Fast and efficient searching of biological data resources—using EB-eye

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Abstract
The EB-eye is a fast and efficient search engine that provides easy and uniform access to the biological data resources hosted at the EMBL-EBI. Currently, users can access information from more than 62 distinct datasets covering some 400 million entries. The data resources represented in the EB-eye include: nucleotide and protein sequences at both the genomic and proteomic levels, structures ranging from chemicals to macro-molecular complexes, gene-expression experiments, binary level molecular interactions as well as reaction maps and pathway models, functional classifications, biological ontologies, and comprehensive literature libraries covering the biomedical sciences and related intellectual property. The EB-eye can be accessed over the web or programmatically using a SOAP Web Services interface. This allows its search and retrieval capabilities to be exploited in workflows and analytical pipe-lines. The EB-eye is a novel alternative to existing biological search and retrieval engines. In this article we describe in detail how to exploit its powerful capabilities.

Keywords: text search; biological databases; integration; interoperability; web services; Apache Lucene

INTRODUCTION
Searching for accurate and functionally related biological concepts through stacks of journals and articles is time consuming. Furthermore, establishing the relationships between genes, transcripts, proteins, expression, and molecular structures using the web is often an error-prone process. Scientists need to use different web resources, which have different search engines that are syntactically and semantically incompatible: results are returned in heterogeneous formats, making deriving a coherent view of the biological meaning of these data cumbersome.

The availability of new tools and libraries for the development of search engines and web portals, allows us to build a system that enables interoperability between distinct data resources and channel these through a single hub. Scientists can now quickly search and identify biological entities, relationships and simply navigate to expert primary resources.

We present here a high-performance, full-feature text search engine that finds and displays biological entities and their associations (i.e. the relationship between genomic sequences, transcripts, proteins...
and their function, molecular structures, gene expression profiles, protein–protein interactions, pathways and published scientific and patent literature), in much the same way as scientists do searches in a library. This web-based search engine is called the ‘EB-eye’ and is built on the free Open Source Apache Lucene Java™ library [1].

What is the EB-eye?
EB-eye is a catalogue of biological entities, similar to a library catalogue that describes publications, and contains enough information to allow for efficient searching. Unlike indexing warehouses such as Entrez [2], SRS [3] and MRS [4], which provide complete access to the data and allow searching over fields with specialist value and which are difficult to search without prior knowledge of their contents, EB-eye focuses on indexing selected textual content, which are the most meaningful while searching biological data (e.g. database names and database identifiers, gene names and synonyms, protein names, chemistry identifiers, reaction equations, authors, titles, various types of descriptions and importantly, cross-references that link entries between distinct databases). This excludes data which requires specialist searching, such as sequences, structure coordinates, expression profiles and ambiguous data, such as numeric counts, for which there exists search tools associated with the primary resources. EB-eye improves the user’s experience by providing a search engine that presents consistent result pages and navigation across all the data resources maintained by EMBL-EBI.

EB-eye is not limited to specific data formats. As well as indexing database dumps, such as flat-files from EMBL-Bank [5] and UniProt [6], database specific XML, web content (e.g. HTML and XHTML), EB-eye uses a custom XML dump format, which has been designed for data resources without an export format. These dumps focus on the essential content required to describe a biological concept in the database, and are produced by the data providers.

The EB-eye is composed of a set of modules, each designed to carry out a distinct task (Figure 1). In the following we will describe the web interface, the back-end data-management and indexing system, and finally, the SOAP Web Services interface that is used to integrate and/or embed its functionality into analytical pipe-lines, external applications and web portals.

THE EB-Eye's WEB INTERFACE
Like internet search engines, the EB-eye has adopted established design principles to provide a simple, coherent and intuitive interface for querying and presentation of results. Of particular importance is achieving good performance when obtaining results for queries against large biological datasets while maintaining the number of operations that separate the user from results within the constraints described by the ‘Three-Click-Rule’ [7].

Global search input box
At the top of every web page of the EMBL-EBI portal (http://www.ebi.ac.uk) there is a text search box. This is the main entry point to the EB-eye search engine. Search terms such as entry identifiers, gene names, article titles, biological or chemical nomenclature terms, or a set of keywords can be used. By default all available data resources are searched and the results are initially presented in the summary overview.

Summary overview
Data within the EB-eye are organised into categories representing biological knowledge domains. Each domain is composed of a hierarchy of sub-domains that focus on related data. For example, the ‘Small molecules’ knowledge domain comprises ChEBI [8]: a dictionary of small chemical compounds of biological interest; Ligands [9]: a dictionary of small chemical components and RESID [10]: a comprehensive collection of annotations and structures for residue modifications. Similarly, the ‘Nucleotide Sequences’ domain, contains the Alternative Splicing and Transcript Diversity database (ASTD) [11]; EMBL Nucleotide Sequence Archive (EMBL-Bank) and the EMBL Coding Sequences database. EMBL-Bank is further broken down into specific sub-domains related to the internal structure of the database (e.g. EMBL-Bank (Release) and EMBL-Bank (Updates)). Following the strategy of initially performing a broad search and then narrowing down the scope if necessary, the results are initially presented in a summary page showing the number of hits in each domain (Figure 2). Clicking the domain name or the number of hits takes the user to a domain-specific results page containing a list of entries found by the query.
Domain-specific results page

For a domain which does not contain sub-domains, an overview of each entry found in the domain is presented in pages of 15 entries. For a domain containing sub-domains the most relevant three entries found in each sub-domain are shown with a ‘more’ link to navigate to all the results found in the sub-domain.

An overview is shown for each entry. This typically contains the primary identifier of the entry, which is displayed first and is hyperlinked to the primary resource, and a descriptive title. Additional annotation may be displayed, which commonly includes secondary database identifiers and classification, dates, authors, alternative names, etc. For example, for an entry in UniProtKB, the identifier,
accession numbers, gene names with synonyms and the descriptions are displayed. In contrast, for a literature database (e.g. MEDLINE [1]) a citation style summary is presented for each entry.

On the right of the domain specific results page there are three boxes: ‘Results summary’ containing a count of the results found within the domain hierarchy; ‘Refine your search’, allowing query refinement through adding additional terms to the query; and ‘Explore related information’ (Figure 3) which displays query refinement suggestions that are dynamically generated from the query results using techniques provided by Carrot2 [12], a search results clustering engine. For example, querying MEDLINE for ‘dopamine receptor’ yields a list of related terms including: ‘Hypothesis of Schizophrenia’, ‘Patients with Parkinson’s Disease’, ‘Depression Component’ and ‘Dopamine Receptors and Hypertension’.

Views
An entry may have ‘Views’ that provide access to other formats and portals. For example, a nucleotide entry in EMBL-Bank has views which show the entry in EMBL flat-file format, in SRS and the entry’s history using the Sequence Version Archive. Likewise, an entry in PDBs [13] can be viewed in PDBSum [14], PDB format and in SRS.

Cross-references
The data indexed by the EB-eye contains cross-references. These are displayed as hyperlinks in the ‘References’ section. These allow navigation between related entries, helping the user build a coherent overview of the biological entities described. For example, from protein sequences (in UniProtKB) discovering associated coding genes (in EMBL-CDS [5]), protein families (in InterPro [15]), literature (in MEDLINE), organism taxonomy (in the NCBI Taxonomy), etc.

The advanced search
To help the user combine terms for querying across all the data resources, the advanced search has four text input fields, which address fields for querying ‘All the words’, ‘The exact phrase’, ‘At least one of
the words’ and ‘None of the words’. It provides easy access to the boolean query operators (i.e. AND, OR and NOT) needed to build complex queries (Figure 4). For example: searching for ‘insulin’ yields overlapping results that contain both ‘insulin’ and ‘insulin-like’. To overcome this ambiguity the user can type ‘insulin’ into the ‘All words matching’ box and ‘insulin-like’ into the ‘None of the words’ box to perform a search which excludes entries containing the term ‘insulin-like’ from the results.

For a ‘domain-specific search’ a tree of domains and sub-domains is shown, from which a single domain can be selected. If a data source (i.e. a leaf of the tree), rather than a collection of data sources is selected, the search can be further constrained to specific fields and cross-references. Multiple fields and/or cross-references can be selected, and the query form will be updated to include specific options for these fields and cross-references.

The EB-eye’s query syntax
The EB-eye uses the Apache Lucene query syntax [16], which is similar to that used by Google and other major internet search engines. Table 1 describes the major syntactical elements supported by EB-eye. A more detailed description can be

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**Table 1**

<table>
<thead>
<tr>
<th>EB-eye's Query Syntax</th>
<th>Supported Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AND</strong></td>
<td>Logical operator</td>
</tr>
<tr>
<td><strong>OR</strong></td>
<td>Logical operator</td>
</tr>
<tr>
<td><strong>NOT</strong></td>
<td>Logical operator</td>
</tr>
<tr>
<td><em><strong>insulin</strong></em></td>
<td>Term</td>
</tr>
<tr>
<td><strong>-insulin-like-</strong></td>
<td>Term, not included</td>
</tr>
<tr>
<td><strong>DB</strong></td>
<td>Data source</td>
</tr>
<tr>
<td><strong>Field</strong></td>
<td>Specific field</td>
</tr>
<tr>
<td><strong>Cross-references</strong></td>
<td>Related fields</td>
</tr>
</tbody>
</table>

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**Figure 3**: The ‘Explore related information’ box in the domain specific results page displays the terms related to a given search query using Carrot2 clustering techniques.
Unlike the aforementioned search engines, multiple search terms are combined with an ‘AND’, which is analogous to the behaviour in Entrez, SRS and MRS. Thus a query containing ‘glutathione transferase’ is treated as ‘glutathione AND transferase’ and will find only those entries containing both terms. The default sort order of results is based on the proximity of the terms in the entries, thus entries where the phrase ‘glutathione transferase’ occurs, will appear first in the list of results.

MRS, Entrez and SRS provide similar capabilities in their query languages (see some examples in Table 2), however the results obtained differ. These differences are related to the data being searched and the nature of the query systems. The syntactical differences between these systems highlight an issue, characteristic to all biological search engines. Although the syntax of each search engine is internally consistent, the names of the fields indexed in these systems are different. EB-eye implements aliasing for fields to common names with equivalent meaning. For example, common field names such as ‘id’, ‘accession’, ‘name’ and ‘description’, which are used across many of the databases in the system to describe fields that have semantically equivalent meaning.

**UPDATING AND INDEXING DATABASES**

Currently, the EB-eye provides access to more than 200 million entries from 56 data sources (http://www.ebi.ac.uk/ebisearch/statistics.ebi). Keeping the system up to date requires a system that
automatically updates and re-indexes data on a daily basis. This comprises two modules (Figure 1), controlled by a set of configuration files:

(i) When data updates are detected, the data are downloaded and optionally decompressed into an off-line directory. For each data resource, a Groovy [17] script is used to configure this process. This addresses the complexity of fetching data, which are accessible using diverse protocols (e.g. http, ftp, fasp (http://www.asperasoft.com), ssh, rsh or simple file system copy). These scripts also handle any additional post-processing required.

(ii) Generating indices from the new data by parsing the data to extract the relevant information. An initial stage examines the data and determines a strategy for performing the parsing in parallel. The indexing task is then farmed out to a number of machines, each machine creating a partial index. Once all the tasks are completed the partial indexes are merged to form the final index.

To ensure the consistency of the index the number of entries in the data resource is checked against the number of entries recorded by the index. In addition, the cross-references are checked against the know cross-references for the data resource. Any discrepancies in the number of entries or cross-references prevent deployment of the index into the on-line environment, and are logged as errors for investigation. If no errors were encountered the completed indexes are deployed and made available to the public.

### EB-eye WEB SERVICES

Scientists require biological data searches in desktop tools and analytical pipe-lines. Many analytical tools in bioinformatics also require the ability to perform searches to obtain the required data for performing and enriching their analysis. EB-eye provides a web service interface to address these requirements. This web service exposes the functionality available in the web interface allowing EB-eye to be integrated into other systems. Detailed documentation including example clients is available from http://www.ebi.ac.uk/Tools/webservices/services/eb-eye, where the reader can find descriptions of the input required for each method as well as of output structures returned.

The web service uses the, widely supported, Simple Object Access Protocol (SOAP) [18] standard, coupled with a Web Services Description Language (WSDL) [19] interface description document. Clients programs can access the service without the need to develop custom code. Web services technologies are platform and programming language neutral, thus EB-eye can be incorporated into existing applications as well as those specifically developed to exploit the EB-eye’s features.

### Methods

The methods provided by the web service can be grouped into three broad categories:

(i) Meta-data: information about the EB-eye and the data domains available.

(ii) Search and Retrieval: performing searches and retrieving data from the results.

(iii) Navigation: using cross-referencing information to navigate between related entries and domains.

The following sections provide an overview of the methods in each of these categories.

### Meta-data

To build a user interface it is necessary to be able to obtain information about the search system, such as the data resources available, the fields available for each resource, which fields can be searched and which fields can be retrieved. The web service

<table>
<thead>
<tr>
<th>Search Engine</th>
<th>Query</th>
</tr>
</thead>
<tbody>
<tr>
<td>EB-eye</td>
<td>(reductase OR transferase) AND glutathione</td>
</tr>
<tr>
<td>MRS</td>
<td>(reductase OR transferase) AND glutathione</td>
</tr>
<tr>
<td>SRS</td>
<td>[UNIPROT-all:(reductase</td>
</tr>
<tr>
<td>Entrez</td>
<td>(reductase OR transferase) AND glutathione</td>
</tr>
<tr>
<td>EB-eye</td>
<td>gene.primary.name:(gst)</td>
</tr>
<tr>
<td>MRS</td>
<td>gngst</td>
</tr>
<tr>
<td>SRS</td>
<td>[UNIPROT:genename:gst]</td>
</tr>
<tr>
<td>Entrez</td>
<td>gsgst[Gene Name]</td>
</tr>
<tr>
<td>EB-eye</td>
<td>gene.primary.name:(gst*)</td>
</tr>
<tr>
<td>MRS</td>
<td>gngst*</td>
</tr>
<tr>
<td>SRS</td>
<td>[UNIPROT:genename:gst*]</td>
</tr>
<tr>
<td>Entrez</td>
<td>gsgst*[Gene Name]</td>
</tr>
</tbody>
</table>

Table 2: Examples of equivalent ways of expressing search queries in EB-eye, MRS, SRS and Entrez.
provides a set of methods to access the meta-data describing the search domains:

(i) **listDomains()**: list of search domains available. These domains correspond to the leaves of the hierarchy of domains.

(ii) **listFields()**: list fields for a domain from which data can be retrieved.

(iii) **getDomainsReferencedInDomain()**: list of EB-eye domains referenced by a domain.

(iv) **getDomainsReferencedInEntry()**: list of EB-eye domains referenced by a specific entry in a domain.

(v) **listAdditionalReferenceFields()**: list of fields referencing data resources which are not available in EB-eye.

(vi) **getDomainsHierarchy()**: get the complete tree of domains.

(vii) **listFieldsInformation()**: detailed information about the fields for a domain, this describes both searchable and retrievable fields.

**Search and Retrieval**

Fundamental features of a search engine are performing searches, retrieving summary data for the results and obtaining pointers to the complete data. The following methods cater for different types of search:

(i) **getNumberOfResults()**: get the number of entries which are found by a query.

(ii) **getDetailedNumberOfResults()**: for a search covering multiple domains get the number of entries found in each of the domains, either as a tree covering the relevant section of the domains hierarchy or a flattened list.

(iii) **getResultsIds()** and **getAllResultsIds()**: get the identifiers of the entries matching a query.

(iv) **getResults()**: retrieve data from specified fields for the entries matching a query.

(v) **getEntry()** and **getEntries()**: retrieve data from specified fields for an entry or a set of entries.

**Cross-references navigation**

Navigation in the EB-eye allows scientists to explore relationships within and between diverse biological knowledge domains. Methods are provided to navigate the cross-references given a specific entry identifier or a search result as the starting point:

(i) **getEntryFieldUrls()** and **getEntriesFieldUrls()**: get the URLs associated with the specified fields.

Used to obtain references to the main site for the data resource.

(ii) **getReferencedEntries()**: for a query get the identifiers of entries in a referenced domain.

(iii) **getReferencedEntriesSet()** and **getReferencedEntriesFlatSet()**: for a query get data from specified fields in the referenced domain.

**Using EB-eye Web Services in pipeline and workflows**

Workflow design tools such as Taverna [20], Triana [21] and KNIME [22] can use the web service WSDL to create the components required to combine the EB-eye with other services in order to create complex workflows. As well as purpose built workflow engines, like the aforementioned, scripting environments such as the UNIX shells (e.g. Bourne shell, C-shell, etc.), or the Microsoft Windows scripting environments (e.g. batch, VBscript, Jscript or PowerShell) can be used with the example clients written in .NET [23], Java [24] or Perl [25] to create similar pipelines.

One example of such a workflow, which could provide a foundation for an annotation process, is using the EB-eye to obtain consolidated identifier mappings from the results of a BLAST [26] search against the UniProtKB. Using the EMBL-EBI’s tools web services [27] a workflow can be constructed which performs a BLAST search using the WSWUBlast (http://www.ebi.ac.uk/Tools/webservices/services/wublast) web service against the UniProtKB database. The BLAST hit identifier list from the sequence search can be used as query terms in an EB-eye search against the UniProt Archive [6] (UniParc). The resulting UniParc entry identifiers are used to retrieve the complete entry using the WSDBfetch web service (http://www.ebi.ac.uk/Tools/webservices/services/dbfetch). Cross-references to RefSeq [28], Ensembl [29], PDB [30] and EMBL-CDS are extracted from these entries to characterise the protein sequence space actually covered by the initial BLAST search. Example implementations of this workflow using Taverna and Bourne shell are available from http://www.ebi.ac.uk/Tools/webservices/.

It is noteworthy, that the services mentioned above as well as more than 1100 other life-sciences relevant web services can be found in the BioCatalogue project portal (http://www.biocatalogue.org) and its content is indexed in the EB-eye.
Integration and embedding

Third-parties can use the EB-eye web services to provide fast full text searching capabilities across their data in their own portal. For example, Ensembl Genomes (http://www.ensemblgenomes.org), which is built on the, Perl-based, Ensembl framework, delegates its text searches to EB-eye and the results obtained are mapped to the entries within the database and presented to the user. As well as the integration of search capabilities the web service can also be used to provide access to the data network, for example in the EBI Sequence Similarity Search Services (http://www.ebi.ac.uk/Tools/sss) the web service is used to obtain details of the domains referenced by each hit in the search result (Figure 5), this provides additional context to the sequence search allowing the scientist to determine which hits provide the most relevant information for the type of search they are performing.

CONCLUSIONS AND FUTURE DIRECTIONS

Finding information about biological entities is a cumbersome and error prone process. Unlike systems such as Entrez, SRS and MRS, which provide both search and data retrieval capabilities, EB-eye focuses solely on the search and cross-reference navigation aspect of the data integration process. By providing access to navigate to the primary data source, where data is up-to-date, well maintained, and displayed in the way expected by the specialists, the EB-eye can integrate a larger range of data sources for an equivalent resource cost. Not to be confused with an integration platform, the EB-eye enables interoperability between resources and allows the user to cross-navigate between heterogeneous knowledge domains in a fast and consistent manner. EB-eye aims to always give the user comprehensive, reproducible and easy to interpret results.

Plans for future work include the capability to search with ranges in numerical fields such as dates, molecular weights and sequence length. In the context of web services, REST-styled interfaces are also on the agenda. Novel types of data, including image metadata and raw experimental data are also being considered for inclusion. Improving the accuracy and integrity of the cross-references network and displaying third party links (i.e. non-EBI resources) in the web interface is high on the list of priorities.

Figure 5: Results of a Smith-Waterman search against UniProtKB/SwissProt showing the cross-reference information obtained for each hit using the EB-eye web service.
Key points
- The EB-eye is a novel approach for searching biological information. It was designed to index key concepts in the data that are relevant to scientists in no particular scientific knowledge domain (e.g. information about a gene may be found in different data resources, ranging from protein and nucleotide sequences, gene expression databases, 3D structures, literature, etc).
- Using the EB-eye is very easy and intuitive. The web interface has been designed to use navigation metaphors most users should be familiar with (e.g. Google).
- The EB-eye search engine is a fast and scalable solution for finding core biological entities as well as related knowledge about these.
- The EB-eye makes extensive use of the cross-references that exist between heterogeneous data resources to help the user identify biological concepts and maintain uniform navigation within the system.
- The EB-eye is an interoperability platform. Integrating the EBI-eye functionality into other web sites, using web services, allows third-parties to use it to build complex pipe-lines, work-flows and provide their users with links and annotations from other databases.

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