GABAagent: a system for integrating data on GABA receptors

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Received on May 20, 1999; revised on September 22, 1999; accepted on September 30, 1999

Abstract
Motivation: Scientific data pertaining to GABA receptors, which are of medical importance, are widely scattered throughout numerous heterogeneous Internet resources. This situation has made the integrated acquisition of such data difficult and substantially time consuming even for researchers who are Internet aficionados. Thus, there exists a genuine need for the development of Internet applications, such as GABAagent, which provide efficient and timely access to concise and integrated information.

Results: We report here the establishment of a novel server (GABAagent) which has been written in Perl script, and which is freely accessible through the Internet. GABAagent is designed to assist researchers in retrieving focused and integrated information related to GABA receptors from various public domain databases.

GABAagent relies on server-side flat-file databases that have been created through data mining from Internet sources such as the PubMed, DDBJ, SWISS-PROT and TrEMBL, in addition to the many World Wide Web (Web) sites which are accessible through Excite (E-Web). These warehouse databases are regularly updated and contain among other things, information concerning: (i) GABA receptor publications, (ii) DNA and protein sequences and (iii) the contents of related E-Web sites along with their addresses. Our system also provides hard links to the above-mentioned Web sites and E-Web sites; the feature which adds to it the character of virtual federation type of database.

The current version of GABAagent provides two user-friendly services. The first is a search engine possessing intelligent query reformulation support (GABAengine), the second an elaborate email alert service was designed into the system (GABAalert). The GABAengine allows the user to search server-side databases exclusively for GABA receptor-related queries. Whereas, GABAalert allows the user, by means of subscription, to receive immediate and/or monthly updates automatically.

Availability: GABAagent is freely accessible at the following Web address http://www.ust.hk/gaba.

Contact: gaba@ust.hk

Introduction
It has been 33 years since γ-aminobutyric acid (GABA) was established as a neurotransmitter along with adrenaline and noradrenaline (Otsuka, 1996). Physiologically, GABA is a ligand that acts on at least two major classes of receptors, known as the GABA_A and GABA_B receptors. While GABA_A receptors belong to the ligand-gated ion channel receptor superfamily that mediates inhibitory neurotransmission (Wang et al., 1999; Olsen et al., 1996), GABA_B receptors activate K⁺ channels by coupling with GTP-binding regulatory proteins (Momose-Sato et al., 1996).

As key components of normal brain function, GABA receptors have long been the focus of major research programs at both the basic and applied levels (Otsuka, 1996). Over the years, a considerable wealth of biomedical research information has accumulated in a large number of varying formats. Today, much of this information is formatted as to be accessible via the Internet (Recipon and Makalowski, 1997).

Many sources of GABA receptor research data are embedded throughout the voluminous entries of scientific literature that are systematically collected and stored in the PubMed database at the National Center for Biotechnology Information (NCBI). The generation of DNA/protein sequence data are currently being amassed in public domain databases such as the DDBJ (http://www.ddbj.nig.ac.jp), as well as, the SWISS-PROT and TrEMBL which can be found on the ExPASy server (http://www.expasy.ch). Additionally, other important information related to GABA receptor research can be found in a vast number of World Wide Web (Web) sites. These Web
sites are easily located through search engines (utilising an appropriate query) such as Excite (http://www.exsite.com).

Researchers working on GABA receptors can easily become overwhelmed by the amount of retrievable data that is displayed by Internet search engines in response to queries using keywords such as ‘mutation AND brain’. From the perspective of our researcher, results of such a search would contain copious amount of unrelated and redundant information and would require considerable time to sort out. This is as well as the considerable time that would be consumed in sorting such information. Thus, there is clearly a need for the development of powerful Internet platforms that can facilitate the economy of time while, providing vital information within the conceptual space of the scientists working on GABA receptors.

Based on the work of Rebhan et al. (1998) in the GeneCards project, GABAagent has been designed primarily for the GABA receptor research community. This Internet platform provides scientists with concise and integrated information related to GABA receptor research by possessing the capability to extracted such information from numerous, diverse and heterogeneous Internet resources.

System and methods

Platform and availability

GABAagent comprises a set of CGI applications that requires a Javascript and ‘forms’ supporting Web browser such as Netscape Navigator version 2.01 or higher and Microsoft Internet Explorer version 3.0 or higher. Higher versions of each of the browsers are preferred. Automatic data extraction (ADE) scripts that build and update server-side databases, in addition to CGI scripts (http://hoohoo.ncsa.uiuc.edu/cgi/) that supports the system’s two modules (see below) are written in Perl 5.003 (Wall et al., 1996), using a Sun computer with a SunOS 5.6 operating system. The GABAagent platform and associated services are available free-of-charge through the Internet at the following URL: (http://www.ust.hk/gaba/).

GABAagent components

GABAagent, as shown in Figure 1, is a modular system that was designed in such a fashion as to allow for the addition or deletion of modules in order to support future development and expansion of the platform. The current version of the server consists of two major modules: a GABA search engine (designated GABAengine) and an e-mail alert facility (designated GABAalert).

The databases creation module. The databases creation module is a set of ADE programs that serves to retrieve GABA receptor research data from five different online databases. These databases include: (i) PubMed, (ii) DDBJ, (iii) SWISS-PROT, (iv) TrEMBL, and (v) E-Web.

The retrieved data are stored in databases that are composed of flat-files with formats that are similar to those of the original sources. Five in-house databases have thus been created and these include PubMed abstracts, DNA sequence entries, Protein sequence entries and related contents of Excite (E-Webs) that have been put in an Old and Recent indexes (see further below).

The database for PubMed abstracts, which contains data that have been dated over two years, have been made to contain, whenever possible, entries with hyperlinks (internal links) to DNA and protein sequence entries found in the related in-house databases, and/or hyperlinks (hard links) to GeneCards Web site http://bioinformatics.weizmann.ac.il/cards/. Other hard links to other online databases and Web sites are also present (see Implementation).

Furthermore, each entry from the DNA or protein in-house databases have also been made to contain internal links to either PubMed abstracts, related DNA, protein sequence entry, and/or hard links to the GeneCards.

The Old index of E-Webs and PubMed abstracts databases are backed up and updated on a monthly basis. The recent index of E-Webs is updated every two weeks. DDBJ and Swiss-Prot/TrEmbl are regularly checked for new GABA-related sequences to be added to the in-house DNA and protein sequence databases. All of GABAagent databases indexed using GlimpseIndex, a program from the Glimpse package (http://glimpse.arizona.edu).

The GABAengine module, data retrieval and results display. GABAengine is a search engine module that uses glimpses to search through the glimpse index of the databases rather than the database files and thus, makes query searching appreciably faster.

When a given search query is successful, a new Web page displays the results in an outline format consisting of a list of relevant hyperlinks. The content of the list depends upon pre-selected options chosen prior to the search (Figure 2).

The main features of the GABAengine may be described as follows.

A. In addition to providing users with needed data, GABAengine strives to provide such data with some level of integrity. This is achieved through the use of internal and/or hard links described earlier (Figure 3).

B. Intelligent query reformulation system is an elaborate system that provides a variety of suggestion-based alternatives that are closely related to the original query input(s) thereby assisting the user
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Fig. 1. Graphical representation of the GABAagent system. The module for automatic data extraction (ADE) extract data from online databases PubMed, DDBJ, SWISS-PROT and E-Web pages. The ADE stores the data as respective databases that are regularly updated. Both GABAengine and GABAalert modules establish hyperlinks to the in-house and online databases, see also Figure 3. Essentially, both modules receive users’ keywords, search databases and send back results when possible. GABAagent provides intelligent query reformulation support.

C. The other useful features of the GABAengine are that it provides users with the capability to access postal and e-mail addresses of other researchers and their affiliated laboratories. The data is extracted from the PubMed abstracts. These particular options are configured as a default parameter, although the users can elect to disable the feature at any time.

The GABAalert module. GABAalert is an ADE module for providing GABA receptors-related information on demand in the form of immediate and/or monthly e-mail alerts. The information retrieved by this function is based on pre-selected options as well as keywords that are to be supplied by the user on the e-mail alert submission form. The module extracts data primarily from the GABAagent databases. Users of this module can expect to receive two different e-mail alert messages. One that indicates abstracts of recently published GABA receptor-related manuscripts to include the principal author’s correspondence/e-mail addresses, and second which indicates selected E-Web sites and a summary of the associated contents.

The module allows for alert requests to be made with the option to search the PubMed directly (Figure 1), in which case the user must employ the proper search syntax for PubMed combined with the appropriate keywords in order to receive GABA receptors-related data only. Users will receive only one e-mail alert regarding abstracts. However, users are required to subscribe to this free service before receiving e-mail alerts along with their query results.

GABAalert options. GABAalert is an elaborate system that allows for parallel multiple submission of different
Fig. 2. Outlines associated with the results for a search query with keywords ‘diazepam AND brain’. Number of resultant hits found in each database is coloured brown and underlined titles are hyperlinks that lead to pages with detailed results. Note the two hyperlinks provided for the PubMed abstracts depending on whether the abstracts have links to DNA/protein sequence data and/or GeneCards.

Fig. 3. The GABAagent dual database systems character. The right and left sides of the picture show a graphical representation of the virtual and warehouse federation databases features respectively of the GABAagent. The system provides integrated data through the use of internal and hard hyperlinks to warehouse and online databases. Internal links are also established between the different databases of the system thereby providing more integrity to the data received by the user.

The submitted data are processed and stored using a CGI Perl script. A description of the module’s primary options are as follows.

A. The List previous submissions option is automatically invoked when a user attempts to submit an alert request with a keyword(s) query that is similar to one previously submitted. If the user has issued one or more submissions, a list of previous alert requests can be displayed by choosing the option ‘List previous submissions’ on the submission form (Figure 5(a)).

B. Change the contents of a previous submission. Changing the contents of a previous alert request can be achieved by selecting the option ‘Resubmission’. If the user has made previous alert requests, the system will display a list of previous submitted requests and at this point the user can choose one of the previous requests in order to exchange it with a new one (Figure 5(b)). Otherwise, the system will treat the request as a new submission.

C. Remove previous alert requests possesses two options, one that allows the selected removal of previous alert requests (‘Unsubscribe some previous submissions’; Figure 5(c)), and another that allows for the removal of all previous alert requests (‘Unsubscribe all previous submissions’).

GABAagent scale up
GABAagent is a module-based system (Figure 1) and new modules can be added through two ways.
Fig. 4. Query reformulation support for a search query that contained a misspelled keyword: ‘mutation LND brain’. (a) The main reformulation support suggestions are presented in a table where original and spelling corrected keywords are presented with choices to do the search again with and without typos and wild card forms. (b) More query reformulation suggestions with the Boolean AND since the query used the LND Boolean, which would have restricted the scope of search. Extra suggestions are offered in a form of a table of related words.

A. Database-like modules such as building a new related database which can be incorporated within the system and made searchable by adding a few lines of Perl script.

B. Service adding modules which can be added to enhance and broaden the scope of service provided by the system. An example of this is the GABAalert. These need writing in a relatively long code and are connected to the system either through real code calls or concept.

Algorithms
The data in the GABAagent databases are extracted using ADE Perl scripts that are mainly based on the algorithm
Fig. 5. GABAalert’s useful options. (a) List of e-mail alerts for the user Wong. The list is produced for the user by choosing the GABAalert option ‘List previous submissions’. (b) A HTML form invoked by the GABAalert option ‘Resubmission’. The user Wong chooses to replace the last e-mail alert’s keywords with new keywords shown at the top of the form. (c) A HTML form invoked by the GABAalert option ‘Unsubscribe some previous submissions’. The user Wong decides to remove the second in the list of multiple alert requests.

described by Rebhan et al. (1998). However, some alterations were made to the algorithm in order to adapt it to this work. Additionally and as improvements on the GeneCards system, new algorithms were designed for data integration, Boolean expressions usage and query reformulation system and GABAalert module.

**Boolean expressions support**

GABAagent’s algorithm supports the use of known Boolean expressions such as AND, OR, NOT, and wildcards. Additionally, a novel Boolean expression designated as LND was incorporated into the function. While the Boolean logical operator AND searches the associated words in a whole text file regardless of the position of the words, the logical operator LND instructs the search engine to register hits only if the words are found in the same line of text and ignore the rest. Selection of the LND operator when performing a search will help minimise the number of matches retrieved against a specified query as compared to the same query using the AND operator. The only drawback of this operator is the possibility of not getting hits that might be useful. However, the system allows unsatisfied users to query the databases with the AND operator.

**Query reformulation and spelling correction**

When a search query is made, the special characters that are associated with the query reading format are usually removed prior to splitting the query into separate keywords. In cases where the glimpse search tool does not find matches in any of the targeted server databases, the query is considered to be either out of scope or contains spelling
errors. In either case, the corresponding keyword(s) are transferred to a Perl script routine which runs glimpse in order to search through a separate dictionary file. This dictionary, which is not included in the glimpse index, contains all words found in the server databases, in addition to their usage frequencies. This function allows for the correction of misspelled keywords, as well as providing a pathway for the build-up of a short list of closely related words.

Both the original keywords and their corrected and/or suggested versions are used to reformulate the query using a variety of options. For all reformulation options, the wildcard and typographical error (typo) level parameters are utilised. Typo levels 0, 1 and 2 (in the form of either insertions, deletions or substitutions) are provided as a means to assist the user in conducting stricter and/or approximate searches, thus improving their odds of retrieving relevant matches.

The typo levels are an application of the hash ‘-#’ option of glimpse which allows the consideration of up to eight typos. In the context of the present version of GABAagent, no more than two typos are permitted in order to keep the search fast and the results as close to the original keywords as possible.

Query reformulation options are presented in table-like formats as follows.

A. Original keywords are represented as reformulation options with and without typo levels and wildcard considerations. Additionally, if any keywords are misspelled, other reformulation options are added directly under each misspelled word. In each case, this includes a spelling corrected word(s) as well as closely related word(s) (Figure 4(a)).

B. In cases where the query is composed of more than one keyword, the query reformulation includes combinations of the keywords with Boolean expressions. If the original query contained Boolean expression(s), the reformulation system keeps them without alteration, otherwise, the Boolean operator ‘AND’ is used. In cases where the query contains the ‘LND’ operator (which would have initially restricted the search, see above) additional reformulation suggestions are given using the operator ‘AND’. If spelling correction is performed, then additional reformulation options are added (Figure 4(b)).

C. When possible, an additional table is provided which contains three other related words, along with their respective hyperlinks, for each of the keywords given in the original query (Figure 4(b)).

The GABAalert algorithm

The CGI Perl script of this module primarily uses the UNIX command for interactive message processing, ‘Mail’. The algorithm has been designed to allow multiple submission of e-mail alert requests, in addition to possessing the capability to track and store each user’s alert requests via recognition of the user’s surname and e-mail address. The program can also discern whether any given submission is repetitive for any particular user by comparing the new submission’s keyword(s) against previous submissions. Thus, in case of repetitive submissions, new submissions are reject and users are asked to issue alert requests with different keywords. The current version of the systems’ algorithm has primarily been designed to allow querying of the GABAagent databases and no attempts are made to store previous alerts’ content.

Implementation

GABAengine usage examples

A successful query such as ‘diazepam AND brain’ submitted with the pre-selected options that include the desires to search for publications within the last six months, including the researchers’ postal and email addresses, E-Web pages, and DNA and protein sequence information, yields a new Web page that displays an outline of the results (Figure 2). A description of the result outlines and their usefulness are as follows.

A. Number of publications accompanied by a respective hyperlink. PubMed abstracts results are represented by two hyperlinks; one that links to abstracts with internal links to DNA/protein data and hard links to GeneCards Web site (GClinks) and a second which links to abstracts without internal links (Figure 2).

Clicking on (choosing) either of the hyperlinks produce a Web page displaying a list of articles denoted by their ready-to-click titles. Each article from the list will be accompanied with hyperlinks to DNA/protein data and/or GeneCards when choosing the GClinks (Figure 6). Selection of any of the article titles generates a Web page, which displays a PubMed abstract of the paper in MEDLINE format. This page also supplies useful information such as the journal of publication as well as other pertinent reference data.

Besides containing a hyperlink to the NCBI PubMed home page, a hyperlink designated ‘Find similar papers’ is also displayed which allows for direct search of the NCBI’s PubMed database for related papers (Figure 7). This is achieved by using the ‘ENTREZ neighbouring’ feature of the NCBI’s ENTREZ system (NCBI, 1992). Clicking on DNA/protein
PubMed’s article(s) for the query ‘diazepam AND brain’:

9901.
The gamma 3-subunit of the GABA(A) receptor confers sensitivity to benzodiazepine receptor ligands.
- View related DNA sequence (DDBJ): Sequence only  Full entry

9902.
Sequence expression of the murine disulfiram binding inhibitor.
- View related protein sequence (SWISS-PROT): Sequence only  Full entry
- View related DNA sequence (DDBJ): Sequence only  Full entry

9903.
Bovine and human DNA sequence encoding a putative benzodiazepine receptor ligand.
- View related protein sequence (SWISS-PROT): Sequence only  Full entry
- View related DNA sequence (DDBJ): Sequence only  Full entry
- View related GeneCard

Fig. 6. Display of detailed results for PubMed abstracts with hyperlinks to DNA/protein data and/or related GeneCards, see also Figure 2. The article titles are hyperlinks to respective PubMed abstracts and DNA/protein links are either to sequence data only or related full entries.

data or GeneCards hyperlinks leads to pages with corresponding results.

B. Number of E-Web pages accompanied by a respective hyperlink. When selected, this hyperlink generates a Web page, which displays a list of ready-to-click titles along with a general description of their respective contents. At the top of the page and located beside a hyperlink pointing to the Web address of the page from which the content was extracted, users can find some other useful hyperlinks such as:

1. A hyperlink designated ‘Similar pages’ which allows users to find related Web pages.
2. A hyperlink entitled ‘Pages linking to this one’ which is capable of performing a search of the page’s Web address, via the HotBot search engine (http://www.hotbot.com), which searches the Internet using complete URL addresses as keywords. This link attempts to broaden the scope of the original search.

C. Number of DNA and/or protein sequences along with their respective hyperlinks. Selection of any of the displayed hyperlinks associated with one of the retrieved DNA or protein sequence results leads to a Web page that provides a list of two additional hyperlink titles. These two hyperlinks are designated ‘Get protein sequence hits only’ and ‘Get protein sequences & full information hits’. The difference between these two hyperlinks, is that selection of the ‘Get protein sequence hits only’ link extracts DNA/protein sequence data in raw format (Figure 8) whereas the other link provides whole DNA/protein entry when selected.

At the top of each page, the user will find a hyperlink to the home page of the associated server and, when possible, another linking to sequence analysis tools provided by the source server (ExPASy or DDBJ).

D. A hyperlink to postal and e-mail addresses. Selection of the hyperlink ‘Click to display’, generates a Web page that displays the titles of retrieved papers followed by various hyperlinks corresponding to each paper’s abstract, as well as to the principal researcher’s postal and/or e-mail address(es) (Figure 9). Because such a page could display substantial quantities of information and not all the listed papers are provided with e-mail addresses, a set of hyperlinks are found at the top of the page to allow the direct reach to those papers possessing e-mail addresses. Furthermore, beside each e-mail address displayed is a hyperlink of the type ‘mailto:’ which provides users with quick access for composing
messages to researchers of interest. Additional hyperlinks are used to facilitate navigation within the page.

GABAalert usage examples

Users submit a form that contains (among other data) information including their e-mail address and keywords. They also have the choice to request searches of the GABAalert databases or a direct search of the NCBI’s PubMed database. While the GABAalert is mainly a monthly based server, users can choose to receive immediate e-mail alerts along with any new queries.

The data sent by e-mail is essentially in HTML format. GABAalert results can be viewed directly by users whose e-mail systems support HTML. Otherwise, users need to save the retrieved e-mails and view them at a later time utilising an appropriate Web browser.

In order not to overburden the users e-mail system, the search results contained in the e-mail alert include only a page of a list of ready-to-click titles that are properly hyperlinked to the GABAalert databases or the NCBI PubMed. The e-mail alerts have basically the same data structure as described above.

Discussion

The aim of this work has been to create a user-friendly Internet application supported by field-specialized in-house and online databases. Such an application was sought as a means to help users in the field of GABA receptor perform database searches for relevant information. The current system conducts subject-related searches targeting a number of heterogeneous resources. All retrieved information related to a given search is then presented to the user in a concise and integrated format.

Several database systems exist that use different approaches in their quest to achieve data integration. The OWL database (Bleasby and Wooten, 1990) is a non-redundant in-house composite protein sequence database built from other databases such as NBRF-PIR, NBRF-NEW, NEWAT86, PSD-KYOTO, SWISS-PROT, as
Fig. 8. Display of a protein sequence with hard and internal links. The link ‘Swiss-Prot & TrEMBL home’ is a hard link and points the browser to the SWISS-PROT home page. The link ‘Sequence analysis tools’ is an internal link that points to the part that display the SWISS-PROT analysis tools found at the end of a full sequence entry which is in turn a file that belongs to the GABAagent’s protein sequence database. The internal link ‘entry’ at the bottom of output page displays the full sequence entry.

well as sequences derived from the Brookhaven protein structure databank. This type of database is known as a warehouse federation. In contrast, the SRS retrieval system (Etzold and Argos, 1993) falls under the database type known as a virtual federation; a generic WWW-based interface relying on links between different but related databases such as the EMBL, SWISS-PROT or PROSITE.

A virtual federation extension of the Worm Community System (Shoman et al., 1995) known as ENQuire (Jamison et al., 1996) has implemented a type of database system that became known as a parallel virtual federation. This system is capable of performing parallel queries against multiple databases. BioKleisli library (Davidson et al., 1996) is another example of a virtual federation. This library implements a query system known as Kleisli and is used to query online servers such as GeneBank, GSDB, GDB, and NCBI-BLAST, and thereby tries to provide data with some level of integrity.

GABAagent is a system that provides integrated data through the use of specialized in-house databases (warehouse database system) that are related to each other through internal links combined with hard links to respective Internet resources. As a result, we have created beside the warehouse databases system an additional virtual federation databases system that involves PubMed, DDBJ, SWISS-PROT, TrEmBL, GeneCards and a significant number of related E-Web sites (Figure 3). It is hoped that such a dual system will help users benefit from the advantages derived from data integration and speed.

One Internet resource, which has recently appeared in the field of GABA receptor research, is the Ligand Gated Ion Channel database (LGIC; http://www.pasteur.fr/units/neubiomol/LGIC.html. The database is the work of Le Novère and Changeux (1998) at the Institut Pasteur. While the LGIC system relies on a warehouse-type database system which is concerned with providing systematic classification of ligand gated ion channel DNA and protein sequences, GABAagent provides, besides sequence data, paper abstracts and related Web sites’ contents and addresses in an integrated frame as well as hyperlinks to useful systems such as PubMed, ExPASy, DDBJ and GeneCards.

With respect to query reformulation support, provision of such a support is an attempt to provide an intelligent interface to assist users to reformulate their queries efficiently. This is important in light of the fact that it has recently been stated that due to time limitations users tend to avoid reading help instructions (Smith et al., 1997;
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Choose from the following links to find labs where e-mail addresses are available:

[Click to display](Figure 2). Hyperlinks are present at the top of the page to facilitate reaching those records with e-mail addresses available.

Pollock and Hockley, 1997). The reformulation support helps users to deal with common usage problems, such as misspelled keywords, and propose reformulated queries to expand or narrow the scope of the search. The current version of the system does not support reformulation help for aliases/dialects words.

While the present version of the GABAalert is devised for the retrieval of scientific publications, when possible with related DNA/protein sequence data, and related E-Web pages content, other alert systems such as the Sequence Alerting System (Hegyi et al., 1997; http://www.bork.embl-heidelberg.de/Alerting/) and Create and Send a Swiss-Shop (http://www.expasy.ch/swisshop/SwissShopReq.html) deal mainly with DNA and/or protein sequence data.

As shown above in GABAagent Scale up and Figure 1, the modular structure of GABAagent allows for the future expansion or upgrade of applicable databases and services. We are also in the process of upgrading our GABAalert service to include e-mail alerts that contain DNA/protein sequence data content.

Acknowledgements

Financial support by the HKSAR Industry Department (grant AF/140/96 and AF9/97) is gratefully acknowledged. We thank Prof. J.Tze-Fei Wong and Dr. David Miller-Martini for helpful discussion and Miss Suk Hang Cheng for technical assistance.

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