 were not. Of the sample of 249 relevant abstracts, 187 were found by this query so 62 were not.

The sixth and final permutation was “**plant embryo development**” and this was expanded by PubMed into the following query:

(("seeds"[TIAB] NOT Medline[SB]) OR "seeds"[MeSH Terms] OR plant embryo[Text Word]) AND ("growth and development"[Subheading] OR ("human development"[TIAB] NOT Medline[SB]) OR "human development"[MeSH Terms] OR development[Text Word])

This query resulted in 3374 different abstracts. Of the 99 sample PathBinderH abstracts not found by the unexpanded version, 47 were found by this query so 52 were not. Of the sample of 249 relevant abstracts, 146 were found by this query while 103 were not.

Each of the expansions above found abstracts found by PathBinderH and in the sample set of 99 not found by the unexpanded query. This finding would suggest that the automated queries were more efficient than the manual query at mimicking the advantages of PathBinderH. But, when the sample of 249 abstracts manually determined to be relevant were analyzed, the unexpanded PubMed query found 150 of them. This was better than 3 of the 6 expanded queries, despite the larger number of abstracts found by all 6 expansions. Thus, for the best expansions, there are still substantial numbers of abstracts that are uniquely found by PathBinderH.

Analysis of relevant characteristics of PubMed records

Up to now we have ignored the possibility, useful if true, that the title and MeSH heading terms in a PubMed record are likely to be particularly important in determining the relevance of the record to a given query. The following analysis was performed to investigate this possibility. If true, the result could be used in advanced biological literature access tools such as PathBinderH and other systems constructed in the future.

In order to incorporate diverse botanical domains into the analysis, five plant taxa were selected (Algae, Arabidopsis, Citrus, Plants, and Volvox). For each taxon, 100 records were randomly selected from the PathBinderH database. From this pool, records were selected if they contained the taxon name in the article title or MeSH heading terms, as opposed to being present

only in other parts of the record such as the abstract text. The selected records were then evaluated for relevancy to the taxon. Relevancy was defined by manually determining whether (a) the record's main idea revolved around the taxon, or (b) the record discussed the taxon in an indirect but significant role.

Algae is the first taxon that was investigated. Out of 100 records 90 were found to be relevant. This a precision of 0.9. When the records in which the taxon was present in the article title or MeSH headings were considered, a recall of 0.89 of the original 100 and precision of 0.93 were observed.

The second taxon to be evaluated was *Arabidopsis*. Eighty-three out of 100 applicable records were found to be relevant to *Arabidopsis*. This constitutes a precision of 0.83. Considering only the records in which the taxon was present in the article title or MeSH headings, a recall of 0.98 of the original 100 and precision of 0.853 were observed.

The third taxon that was evaluated was *Citrus*. Of 100 records containing the term "citrus," 76 were determined to be relevant to *Citrus*, a precision of 0.76. Considering only those containing the term in the article title or MeSH headings, a recall of 0.92 and a precision of 0.83 were observed.

The fourth taxon to be evaluated was plants. Eighty-five out of 100 records were found to be relevant, a precision of 0.85. However when considering relevance of only those records containing the term in the article title or MeSH heading terms, a recall of 0.87 and a precision of 0.90 were found.

The final taxon to be evaluated was *Volvox*. There were 98 relevant records out of the pool of 100. Precision was 0.98. Of those containing the term in the article title or MeSH headings, a recall of 0.98 and precision of 0.98 were observed.

When all five results described above were combined to give composite results (Table III), an overall precision of 0.86 was observed for the resulting pool of 500 records. When only

those records from the pool that contained the applicable taxon term in the title or MeSH

headings were considered, recall was 0.93 and precision was 0.90.

	Algae	Arabidopsis	Citrus	Plants	Volvox	mean
Precision (anywhere in record)	0.90	0.83	0.76	0.85	0.98	0.86
Recall (In title or MeSH terms)	0.89	0.98	0.92	0.87	0.98	0.93
Precision (In title or MeSH terms)	0.93	0.85	0.83	0.90	0.98	0.90

Table III. Comparative results for presence of a taxon term of interest in PubMed records.

Presence anywhere in the record is compared to presence in only the title or MeSH terms.

The above analysis shows that by requiring taxa terms of interest to be in an article title or the MeSH terms associated with a PubMed record, the precision increased. Precision is important due to the need to retrieve records that are relevant by weeding out those abstracts which are not. For four of the five taxa investigated, precision was improved by selecting records containing the applicable taxon term in the article title or MeSH heading terms (one taxon had a precision that did not change). This suggests an advantage to focusing on article titles and MeSH terms for determining PubMed record relevancy given specific taxa of interest.

DISCUSSION

The text mining process behind PathBinderH is limited by the difficulty of highly dependable analysis of natural language, which is due to its flexible, human-oriented character. In language processing problems not characterized by highly constrained text structures, successful solutions typically also highlight second-order limitations. This general problem has pervaded automatic natural language analysis-based applications for decades. These second-order considerations can

serve to motivate further advances and thus are useful to catalog, so we note the following limitations in results provided by PathBinderH.

- The crawler module uses a fuzzy string-matching algorithm based on a tokenizer which ignores spaces in multiple-word terms. While this successfully merges terms like *UCP 3*, *UCP3*, and *UCP-3*, it sometimes leads to incorrect mergings. For example, in S1, the phrase “act in” was mistakenly labeled as the molecule “actin.” plants.”

*S1: The calcium channel blocker verapamil and arsenite **act in** synergy in cells exhibiting the efflux system. (PMID: 7838183)*

- Some PubMed entries may slip through the taxonomy filter even though they have nothing to do with the species of interest. This is because some taxa have ambiguous synonyms. For example, the “plants” in S2 are not “green plants” (*Viridiplantae*), but “water-treatment plants.”

*S2: The efficiency of the **plants** in removing nonylphenolic compounds from drinking water is highly variable, ranging from 11% to 99%. (PMID: 15172597)*

Fortunately, existing works suggest that the presence of an ambiguous taxon name in the same PubMed entry as a query term meaningfully related to it will tend to be used in its relevant sense (i.e., as a taxon name). Although those works did not specifically investigate PubMed texts, they did find that collocations separated by large distances (as much as 10,000 words) had significant disambiguating effects in texts concerning a range of different topics, including medicine (Gale et al., 1992; Yarowsky, 1993). Fortunately our query strategy, which requires specifying a second term to co-occur in the same sentence as another possibly ambiguous term of interest, is typically sufficient to screen out sentences in which the ambiguous term is used in an undesired sense (see Yarowsky, 1993).

- In some cases, plant taxa names can legitimately be extracted from an abstract even though the abstract is mainly about something else, as in S3 and S4.

*S3: Pregnant dams received either subcutaneous injections of 1 microg of E on Day 2 of pregnancy only (vaginal plug = Day 1), or 5.0mg of MXC on Days 2-4 of pregnancy in **sesame** oil. (PMID: 15013069)*

*S4: Detailed expression analysis from gastrula to neurula stages showed that these four genes named *crescent*, *P7E4* (homologous to human hypothetical genes), *P8F7* (an unclassified gene), and *P17F11* (homologous to human and *Arabidopsis* hypothetical genes) demarcate spatiotemporally distinct subregions of the AEM corresponding to the head organizer region. (PMID: 11784032)*

As in the case of ambiguous taxon names, the additional query terms required to be present should often filter out such irrelevant PubMed entries.

CONCLUSION

PathBinderH is a resource available for public use over the Web. It supports a novel approach to focused access to the biological literature, using keyword queries limited to those PubMed entries that concern both specified and implied plant species and other taxa. For example, the user can browse the taxonomy and click on “poaceae” (grasses), thereby delimiting the pool of PubMed entries within which to search to those containing the name of any species of grain (e.g. wheat, maize, and rice) or other grass, any genus below the poaceae family in the biological taxonomy, or the term poaceae itself or its common synonym “grasses.” The plant taxonomy-sensitive approach used by PathBinderH forms a model for the analogous treatment of other taxonomies and biological ontologies. Taxonomy-sensitive retrieval supports the needs of biologists and is expected to contribute to a range of useful applications.

An additional outcome of the present work is support for literature searches seeking relationships between key terms, because requiring terms to co-occur within a single sentence enhances the likelihood that they are conceptually explicitly connected in the retrieved PubMed entries. Another potential outcome that is now within reach is conveniently accessible gene annotations mined from the literature. Thus, PathBinder provides an effective entrée to the literature based on the concepts of (1) query term collocation within sentences, and (2) biological taxonomy.

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