

Research on Graphical Interfaces to Perform Anatomical Queries on Large Collections of Gene Expression Images

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Abstract

How to find the most interesting image when tens of thousands are involved? How to present relevant information to help users gain a deeper understanding of this data? As image information is increasing sharply, searching and presenting of images in large databases became more and more important in image management. In this paper, we focus on large neuro-anatomical image collections of *Drosophila* (fruit fly) brains. Our goal is to propose a design for optimizing a graphical query interface for anatomical search to present more valuable information behind the images and also improve the usability. In order to achieve this, we first investigated different relevant websites such as “Fly Circuit”, “Fly Light” and “Allen Mouse Brain Atlas” and also image management programs such as PivotViewer and Zegami, analyze and compare these websites and programs with different perspectives, and try to define guidelines for best practices out of them. Based on our findings we propose several mockups for neuro-anatomical query interfaces.

Keywords: Image Management, User Interface, Usability

1 Introduction

Brainbase [2] is a large database of confocal microscopy images of the *Drosophila* nervous system. BrainBaseWeb is the UI of BrainBase, in which users can search and browse the confocal microscopy images and related anatomical data. In this paper, we propose a redesign concept for an important component of BrainBaseWeb: the anatomical search interface. The anatomical search is a graphical interface to perform anatomical queries on large collections of gene expression images. It allows users to retrieve images with a certain staining expression. However, currently over 12 000 images are publically available and over 50 000 images are used internally by our collaboration partners. How to search the right image out of tens of thousands and what is the most useful and relevant

information we should provide for the users are the major questions. To be addressed in this context, we discuss them and try to solve these issues in the following Sections. In order to get some inspirations and ideas, we first investigate similar websites, which also provide a large collection of anatomical data sets of brains (See Section 3). We compare the content, the data provided, and different functions of each website – for example, how users interact with these websites and which components are used for the interaction. Then, we analyze their advantages and disadvantages and try to find best practices, which we can use for redesigning the functionalities in BrainBaseWeb. We also investigate different image management applications (see Section 4) with respect to how these applications are designed to manage large collections of different kinds of images and how images can be searched, filtered, grouped and combined with associated metadata. Based on our findings and advice from experts, we propose a redesign of the anatomical search of BrainBaseWeb.

2 Related Work

Besides of BrainBase there are several other databases on resources of neuro-anatomical data available that also provide extensive query possibilities. Examples further investigated in this context are: FlyCircuit [6], FlyLight [7], Allen Mouse Brain Atlas [1], FlyBase [4] and Virtual Fly Brain [9]. Those websites are all interfaces for neurobiologist to explore the nervous system, for instance the connectivity, expression of neurons. We also study different image management tools, such as Zegami [10] and PivotViewer [8].

In addition to the relevant websites, we also investigate works of prominent UX authors, such as Ben Shneiderman, his Eight Golden Rules of Interface Design [19]. In his theory, there are several principles that the designer has to follow, in order to design an effective user interface: for example, the interface should be designed consistently, with using similar icons, colors and sequences of actions which helps users learn more quickly to use the website. Furthermore, users should always be offered with informative feedback. Another eminent author in this area is Don Norman, in his theories, visibility, feedback, constraints,

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mapping, consistency and affordance are promoted as the main interface design principles [18, 16].

Searching for images in large databases is also a problem which we want to solve in our research. There have been a wealth of papers, articles and books proposing different techniques. Most techniques can be divided into two categories: description-based image retrieval and context-based image retrieval (CBIR). With using description-based image retrieval, users are allowed to search images by keywords, tags, labels, subject heading, caption or descriptions associated with the image [13]. However, it requires users to annotate the images manually. If the image database is very large, it becomes unfeasible. On the other side, content-based image retrieval allows users to search images based on their content and features, such as colors, shapes, textures and structure [14]. Next, we walk through several examples and demonstrate the technologies.

Traditional content-based image retrieval is based on the idea of Query-by-Example and requires users to upload images. Interesting features of the image will be extracted, compared with other images in the database and similar images will be shown as result. Nakazato et al. [17] present an advanced interface, which allows users to search, annotate, and organize digital images by group (Query-by-Group). Users can drag and group images on the interface and create groups of queries. The result will be shown on another pane beside the query pane, so that users can see the result interactively. Besides of grouping images, users can also combine simple algorithms to create a query. An approach introduced by Eidenberger [15] combines several simple algorithms and groups them into query models in order to retrieve images. Query-by-Memory is another often-used concept in CBIR. Unlike Query-by-Example, Query-by-Memory uses a set of image features (color, shape, texture, spatial attributes) as query. A color-selection interface developed by Egon L. van den Broek et al. [21] is based on the concept of Query-by-Memory.

There are large number of techniques that have been developed to retrieve images. However, it is still difficult to search the related images. Based on our research, there are two main reasons. One reason is the enormous amounts of images. Another reason is the complexity of images. Images carry a wealth of messages within them, including their intensities, shapes, textures, structures and specific meaning that pertain to a particular context. For instance, the sparsity of gene expression patterns in neuropil is an important criterion of neuro-anatomical images for the query. On the other hand, for other types of images, shapes or intensity might be major criteria for retrieving. Different kinds of images require different search criteria. It also requires specialized knowledge to specify the search types and search parameters.

Furthermore, an intuitive and user-friendly interface seems to be lacking. Communication and cooperation between users and designers are very important to solve this

problem. In a world of information overload, it is hard for the designers to figure out what the users are trying to accomplish. Sometimes, the users themselves do not even know what they want or how to solve the problems. At this point, designers could inspire users and propose several mockups for them. Otherwise, it could happen, that the designer designs a function, which he think it is convenient to use and easy to understand – however, the users think it is not intuitive and complicated to use at all.

In this paper, we study different websites and image management tools, consider advice from experts, try to integrate them and propose a design for an interactive user-friendly interface.

3 Investigation of relevant websites

This Section compares query interfaces for neuro-anatomical image on 3D neuron collections: Fly Circuit, Fly Light, Allen Mouse Brain Atlas, Fly Base, Virtual Fly Brain and Brain Base. We will investigate the data and functions provided by the websites and the advantages and disadvantages we found while using the websites.

3.1 Overview of the relevant websites

3.1.1 FlyCircuit

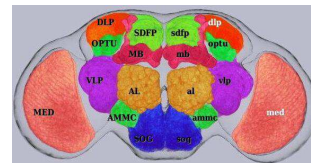


Figure 1: Image-based Search (FlyCircuit) [6]

The first website we investigate is a Taiwanese Database of Drosophila Brain [6]. This website provides functions such as basic browsing and searching, and also online archiving, data analysis and 3D visualization. 23583 images of single neurons are accessible and searchable via this website. Users can select single neurons and browse their general information (such as name, driver, gender and age), images (confocal image, segmentation, skeleton), spatial distribution, similar neurons and their neighbor neurons. Furthermore, users can select several neuron images and collocate them to create a 3D visualization.

Two different search features are provided. Users are allowed to use images-based search or text-based search to retrieve the neurons they want. To apply the images-based search (see Figure 1), users just simply click on the image to select neurons in the neuropil. To apply text-based search, users have to enter search terms in the appropriate boxes or select options from the drop-down lists (such as name list, driver, annotation and innervation).

Besides all the functionality we mentioned above, Fly-Circuit also allows users to analyze the connectivity and

similarity of the neurons. Users can search neurons with similar structure by cell body neighborhood and neuron morphology, find tracts between neuropils and find wiring diagram to neuropils.

3.1.2 FlyLight

FlyLight is a database for GAL4 line and LexA line images [7]. When browsing different GAL4 and LexA driver lines, general information of this line is provided. Users can also browse information such as projection, translation movie, or substack of the lines. This website provides several text-based search features, such as search by line or associated gene and search by anatomical expression. In this paper we focus on the search by anatomical expression. In the anatomical user interface, users can select neuropils by dragging them from the anatomical term list on the left into the pane on the right side. After doing this, they can specify the intensity and distribution with two quantifiers (from 1 to 5) in order to retrieve images.

3.1.3 Allen Mouse Brain Atlas

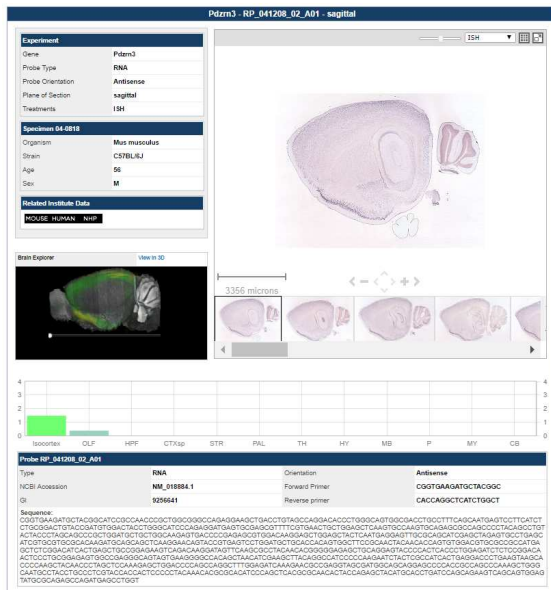


Figure 2: Browsing Window (Allen Mouse Brain) [1]

The Allen Mouse Brain Atlas provides large anatomical data sets of adult mice brain with powerful browsing and search features (such as gene searches, ISH image viewer, microarray and RNA sequencing data, Brain Explorer software for 3D visualization and atlas viewer) [20, 1]. It supports a large number of functionalities to browse and explore gene expressions. First of all, the browsing page (see Figure 2) of an individual gene includes experiment details as well as general information of the gene, a 3D thumbnail view expression and an ISH image viewer. With using the ISH image viewer, users are allowed to zoom and pan the gene expression images in different slices. At

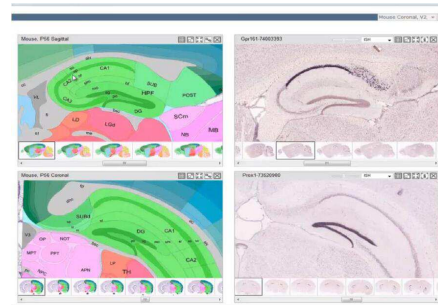


Figure 3: Left: Reference Atlases, Right: two different expression patterns (Allen Mouse Brain) [1]

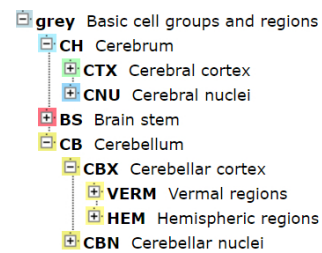


Figure 4: Anatomical Search (Allen Mouse Brain) [1]

the bottom of the browsing page, a histogram is shown, which provides a quantitation of a gene expression. 12 large structures are represented on the histogram. When the users move their mouse over the structure, gene expression values will be indicated. A powerful tool called Reference Atlas Viewer is available on their website. It provides users a reference when exploring and analyzing gene expression images. Furthermore, users can explore several genes at the same time, add reference atlases which we mentioned above and synchronize all the expression patterns (see Figure 3). In addition, a 3D viewer called Brain Explorer is also provided. It is an extension of the Reference Atlas Viewer. Users can view 3D visualized data with an associated reference atlas and metadata.

Allen Mouse Brain provides mainly two different search features: gene search and anatomical search. Gene search allows users to search gene expressions using gene symbols and gene names. Anatomical search allows users to select certain anatomical terms from a drop-down list, in order to retrieve gene expressions in a particular brain structure (see Figure 4). Beside gene search and anatomical search, a correlate gene search is also provided. Users can find other genes with similar expressions, accomplished using the NeuroBlast Search. Once a gene has been selected and the query has been applied, a list of genes matching the selection criteria with similar expression profiles will be returned.

3.1.4 FlyBase

FlyBase is the database most frequently used by Drosophila researchers. It provides the most complete

amount of information, such as information of expression data, stocks, mutants, researchers, publications, references and more [4, 5]. However, FlyBase does not host large image collections, but only links to other collections. When browsing different gene expressions in FlyBase, general information, genomic Location, Families, Domain and Molecular function and Gene Ontology are available for users to view.

According to search features, FlyBase provides also different search tools. QuickSearch, QueryBuilder and TermLink are the main tools for searching. The search features are mainly text-based. Users can select options from drop-down lists, enter search terms, and have check boxes or option buttons available to specify queries.

3.1.5 Virtual Fly Brain

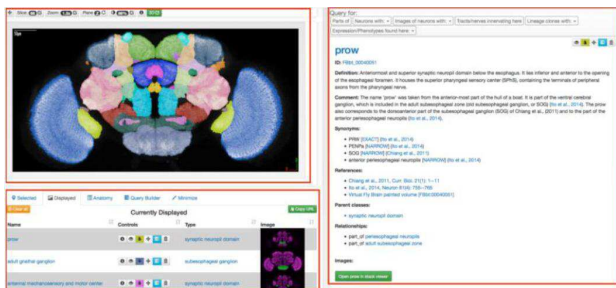


Figure 5: Browsing Window (Virtual Fly Brain) [9]

Virtual Fly Brain is another interactive tool to explore the nervous system of *Drosophila*, such as its connectivity, anatomy and expressions [9]. Image datasets are integrated onto 3 different brain templates, in order to determine position of the expression and to find similar neurons or neuropils. The Browsing window of Virtual Fly Brain is divided into 3 parts: Stack Viewer (upper left), Info Window (right) and Viewer Menu (bottom left) (see Figure 5). Stack Viewer is a slice browser: Users can view the neuropils in different slices and also zoom and pan the slices. With Clicking on the image, the name of the selected neuropil will be shown on the Stack Viewer, and the general information about this neuropil will be shown on the right side in the Info Window. In the Viewer Menu (bottom left), users can modify the selected neuropils, they can choose if they want to show the neuropil in the Stack Viewer, and they can delete or add a neuropil to the Viewer Menu. Users can also switch to Anatomy view to select specific anatomical terms to add. Furthermore, users can apply queries for a particular neuropils, by clicking the “Query for” menu bar above the Info Window. The “Query for” menu bar is context dependent. It includes query options such as “search neurons with some part here”, “search tracts/nerves innervating here”.

In addition to these, Virtual Fly Brain provides analysis features, such as “One against all search”, “Pairwise comparison”, “Upload tracing” and “GAL4 Search”. “One

against all search” allows users to compare one neuron against to all other neurons stored in Virtual Fly Brain, in order to find the nearest neighbor and same type of neurons. Pairwise comparison makes it possible to compare two different neurons, to know if they are related. “Upload tracing” and “GAL4 Search” request users to upload a tracing or enter a neuron to compare against all cluster example or neuropil based staining patterns of GAL4 lines stored in Virtual Fly Brain. All the results and neurons found will be listed and shown in a 3D view. Users can interact with the 3D model and download the Information of the neurons.

3.1.6 BrainBaseWeb

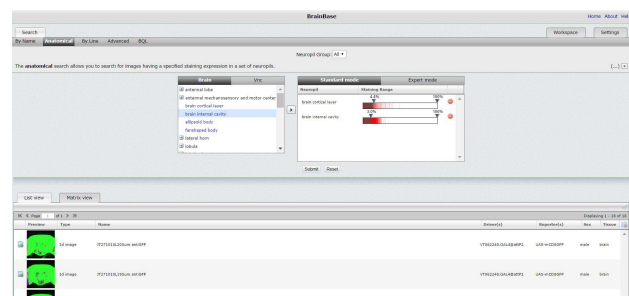


Figure 6: Anatomical Search (BrainBaseWeb) [2]

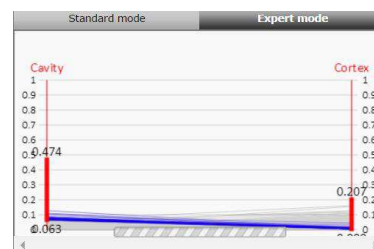


Figure 7: Parallel Coordinate (BrainBaseWeb) [2]

BrainBase is a large database of confocal microscopy images of the *Drosophila* nervous system. BrainBaseWeb is the user interface of BrainBase [2, 3]. The anatomical search of BrainBaseWeb allows users to retrieve images which have a certain staining expression. The search interface is divided into three parts: available anatomical terms which can be selected are positioned at the upper left, standard mode and expert mode used for searching are at the upper right, list view and matrix view used to view the results are at the bottom (see Figure 6). To apply a query, users can simply select neuropils and add them to the search mode area. There are two different search modes. In the standard mode, each selected neuropil is shown as a slider in the search mode area. Users can use the slider to specify a staining expression range within a neuropil. In the expert mode, the selected neuropils are shown as vertical lines. Users can use the parallel coordinate widget to specify complex staining patterns over sev-

eral neuropils (see Figure 7). One advantage of the parallel coordinate widget is that the user get immediate feedback on the number of images corresponding to the defined pattern while defining the expression range for each neuropil. If no result is found, all the lines will be gray; otherwise, the result lines will be drawn in blue. If users use standard mode, the results cannot be explored simultaneously. Therefore, it could happen that users cannot find any results with the expression range they specified.

3.2 Comparison & Analysis

Most browsing windows for individual neurons include general information (such as gene type and gender of neurons), publications, experiments and references associated with the neurons. On some websites, similar neurons and their neighborhoods are also shown in the browsing window, but in the meanwhile, some websites have designed this aspect as a query request. For instance, in Virtual Fly Brain, users have to select query options in the “Query for” bar in order to retrieve the similar neurons or neighborhoods (see Figure 5). The Allen Mouse Brain Atlas encodes the gene expression distribution into a histogram. It is a great example of providing mapping, making it intuitive and easier to gain a better understanding of the gene expression distribution. In addition to this, the Allen Mouse Brain Atlas provides a legend viewer called reference atlases. It provides users an atlas while exploring gene expression images (see Figure 3). Besides the meta information and tools provided by individual websites to help the users to better explore gene expressions, almost every website provides a 3D visualization of neurons. Some websites provide a small 3D thumbnail, while some websites provide a more advanced tool such as Brain Explorer from Allen Mouse Brain, which integrates the reference atlas viewer we mentioned before with 3D visualized data and metadata. 3D visualization helps users better explore the neurons and increase the interactivity, we also use it in our redesign.

In order to search effectively, each website offers its own search features. Most of the search features are text-based. Users enter search terms in the appropriate boxes or select options from the drop-down lists (for instance by selecting anatomical terms from a list of particular brain areas) or select checkboxes. Moreover, FlyLight developed a quantifier for the intensity and the distribution for the anatomical search. Some of the websites also developed an image-based search. For example, in FlyCircuit and Virtual Fly Brain, users can simply click on the template of neuropils to retrieve neurons or neuropils in a certain brain region (see Figure 1 and Figure 5).

User experience and interaction design components, which frequently used for searching, are: a) Textfield b) Checkbox c) Option Buttons d) Drop-down list e) Radio box. According to the style of these websites, most of the websites are designed pretty simple and not that fancy. Green, blue, orange, and yellow are often used color on

these websites.

4 Investigation of image management applications

Zegami and PivotViewer are two image management tools, helping users to search, sort, filter and group their images and associate the images with metadata [10, 8]. While using Zegami and PivotViewer, users are allowed to explore and manage tens of thousands of images all at once. Zegami is the extension of PivotViewer. In Zegami, more features are integrated, and more images can be manipulated and managed than in PivotViewer. So we only introduce the functionalities and interface design of Zegami in this Section.

The browsing window of Zegami is divided into three parts: Filter Panel, Toolbar and View (see Figure 9). In Toolbar, users can switch between four different views: grid view, graph view, table view or map view. In grid view, images are shown in a grid. In graph view, images are sorted and grouped according to several criteria, and shown as histograms in different columns. In table view, all information of a neuron will be shown in a list. In map view, labels showing the amount of the images taken in this region are displayed. Besides different views, users can also use the “sort by” and “group by” drop-down lists to sort and group the images with different criteria. In addition to this, users can use the filters options in the Filter Panel to filter the images. In Figure 9, possible filters are tags, path, project name, dataset ID and so on. For different datasets, different filter, group and sort criteria should be used. If the user clicks on the image, the details of the selected image will be displayed on the right side. With selecting “find 10 similar” users can use image similarity search to find the similar images associated to this image.

5 Mockups

In this Section, we present mockups for a neuro-anatomical search for BrainBaseWeb. Before showing the mockups, we first describe the requirements and goals of the redesign, what the advantages of the current user interface of BrainBaseWeb are, and what can be improved.

As we mentioned in Section 3.1.6, the current search interface is divided into three parts: available anatomical terms which can be selected, standard mode and expert mode used for searching, and list view and matrix view used to view the results (see Figure 6). In the expert mode, users use parallel coordinate widgets to specify the staining expression range to retrieve images having a specific staining (see Figure 7). The search result is displayed instantaneously while the users are specifying the staining expression range of each neuropils. If no result is found, all the lines will be gray; if results are found, the lines will be drawn in blue. It helps users to better specify the

anatomical search interface analysis	FlyCircuit	FlyLight	Allen Mouse Brain Atlas	FlyBase	Virtual Fly Brain	BrainBaseWeb
browsing (such as name, driver, gender and age)	X	X	X	X	X	X
similar/neighbor neurons	X		X	X	X	X
spatial distribution	X		X			
projection, translation movie		X				
3D thumbnail of neuron		X	X			X
3D viewer	X	X	X		X	X
slice viewer			X		X	
atlas viewer			X			
related experiments/publications			X	X	X	
anatomical searching						
text-based search (select anatomical terms from a list)	X	X	X		X	X
image-based search (select neuropils from a template)	X				X	
quantifier to specify staining (e.g. slider, parallel coordinates)		X				X
grid view	X					X
list view	X	X	X	X	X	X
graph view						

Figure 8: Anatomical search interface analysis

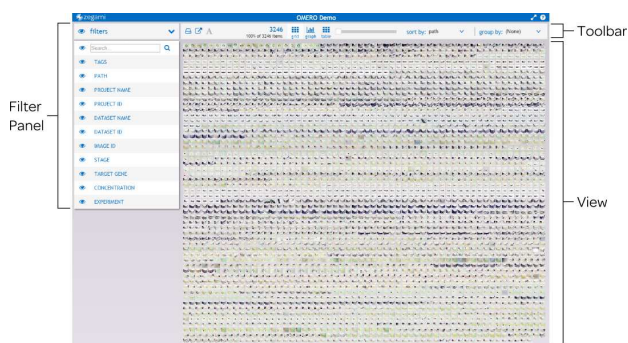


Figure 9: User Interface (Zegami) [12]

expression range of neuropils in order to get any results. However, we get feedback from users, that from their perspective parallel coordinates are not intuitive enough, and are difficult to understand in terms of how to use them. Therefore, we plan to make minor adjustments based on their feedback. We will add standard mode next to expert mode and synchronize them. In addition to this, we will create a 3D viewer. The selected neuropils or axon tracts will be highlighted on a 3D larval template. If the user reduces the staining percent, the highlighted region will be darker; if they increase the staining percent, the highlighted region will be brighter.

Furthermore, we add more view options: In the current anatomical search interface, users are only allowed to view the results using list view and matrix view. We will extend this in our redesign, so that users will be able to view the results with three different views: grid, graph and list views (name derived from Zegami [10]).

Moreover, we will also add some filter criteria, sort criteria and group criteria. For instance, to filter the images,

we will implement criteria such as name, template, sex, drivers, reporters, slide name, sample number, stain score, symmetry score, genotype, tissue, tag, creator and creation date. To sort the image, we will use criteria such as staining range, genotype, creation date, similarity and sparsity. To group the images, we employ criteria such as similarity, sparsity, template, sex, drivers, reporters and creator.

Based on our insights from other interfaces and the analysis of gaps in the anatomical query possibilities of BrainBaseWeb we propose the following new design: Figure 10 is the home page for anatomical search. Available neuropils are displayed at the left side. To add a neuropil or axon tracts to the search, simply select it in the list and drag/drop it with pressed left mouse button in the search mode area below the list of neuropils. Users can specify the allowed minimum and maximum staining of an image within the neuropil in percent of the neuropil's total volume. On the right side of the slider widget are the parallel coordinates, each vertical line represents a neuropil. Each horizontal line represents an image with its staining expression in the individual neuropils. The wanted staining expression range within a neuropil can be specified by dragging the mouse with pressed left mouse button along a vertical line representing a neuropil. The slider widget and parallel coordinates are synchronized: If the user specifies the range in slider widget, the result will also be shown in parallel coordinates. The selected neuropils or axon tracts will be highlighted on a 3D larval template on the right side. If the user drags the slider control to reduce the staining percent, the highlighted region will be darker, if the user increase the staining percent, the highlighted region will be brighter.

If the users scroll down, they can see the results and filter, and sort and group them (see Figure 11). There

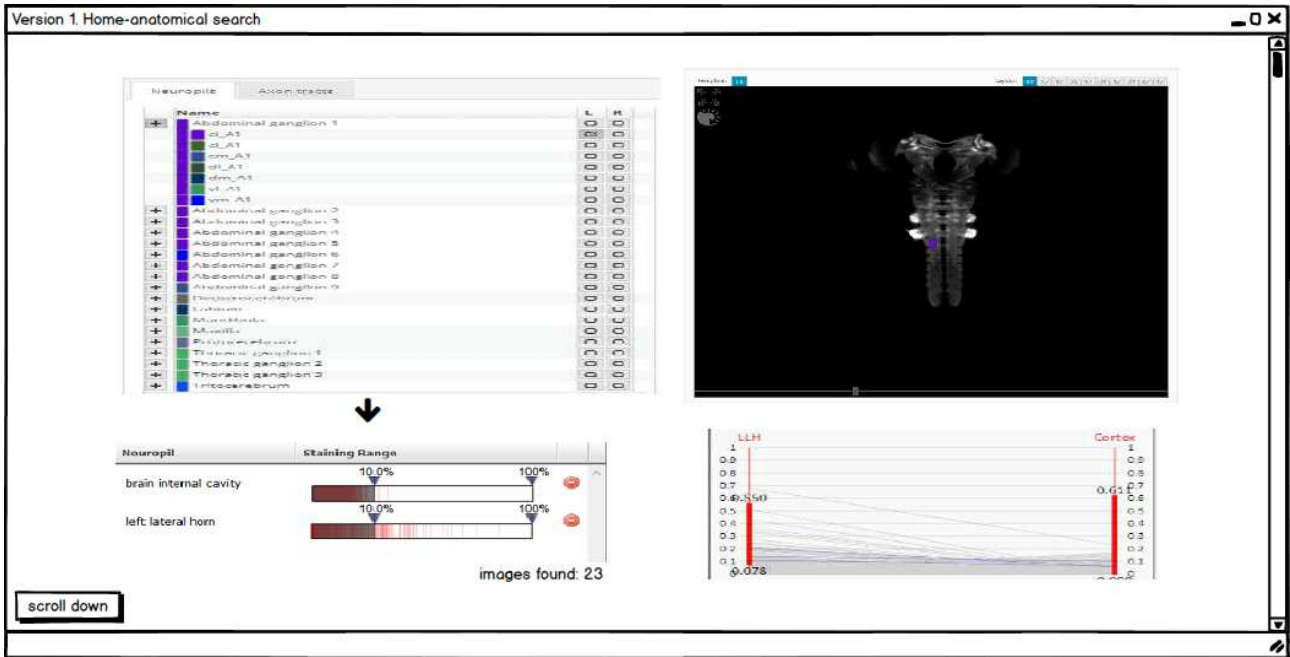


Figure 10: Mockup: Anatomical Search User Interface

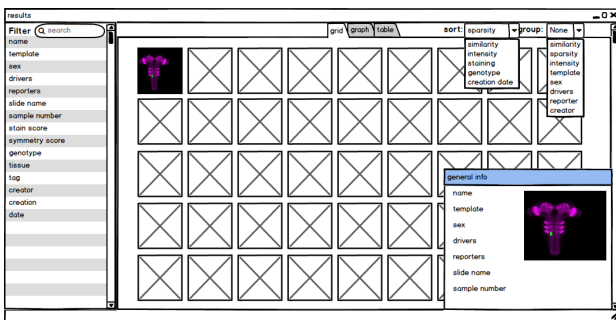


Figure 11: Mockup: Grid View

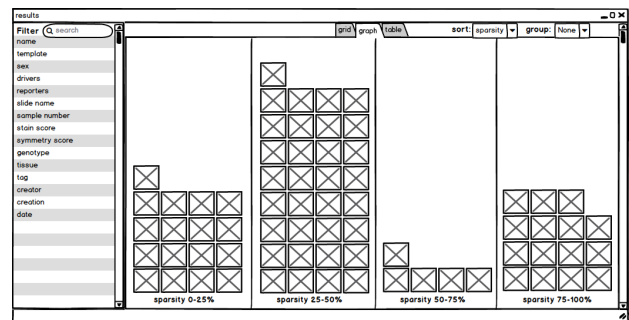


Figure 12: Mockup: Graph View - images are classified into different categories, in this example, images are classified into different categories based on sparsity.

are three views available, users can switch between grid, graph (see Figure 12) and list views (see Figure 13). Using the “sort” and “group” drop-down list and the “filters” in the Filter Panel, users can sort, group and filter the images. Users can zoom the result and select images. Once an image is selected, the general info of the image will be displayed on the right side. Users can tag and annotate an image. By double clicking the image, the details of the image will be shown in another window.

In Figure 14, the details page of the image is shown. On the left side is the general info, details on the experiment and related papers of the image. Below is a 3D preview of the neuropils. On the right side is a 2D slice view, where users can change slices, zoom, and change the plane of view and the background color. The neuropil will be colored in this 2D slice view. There is also an expression pattern below, a histogram that provides quantitation of a gene expression. Large structures are represented on the

histogram, and when user hovers over the structure, gene expression values are indicated there.

6 Conclusions & Future Work

After we investigated and studied the websites and image management tools, we propose some mockups of the web frontend of the anatomical research platform BrainBase. We add different “filter”, “group”, and “sort” criteria in order to manage the images. To improve the search features, we use both expert mode and standard mode to specify the staining expression range and synchronize them. We add a 3D template on the right side. The selected neuropils will be highlighted on the template. When the user reduces the staining percent, the highlighted region will be darker, when increased, the highlighted region will be

name	template	sex	drivers	reporters	slide name	sample num	stain score	symmetry acc	genotype
Lox264RYKRB	T1	mal	VT006035.GAL4@ol	UAS-mCDBG	Lox2640	0	4	4	+UAS-mCDBGF/+V
PM25ALESSum	T1	mal	VT045107.GAL4@ol	UAS-mCDBG	PM25A	0	4	4	+UAS-mCDBGF/+V
Lox239L50	T1	mal	VT039642.GAL4@ol	UAS-mCDBG	Lox2394	0	4	4	+UAS-mCDBGF/+V

Figure 13: Mockup: List View - all information of a neuron will be shown in a list.

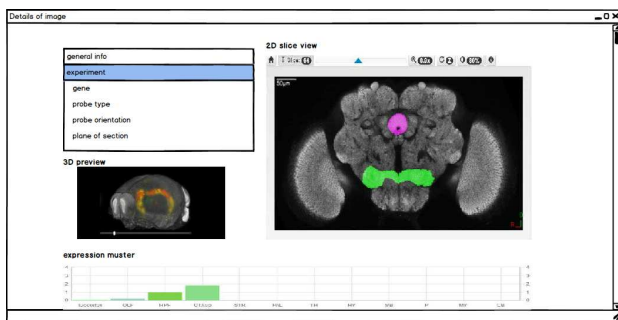


Figure 14: Mockup: Details and associated metadata of the image

brighter. We asked Drosophila researchers for their feedback and are now working on implementing the suggested features. After finish implementing the features, we will test, improve and also evaluate the interface.

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