# neuroMap - Interactive Graph-Visualization of the Fruit Fly's Neural Circuit

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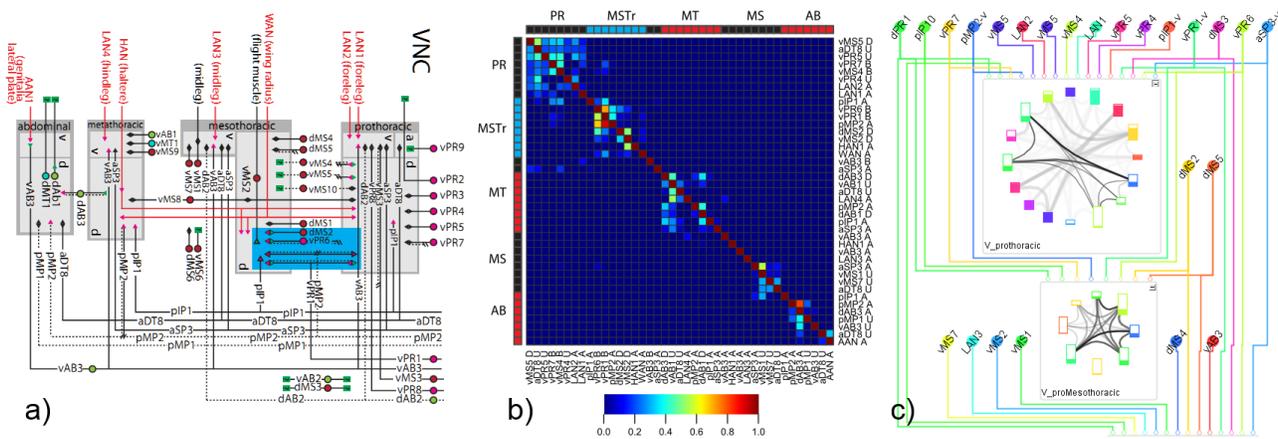
Figure 1: a) The original drawing from Yu's publication [36], b) the heat map indicating arborization overlaps in Yu's drawing, c) neuroMap combines network and overlap information.

## ABSTRACT

Neuroscientists study the function of neural circuits in the brain of the common fruit fly *Drosophila melanogaster* to discover how complex behavior is generated. To establish models of neural information processing, knowledge about potential connections between individual neurons is required. Connections can occur when the arborizations of two neurons overlap. Judging connectivity by analyzing overlaps using traditional volumetric visualization is difficult since the examined objects occlude each other. A more abstract form of representation is therefore desirable. In collaboration with a group of neuroscientists, we designed and implemented neuroMap, an interactive two-dimensional graph that renders the brain and its interconnections in the form of a circuit-style wiring diagram. neuroMap provides a clearly structured overview of all possible connections between neurons and offers means for interactive exploration of the underlying neuronal database. In this paper, we discuss the design decisions that formed neuroMap and evaluate its application in discussions with the scientists.

**Index Terms:** J.3 [Computer Applications]: Life and Medical Sciences—Biology and Genetics; H.5.m [Information Systems]: Information Interfaces and Presentation—Miscellaneous

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## 1 INTRODUCTION

A major goal in circuit neuroscience is to discover how behavior is generated through information processing by complex neuronal circuits in the brain. The brain of model organisms such as the *Drosophila melanogaster* is studied in order to find out how the function of neural circuits drives behavior [25]. Using genetic tools and confocal microscopy, scientists produce three-dimensional images of the fly's brain and its neuronal structures [29].

Knowledge about neuron connectivity is essential to understand how information is processed and transmitted within the brain. Thus, one of the tasks of our collaborators is to discover connections between neurons in the fruit fly's brain. A necessary but not sufficient condition for the existence of a connection is an overlap between the arborizations (the treelike terminal branching of nerve fibers) of two neurons. Visualization of these overlaps, i.e., potential connections, would support the analysis of neural structures and the formation of hypotheses about neuronal circuits. Judging overlaps between three-dimensional representations is difficult, since the objects occlude each other. A more abstract form of representation is therefore desirable and also more feasible because for the analysis of overlaps, anatomical accuracy and exact spatial positioning of the visualized entities are not as important as the ability to display large amounts of data in a clearly structured overview. Jai Y. Yu created such a representation [36]. It displays the innervation of neurons into brain regions (Fig. 1 a)). A separate heat map depicts the amount of overlap between the involved arborizations (Fig. 1 b)). Yu's wiring diagram was created manually in Adobe Illustrator in multiple iterations over several months. The positive response towards Yu's drawing within the group of researchers and the scientific community motivated us to create a tool that replicates and expands on the features of this graph.

neuroMap was developed with the goal of supplying neuroscientists with an abstract representation of their accumulated neuronal data in order to support and facilitate their research by supplying:

- *Easier, more intuitive neuron connectivity hypothesis-formation:* By combining the information of heat map and wiring diagram into a single automatically generated graph,

neuroMap visualizes arborizations as nodes and the potential connections between them as edges, thus letting the user grasp all potential connections of the analyzed data at a single glance (Fig. 1 c)).

- *Visual exploration of the accumulated neuronal data:* Features such as arborization overlap queries, filter mechanisms, and the merging of brain regions allow the user to extend the graph in directions of interest, to focus on important details and to filter out less relevant information, thus enabling interactive exploration of the neuronal database from within the visualization.

- *Fast generation of neural circuit graphics for presentation purposes:* Researchers use diagrams of neural structures to demonstrate scientific findings in papers or presentations [36, 18, 35]. Creating these diagrams manually is a laborious, time-consuming task. neuroMap generates these structures automatically while offering a variety of layout algorithms to achieve results that are meaningful and visually pleasing.

Using two-dimensional graphs to visualize biological networks is not an entirely new idea [15]. Nevertheless, there are still open problems in biological network visualization, as stated by Albrecht et al. [1]. Problems relevant to our approach include the following: *the visualization of multiple attributes* (object type, overlap amount, gender, neuron association), *location constraints* (assignment of nodes to specific brain regions), *visualization of flows and paths* (highlighting of related entities). Existing tools tackle some of these problems, but not in a combination that is desirable for our approach, as discussed in section 3. This, along with the requirement to integrate the visualization into an existing framework, led to the development of our solution.

This paper introduces and evaluates a novel approach for visualizing and exploring potential neuronal connections. neuroMap is the first interactive tool that enables visualization and exploration of neural networks at the arborization level with overlap information that indicates the probability of a connection.

## 2 BIOLOGICAL BACKGROUND

### 2.1 Research Tasks

The neuroscientist aims to understand information-processing and storage within the nervous system. Neural functions are critically dependent on neural structure, particularly on the pattern of connections between individual neurons. However, the nervous system typically contains hundreds to billions of individual neurons with little stereotype at the cellular level. Some invertebrates, such as *Drosophila melanogaster* and *C. elegans*, have relatively small and stereotyped nervous systems, making it possible to define their neuronal organization at the cellular level. Knowing the cellular organization of the nervous system, the investigator can begin to formulate and test hypotheses regarding the functions of individual neurons, both at the behavioral level and in terms of the neural computations they perform. However, the complex architecture of the nervous system, even for these simple invertebrate models, makes visual representations of neuronal connectivity particularly challenging. A task of our collaborating group of scientists is to find the neuron relay for a specific sensory input. Gustatory and olfactory sensory inputs are known to play important roles in the fly's courtship behavior. After determining primary (sensory) neurons and secondary neurons, which relay the information from the primary neurons, the next step is to identify the third order of neurons in this circuit. Based on the anatomy of neurons, the scientists formulate functional models that can be tested using the genetic tools available in these organisms to directly monitor or manipulate neuronal activity.
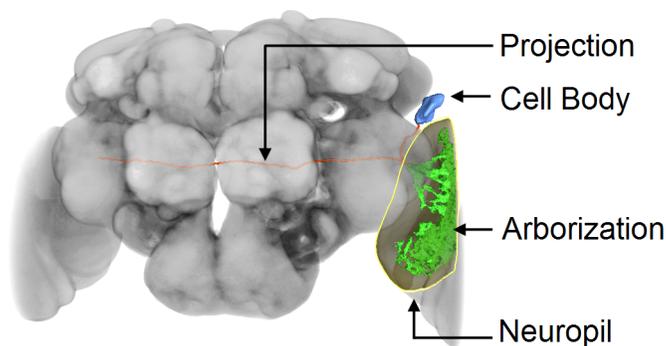


Figure 2: Surface geometry of a segmented neuron shown in the context of the standard brain template.

### 2.2 The Drosophila Nervous System

The central nervous system of the *Drosophila* consists of the brain and the ventral nerve cord and is composed of neurons, which, in turn, can be divided into cell body, arborizations and projections (Fig. 2). The **cell body** contains the cell's nucleus, the control center of the cell. **Arborizations** are terminal branchings of nerve fibers that form synapses where communication with other neurons occurs. Synapses (connections) between two overlapping arborizations can only exist if one terminal is dendritic and the other is axonal. In common invertebrates like the fruit fly, the cell bodies are located in the cortex. A **projection** is branch of a neuron which connects an arborization to its cell body [6]. Brain and VNC are divided into 60 **neuropils**, which are functional or spatial subregions of the nervous system.

### 2.3 Peters' Rule

The relationship between the connection of two neurons and the overlap of their arborizations can be described by Peters' rule [7]. Peters' rule states that the probability of the existence of a *structural* synapse between two neurons can be estimated based on the size of their arborizations' mutual overlap. A larger overlap indicates more structural synapses and therefore a higher connection probability. Although Peters' rule makes no explicit inference about the *functional* strengths of connections, it provides a blueprint of the implied functional circuit if the synaptic strength per unit of axon-dendrite overlap (per potential synapse) is assumed to be constant on average [28].

### 2.4 Data Acquisition & Storage

Our collaborators use the GAL4/UAS System [8] to highlight specific neurons in *Drosophila's* brain and confocal microscopy to generate high resolution 3D images showing brain tissue in one channel and the highlighted neurons in a second channel. The acquired scans are registered applying a non-rigid registration method [27] to a standard brain using the first channel.

After successful registration, interesting neurons are segmented semi-automatically using Amira [31]. Cell bodies, projections and arborizations are segmented separately and stored as binary masks and geometry. Each object is assigned to a single neuron. These relations, image references, binary masks and generated surface geometry are stored in a relational database. We apply an object-indexing scheme similar to that of Bruckner et al. [9] to detect overlapping arborizations and neuropils efficiently and to compute the absolute amount and percentage of arborization-arborization overlaps, arborization-neuropil overlaps and arborization-arborization-neuropil overlaps automatically. These values are precomputed and stored in the database to allow fast access for future visualization and exploration.

## 2.5 Existing Infrastructure

Our collaborators' visualization and data-mining framework provides interactive 3D visualization for volume and geometry data, and parallel coordinates and heat maps for data analysis. To select data for display and analysis, two paths are provided: a database interface for defining semantic queries and a visual query interface for exploration based on spatial relationships. Query results can be loaded into the framework's workspace from which they can be assigned to different views. However, for the task of connectivity hypothesis formation, the available features are not optimally suited. Judging overlaps in 3D is infeasible due to occlusion. The available 2D visualizations are static (heat map) or too abstract (parallel coordinates) for intuitive exploration of overlaps.

## 2.6 Yu's Drawing

The motivation for and starting point of neuroMap's design process was Yu's wiring diagram of a courtship behavior-related neural circuit (Fig. 1 a)) [36]. The drawing depicts neural pathways of a group of neurons that extend from sensory input to motor output in a schematic overview. The diagram was used to present the publication's findings to the scientific community and to inspire hypothesis formation about potential functional neural connections. Compared to traditional 3D visualization, our collaborators regarded Yu's diagram as an improved way of viewing the brain's wiring because it offers more information at a glance through its abstraction of the examined data.

The visual elements of the graph are cell bodies, projection edges and neuropils (Fig. 3 a)c)e)). From each cell body, projection edges lead to the neuropils where the neuron's arborization has a synaptic terminal, i.e., *innervation*. Sensory afferent neurons are visually distinguished from other neurons by pink cell bodies and projection edges. The arrow tip of the projection edge gives information about the type of terminal. Presynaptic terminals are represented by pink triangles, dendritic terminals by green ones, and unresolved terminals by a black diamond shape. The actual existence and amount of an overlap between a pair of arborizations in a certain neuropil is indicated in a separate heat map (Fig. 1 b)).

The layout combines anatomically motivated neuropil placement in the VNC with arbitrary neuropil placement in the brain.

## 3 RELATED WORK

Even though a wide range of brain atlases for the exploration of collected neuroscientific data on various species are available [2, 22], the depiction and exploration of neural network structures, especially at single-cell resolution, is not yet common.

FlyCircuit is a web service that grants access to a public database of the fruit fly's neurons [11]. The page offers a static wiring diagram that displays, which brain regions are interconnected. Neuron Navigator is a visual query interface to FlyCircuit's database focused on observing and discovering potential neural connections [21]. Query regions are defined in a three-dimensional representation of the brain. Neurons are not rendered as volumes but as lines, colored according to their neuron-transmitter category. Due to the absence of overlap information, the query only returns objects that are in the same defined region.

Bhatla created a web application that displays the neural network of the *C. elegans* as an interactive graph at the neuron level [5]. A query interface allows the user to find the shortest path between two neurons. The layout is constrained to three circular layers that can become cluttered quickly.

The *Partner Tree* displays all partnerships for a given *C. elegans* neuron [12], similar to Bhatla's web application. The nodes are again distributed to radial layers around a selected neuron. The first layer divides partnerships into synapse classes. The second layer shows the neuron partners and the third shows the individual synapses. A textual query interface is used to interact with the underlying data. Since the *C. elegans* nervous system is already completely deciphered, the uncertainty of a connection is not a factor.

Irimia et al. developed a circular representation of human cortical networks for the classification of neuron connectivity relationships at brain region level [17]. The outermost ring of the connectogram shows the various brain regions. Bent edges represent the computed degrees of connectivity between them.

Li et al. implemented a tool for facilitating quantitative analysis of brain connectivity [20]. The tool relies on the identification of regions of interest (ROIs) for brain network construction. Connectivity strength is represented by the width and the opacity of the edges. ROIs are represented by spheres, rendered at their three-dimensional positions in the brain, giving a direct frame reference to the linked 3D view. However, since the three-dimensional graph occludes itself, the whole network can only be comprehended by rotating the view accordingly.

Jianu et al. created a tool for visualizing tractography datasets as two-dimensional paths [19] in order to explore and analyze connectivity in the human brain. The design of the visualization was inspired by illustrations in medical textbooks.

The value of a physical frame of reference when visualizing abstract data has been recognized by Jianu et al. [19], Li et al. [20], and Lin et al. [21] in their respective works as they consider the spatial attributes of the displayed data. Only WormWeb [5], the Partner Tree [12] and Neuron Navigator [21] display their data at single-cell resolution. Connection uncertainty is handled in [20, 17, 32].

While network visualization of neural structures is still in a relatively early stage, a wide range of biomedical network visualization tools has been published in other areas as discussed in previous work [15, 26, 1]. Many of these tools are very specialized and focus on tasks like handling protein interaction [4], gene expression [16, 3] or metabolic profile data [23] and connect directly to associated public databases [13, 16], while some allow for more general use [30]. Nevertheless, there are some parallels to neural network visualization, like locational constraints and connection uncertainty. Barsky et al. developed a Cytoscape plugin for analyzing protein interactions that emulates the visual style of traditional pathway diagrams [4]. It allows the user to pose location constraints on the graph's structure by assigning the graph's nodes to hierarchical layers. The STRING database contains predicted functional associations between proteins and assigns a confidence score to each prediction [32].

Considering the state-of-the-art, the approach that we took with neuroMap in incorporating a physical frame of reference and connection uncertainty into an interactive graph in the context of neural network visualization at arborization resolution is entirely novel, as will be documented in the following sections of this paper.

## 4 VISUAL ENCODING

### 4.1 Abstraction to Graph Elements

In order to represent the structure of the brain in graph form, a neuron and its parts are abstracted to graph elements, i.e., nodes and edges. A neuron's abstract representation in neuroMap is partitioned into a single **cell body** *node*, one or more **projection** *edges* and, in contrast to Yu's drawing, also **arborization** *nodes*. A projection edge links an arborization node to its cell body node. By giving the arborization its own representation, its associated information (such as size, neuropil overlap, or sex) can be directly encoded within the visualization. **Neuropils** are represented as *group-nodes* that contain the arborization nodes that overlap with them.

The **overlap** between two arborizations that was visualized in a separate heat map in Yu's publication [36] is represented directly within the graph in the form of an *edge* that connects the overlapping arborizations. Fig. 3 displays neuroMap's graph elements in comparison to Yu's diagram and their anatomical counterparts.

| | Anatomical | Yu's Diagram | neuroMap |
|---|---|---|---|
| a) Cell body | | aSP4 ⬤ | aSP4 |
| b) Arborization | | n/a | aSP4_arbM |
| c) Projection | | | |
| d) Overlap | | | |
| e) Neuropil | | AL | AL |
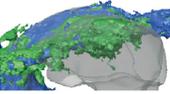
Figure 3: Direct comparison of neuroMap's elements with their anatomically accurate counterparts and representation in Yu's graph.



a)

b)

Figure 4: Abstraction of a single neuron with and without innervations into specific neuropils: a) Simple View, b) Complete View

## 4.2 Views on the Data

neuroMap's views focus on different user goals:

**Simple View** The purpose of the *Simple View* is to offer a direct overview of arborization-arborization overlaps and therefore potential neuronal connectivity without encoding locational information. Each arborization is displayed as a single node, and each overlap between a pair of arborizations is displayed as a single edge (Fig. 4 a)).

**Complete View** The purpose of the *Complete View* is to give locational and functional context to the displayed data by including arborization-neuropil overlap information in the visualization. Since some neuropils are associated with a certain functionality, an overlap between arborizations in such a neuropil can give the scientists important insights into the neurons' function.

Since arborizations can overlap with multiple neuropils, in this view a single arborization is represented by multiple nodes, one in each overlapping neuropil (Fig. 4 b)). The overlap (edge) between two arborizations is therefore partitioned as well.

## 4.3 Graph Element Design

According to Peters' rule, larger overlaps between arborizations are more important than smaller ones. To guide the user towards potentially more important connections, graph elements that are more likely to be part of a neural connection are visually enforced as described in the following.

Like in Yu's drawing, **cell body nodes** are depicted as circles labeled with the neuron name (Fig. 3 a)). In neuroMap, however, the node size scales with the number of connected projection edges to indicate neurons with a higher degree centrality [14].

The visual design of **arborization nodes** depends on the selected viewing mode (Fig. 4). In the Simple View, each arborization is represented by a single square, scaled by the arborization's volume. Because arborization volumes differ drastically in size, with a range of about 200 to 700000 $\mu m^3$, the applied scale is logarithmic.

In the Complete View, an arborization consists of multiple nodes, partitioned over its overlapping neuropils. Nodes are represented as rectangles that are vertically scaled according to the arborization's volume. To let the user easily grasp this distribution, each node is filled according to the arborization's overlap percentage with the respective neuropil. The partitions of an arborization therefore have the same size; only the filling varies with the amount of overlap.

**Projection edges** tie a cell body and its associated arborizations together. As in Yu's drawing, the end point of a projection edge can convey the terminal type of an arborization (Fig. 3 c)). However, since the database does not yet include synaptic information, all arrow tips are uniformly represented by a white diamond shape as placeholder for the actual terminal information. Nevertheless, neuroMap is built with synaptic terminals in mind, so the appearance of the graph can be adapted as soon as the required information is available.
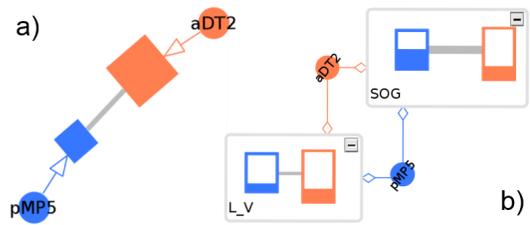
To avoid cluttered neuropil nodes in the Complete View, projection edges terminate at the border of the neuropil node instead of connecting directly to an arborization. The visual connection between cell body, projection, and arborization is made through neuroMap's color scheme. The color scheme gives all items that belong to the same neuron a uniform color to visually link associated elements.

The **overlap edge** between two arborizations encodes the overlap percentage in its grayscale and transparency value (Fig. 3 d)). An overlap of 100% results in a solid black line, while an overlap of 1% will be rendered in a transparent light gray. The contrast to the white canvas will direct the viewer's attention towards darker edges [33] that are more likely to form a connection according to Peters' rule.

As an overlap between two arborizations can lie within multiple neuropils, each of these neuropils holds a certain percentage of the arborizations' total overlap volume. The distribution of the overlap across neuropils is encoded in the line thickness. A thick line indicates that a large percentage of the overlap lies in a neuropil, while a less significant portion of the total overlap is indicated by a thin line (Fig. 4 b)). This makes it easier to spot the neuropils where a connection is more likely to occur.

The amount of overlap is bidirectional, since the overlap volume holds a certain percentage of each overlapping arborization. For a more streamlined view and less visual clutter, only the larger of both overlaps is directly encoded in the graph, since it is a better indicator for the plausibility of a connection. The smaller overlap can still be reviewed in a *tooltip window*. Tooltip windows can be used for retrieving detailed information from each type of graph element (see Fig. 5).

The visual design of **neuropil group nodes** is simple so as to avoid distraction from their content. The nodes are represented as rectangles with white backgrounds, containing a label with the abbreviation of the neuropil name and a state icon. The full name of a neuropil can be obtained from its tooltip window. A neuropil node has two states, opened and closed. When opened, the node's size scales automatically to accommodate the size of its content. In the closed state, the node's content is hidden and its size is reduced according to the number of contained arborizations in order to occupy less space than in opened state. Users can hide unwanted details, while neuropil size and incoming projections still give information about its content. Neuropils in both states can be seen in Fig. 5. Neuropils that do not overlap with the displayed data are omitted from the visualization.
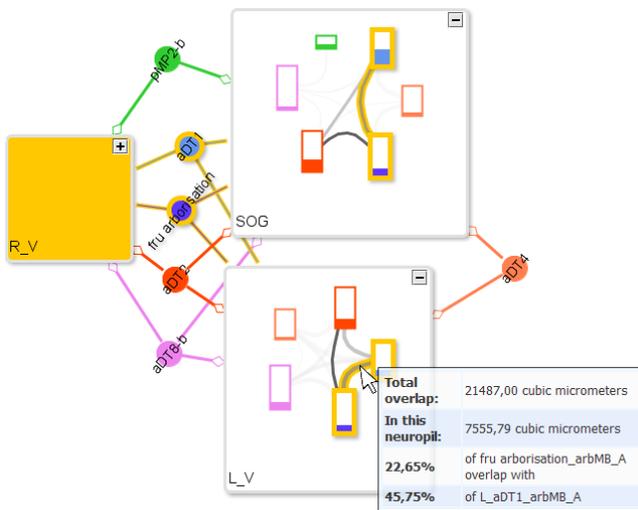
Figure 5: The overlap edges between arborization nodes encode the amount of overlap. Tooltips and highlighting allow effective exploration of the graph's multiple information layers.



Figure 6: neuroMap's anatomical layout emulates an abstract view of the fruit fly's brain.

## 4.4 Layouts

**Graph Layout**   neuroMap offers five different layout modes: circular, force-based, orthogonal, hierarchical, and our novel *anatomical layout*.

The circular and force-based layouts can be used to expose neural clusters, i.e., visually group elements that are tightly connected to each other. The orthogonal and hierarchical layout algorithm produce compact drawings that have a circuit diagram look. However, the distance from one node to another one does not convey any intrinsic information, as in the circular or organic layout.

However, the node positions in these layouts have no relation to their actual locations in the brain. We implemented the anatomical layout (Fig. 6) to address this shortcoming by partitioning the canvas into 19 different compartments that form an abstract representation of actual brain regions. Neuropil nodes are automatically placed in these compartments, according to the specifications of our collaborators. This makes the neural circuit more meaningful than a graph without anatomical relevance. Compartments are represented by blue areas that contain the assigned neuropils. Cell body nodes are placed in the center of the layout to avoid clutter in compartments and to achieve a more structured view, as all projection edges originate from the center of the graph. As in Yu's graph, cell body nodes of sensory afferent neurons are placed separately outside the graph, to the left of the brain's representation. This visually suggests the information flow of external stimuli into the brain and distinguishes these neurons from non-sensory afferent ones. The left and right brain hemispheres are switched to match the scientists' accustomed view on the data.

The anatomical layout uses a hierarchic layout algorithm that highlights the main direction of the flow within a directed graph and allows constrained node placement on a grid. The fixed compartment positions help to preserve the mental map of the graph [1], since node positions cannot change when the graph is extended, as opposed to conventional layout algorithms.

**Neuropil Internal Layout**   The content of a neuropil node is laid out in a circular fashion in order to achieve a uniform look for all neuropil nodes and to ensure compact node size even when displaying many arborizations. Edges are bent towards the middle of the circle to reduce occlusion. Additionally, overlap edges in each neuropil are sorted by their overlap amount to ensure that important
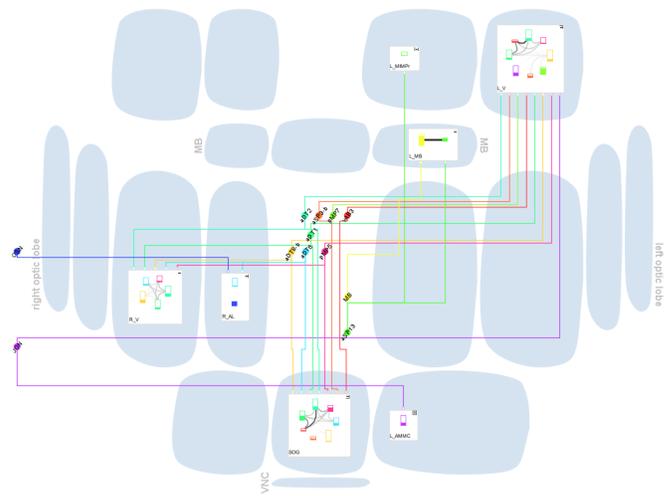
overlaps are the most prominent. The use of transparency makes it easier to trace the path of partially occluded edges.

## 5   INTERACTING WITH THE GRAPH

In order to enable the exploration of the graph and the underlying neural database, the following features were included in neuroMap.

**Creation**   To create a graph, users have two options: all of the content of the workspace can be directly imported or a subset of the workspace's content can be dragged and dropped directly onto neuroMap's canvas. By dragging and dropping additional items, an existing graph will be extended. Dropping a single arborization on the canvas loads the arborization (or its partitions and all overlapping neuropil nodes in the Complete View) and the related cell body node. When more than one arborization is loaded, the overlaps between all arborizations are calculated and visualized.

**Extending the Graph Structure**   In order to find connection candidates for a certain neuron, neuroMap's right-click context menu allows the user to query for overlapping arborizations from within the visualization and to load the results directly into graph and workspace. The query is defined by the graph element on which it is issued. Each type of element has a different effect on the query. For a neuropil or arborization node, all arborizations that overlap with this neuropil or arborization are loaded. For a cell body, all arborizations that are associated with the cell body's neuron are loaded.

**Filtering**   In order to limit the range of an overlap query, thresholds for the minimal arborization partition volume and arborization-arborization overlap volume can be specified either relatively, by overlap percentage, or absolutely, by overlap volume, with a range-slider in neuroMap's menu. Since arborization size can vary drastically, the threshold needs to be adjustable, e.g., to filter out arborization-arborization overlaps or arborization partitions that are too small to be significant in a scenario with large arborizations.

The sexual dimorphism of neurons in the *Drosophila* brain has been reported to have significant impact on its sexual dimorphic behavior [10]. We therefore provided the option to quickly filter male and female neural elements from the visualization to allow the scientists easier investigation of the circuit's dimorphism.

**Reduction of Visual Complexity**  Besides the option to reduce a graph's complexity by closing non-relevant neuropil nodes or switching to the Simple View, neuroMap allows the *merging of neuropil nodes*. As mentioned in section 2.2, neuropils are spatial or functional partitions of the nervous system. A neuron that overlaps with multiple functional neuropils is likely to have multiple functions. By merging these neuropils, the scientist can compare the overlap between the functionally relevant parts of arborizations.

By dragging and dropping one neuropil node on another, both are merged into a single node. The arborization and overlap information from the original nodes is combined as well, i.e., the thickness of overlap-edges, and the size or filling of arborization nodes.

*Deletion* of irrelevant graph elements is performed via the right-click context menu and is context sensitive, i.e., is handled differently based on the type of the deleted neural entity. When the user deletes an arborization partition, for example, all dependent graph elements, such as remaining arborization partitions, overlap edges, and the cell body, are deleted as well.

**Layout Adjustment**  A neuron can be *flagged as sensory afferent* via the right-click context menu. The neuron's cell body is then placed to the left of the graph in the anatomical layout to indicate external neural stimuli.

**Highlighting**  To emphasize relationships between elements that could be difficult to grasp in a large graph, context-sensitive highlighting of graph elements was implemented. Depending on the origin of the highlighting request, different relationships are accentuated. Highlighting an overlap edge, for example, will show the user the other neuropils in which the given overlap is found (Fig. 5).

Selection of graph elements is *linked* with the framework's 3D view and workspace. Selected elements are highlighted in order to facilitate orientation between views.

**Semantic Zooming**  Semantic Zooming supplies the user with the most essential information for each zoom level. When zoomed out, the overall structure of the graph, i.e., edge thickness, is enforced while small details, i.e., node labels, are omitted. In the close-up view, additional information such as the names of arborizations are displayed.

## 6 IMPLEMENTATION

neuroMap is built as a web service with the yFiles AJAX toolkit [34]. yFiles provides the graph logic, layout algorithms, and client/server architecture upon which neuroMap is built. The client runs in a JavaScript Dojo widget and is responsible for displaying the graph as well as handling user interactions. The server contains an interface to the yFiles for Java graph drawing library and holds the actual graph information. Manipulation and rendering of the graph is handled on the server side as well. All information that is necessary to create a wiring diagram is directly retrieved from the neural database, e.g., object names, Ids, overlap candidates, and volume/overlap size.

yFiles can be extended with proprietary layout stages, as well as custom renderers. The standard routing in the internal layout of neuropil nodes was replaced by a custom layout stage to bend edges towards the center of the circular layout. The painters of each node- and edge-type were adapted to support neuroMap's look, LoD rendering, and highlighting features. A custom background painter was implemented for rendering the partitions in the anatomical layout. The client was adapted to handle features such as highlighting, tooltips, node-merging, and drag&drop graph creation.

neuroMap is integrated into our collaborators' visualization and data-mining framework as an additional view (see Fig. 7) and receives graph creation requests, selection ids, and color information via Qt's JavaScript bridge.
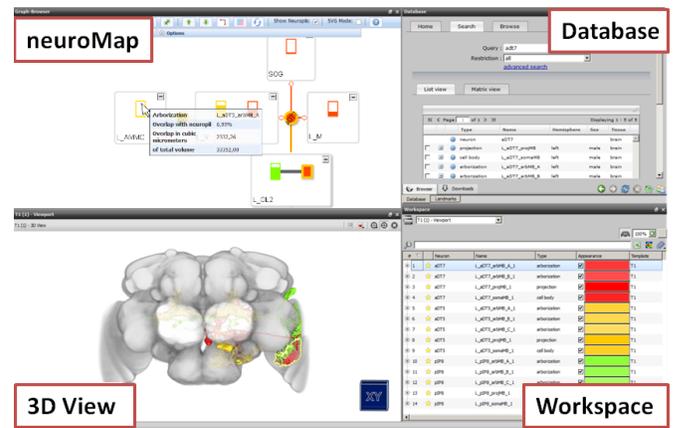


Figure 7: Screenshot of neuroMap integrated into the data mining infrastructure. Highlighting, editing, deletion and adding of objects is instantly propagated among the software's views.

## 7 EVALUATION

For the validation of neuroMap, we adapted the evaluation process to the nested four layer model for visualization design and validation that Munzner proposed in [24]. As the focus of this paper lies in neuroMap's visual encoding and functionality in relation to the semantics of the neuronal data and the tasks of our collaborators, the evaluation should prove that the chosen design is effective at communicating the desired abstraction. The evaluation method we chose is a qualitative discussion of the visualization and its features with our collaborators in regard to the goals that were stated in the introduction.

To guide the development of neuroMap, regular feedback meetings with a representative of our collaborating group of scientists were arranged. These discussions gave great insight into the scientists' workflow and helped us to understand their mode of thought, which in turn enabled us to improve neuroMap's features.

### 7.1 User Discussions

In addition to the regular feedback meetings during the implementation phase, we held two in-depth evaluative sessions with individual scientists. One session was held with four members of our collaborating group, and the other with three. A questionnaire served as checklist and guideline to structure the discussion. The participants consisted of a post-doc researcher, two PhD students and a master student.

The first session included questions about the subject's accustomed workflow in the context of connectivity hypothesis formation, database exploration, and the preparation of the presentation of findings. This was followed by a walkthrough and discussion of neuroMap's visual and interaction features, and a comparison to the scientists' accustomed workflow. In the second session, we introduced and discussed the new features that were partially added from the feedback of the first session and asked the scientists about their hands on experience with neuroMap. The following insights were gained during these discussions.

**Easier Hypothesis Formation**  Before the integration of neuroMap into our collaborators' framework, our collaborators formed hypotheses about neural connectivity by analyzing arborizations of interest in 3D and then generating an overlap heat map of a specified group of these arborizations. In the heat map, significant overlap cells are searched for, then checked again in 3D for their location. All arborizations that are to be investigated in the heat map must be explicitly specified. The heat map itself is static and must be regenerated from scratch for each update, which

severely hinders the exploration of overlaps. The scientists referred to this workflow as cumbersome and found searching through the rows and columns of a heat map for a specific overlap unintuitive.

We learned that Yu's diagram made the search for potential connections more intuitive than in 3D, even though the actual overlap still had to be checked in a separate heat map. The strengths of Yu's graph lie in the clarity of its overview due to its visual simplicity. However, the manual construction of a network of such complexity is prone to human errors that can cause researchers to form hypotheses based on non-existent connections, as one scientist commented.

The scientists deemed neuroMap's abstract representation more intuitive than the combination of 3D view and heat map. neuroMap was perceived to offer more precision and more detail as compared to Yu's graph by indicating of the probability of connections through the inclusion of overlap information and by eliminating of manual errors through the automatic generation based on database information. Yu's graph omits this information, but it is also simpler for this reason. The scientists affirmed that neuroMap improves their workflow by facilitating the process of visualizing connection candidates through the automatic generation of the graph and through its dynamic nature.

The scientists preferred the Simple View to gain an overview of potential connections since it shows arborization-arborization overlaps directly without splitting them up. They told us that the Complete View, with its locational information, is more suitable for the formation of actual hypotheses, since the region of an overlap can decide the direction of the information flow. This is particularly true if the neuron of interest overlaps with primary or secondary neurons, since their polarity is known.

Compared to the conventional layout algorithms that are available in neuroMap, the anatomical layout was uniformly considered the most intuitive, due to the assignment of neuropils to partitions that resemble the anatomy of the brain. For the scientists, this makes the neural circuit more meaningful than a graph without anatomical relevance. The scientists would have preferred anatomically correct positioning of cell bodies as well. Nevertheless, the necessary information is not available in the database yet. In the meantime, they consider the positioning of the cell bodies in the middle of the graph as a promising alternative, since they form a central point from which the flow of projection edges originates.

neuroMap has already been adapted by our collaborators, i.e., to make biased screenings where connection candidates are determined for or dismissed from further observations depending on their overlap with the inspected neuron.

**Exploration of the Neural Database**   The scientists stated that neuroMap's query feature complements the textual database queries and the spatial queries of the 3D view well, since the results are directly visualized in the graph as opposed to a textual list for the latter two, and overlap filters allow intuitive specification of thresholds in contrast to the textual query interface.

The highlighting of graph relations was well received because it facilitates orientation and exploration, especially in larger graphs. The highlighting of overlap edges generated the most interest, since it instantly shows the user all partitions of an overlap, as well as the involved arborization partitions. The discussions also revealed that the scientists were interested in additional ways to highlight neural patterns in the graph structure, e.g., to emphasize indirect connections between a pair of selected neurons.

The linked selection between neuroMap and the views of the data mining infrastructure was adopted seamlessly since our collaborators already used the feature efficiently to orient themselves within the different views during the second evaluation session.

**Presentation**   We learned that the conventional way of presenting scientific findings is with renderings of overlap volumes in combination with the segmented original images and hand drawn schematics. This is expensive but suitable in scenarios where just a handful of well-known neurons are discussed. Representations like Yu's drawing, on the other hand, are well suited for presenting larger groups of neurons that are not yet well researched, as the scientists explained. According to them, neuroMap is also especially suited for presenting findings in a circuit with a larger number of neurons, where it would be too expensive or infeasible to draw a circuit manually or to edit staining images of multiple arborizations.

The scientists saw visual simplicity as an important requirement for presenting theories or findings in meetings or publications. neuroMap encodes more information and is therefore more visually complex than Yu's graph. The Simple View was therefore considered favorable in presentation scenarios where the location of an overlap does not play an important role. When positions are important, the Complete View's neuropil merging and node closing were seen as good measures for increasing the visual simplicity.

The preferred layout for presentation purposes in the Complete View was the anatomical layout. However, our collaborators desired a look even more similar to the template of the brain in terms of partition placement and size. This would make the layout even more intuitive for untrained persons.

neuroMap is already actively used for presentation purposes in meetings and was announced to be used in future publications.

## 7.2  Scalability

A typical biased screening in neuroMap involves only a handful of arborizations. Yu's drawing displayed all neurons involved in the paper's study, which amounted to about 80. Nevertheless, a scenario where a user would want to look at all neurons in the database cannot be ruled out. To evaluate the scalability of neuroMap's graphs, a stress test with a graph containing all 213 arborization items that were available in the database at the time of writing was conducted. This resulted in a graph with 625 nodes and 3850 edges in the Complete View. The main concern in this scenario is that the circular layout of arborization partitions within neuropil nodes is so cluttered that overlap edges occlude each other to a degree that makes it hard to discern individual edges.

In our test case, the overlaps were distributed over neuropils in a way that it was still possible to make out and select all individual edges when zoomed in. Few neuropils overlap with so many arborizations simultaneously that edge occlusion was a problem. Nodes themselves are never occluded since they are drawn on top of edges. With increasing size of the database's content, however, overlap edge occlusion will pose a challenge that demands additional visualization methods, such as magic lenses for instance.

Nevertheless, neuroMap stays responsive for interactions like zooming and panning, highlighting, or neuropil node closing, even when dealing with large graphs.

## 8  CONCLUSION & OUTLOOK

In this paper, we presented neuroMap, a new approach to visualizing potential neuronal connections in the fruit fly's brain as an interactive circuit-style wiring diagram. neuroMap's creation was motivated by Yu's manually constructed wiring diagram [36]. The desirable aspects of this drawing are its two-dimensional abstraction of complex volumetric data that enables a clear overview and highlights features that would be lost in a three-dimensional representation. neuroMap's aim is to support hypothesis formation, data exploration, and rapid creation of graphs for presentation purposes by replicating the visual style and encoded information of Yu's drawing in an interactive visualization.

neuroMap was developed in collaboration with a group of neuroscientists. We evaluated the implemented visual and interaction features in qualitative discussions. The neuroscientists affirmed that the inclusion of neuroMap into their existing data mining and visualization infrastructure facilitates their research by giving them more precision in the exploration of overlaps and by facilitating the

workflow required for finding these overlaps. The discussions indicated that the stated goal of providing means for easier hypothesis formation was met.

Future efforts will go towards improving the visual style of the anatomical layout to make it more suitable for publication purposes, ensuring the scalability of the content of neuropil nodes, and exploring further highlighting options for graph structures. We plan to release a public standalone version of neuroMap in the future.

The high interest and enthusiasm towards neuroMap show that there is potential in its deployment. We are excited to see how not only our collaborators, but also the broader neuroscientific community can benefit from this novel way of looking at neuronal data.

**REFERENCES**

[1] M. Albrecht, A. Kerren, K. Klein, O. Kohlbacher, P. Mutzel, W. Paul, F. Schreiber, and M. Wybrow. On open problems in biological network visualization. In *Graph Drawing*, volume 5849, pages 256–267. Springer Berlin Heidelberg, 2010.

[2] J. Armstrong, K. Kaiser, A. Müller, K. Fischbach, N. Merchant, and N. Strausfeld. Flybrain, an On-Line Atlas and Database of the Drosophila Nervous System. *Neuron*, 15(1):17–20, 1995.

[3] C. Baker, M. Carpendale, P. Prusinkiewicz, and M. Surette. GeneVis: Visualization Tools for Genetic Regulatory Network Dynamics. In *Proceedings of the Conference on Visualization '02*, VIS '02, pages 243–250, Washington, DC, USA, 2002. IEEE Computer Society.

[4] A. Barsky, T. Munzner, J. Gardy, and R. Kincaid. Cerebral: Visualizing Multiple Experimental Conditions on a Graph with Biological Context. *IEEE Transactions on Visualization and Computer Graphics*, 14:1253–1260, 2008.

[5] N. Bhatla. An Interactive Visualization of the C. Elegans Neural Network . http://wormweb.org/neuralnet, June 2009. Accessed: 07/2012.

[6] J. E. Blankenship and B. Houck. *Nervous System (Invertebrate)*. McGraw-Hill's AccessScience, 2012.

[7] V. Braitenberg and A. Schüz. *Cortex: Statistics and Geometry of Neuronal Connectivity*, volume 249. Springer Berlin Heidelberg, 1998.

[8] A. Brand and N. Perrimon. Targeted Gene Expression as a Means of Altering Cell Fates and Generating Dominant Phenotypes. *Development*, 118(2):401–415, 1993.

[9] S. Bruckner, V. Solteszova, M. Gröller, J. Hladuvka, K. Bühler, J. Yu, and B. Dickson. Braingazer - visual queries for neurobiology research. *Visualization and Computer Graphics, IEEE Transactions on*, 15(6):1497 –1504, nov.-dec. 2009.

[10] S. Cachero, A. D. Ostrovsky, J. Y. Yu, B. J. Dickson, and G. S. Jefferis. Sexual dimorphism in the fly brain. *Current Biology*, 20(18):1589 – 1601, 2010.

[11] A. Chiang, C. Lin, C. Chuang, H. Chang, C. Hsieh, C. Yeh, C. Shih, J. Wu, G. Wang, and Y. Chen. Three-Dimensional Reconstruction of Brain-Wide Wiring Networks in Drosophila at Single-Cell Resolution. *Current Biology*, 21(1):1–11, 2011.

[12] S. Cook, C. Brittin, D. Hall, and S. Emmons. The Worm Wiring Project . http://www.wormwiring.org/, June 2012. Accessed: 07/2012.

[13] E. Demir, O. Babur, U. Dogrusoz, A. Gursoy, G. Nisanci, R. Cetin-Atalay, and M. Ozturk. Patika: An Integrated Visual Environment for Collaborative Construction and Analysis of Cellular Pathways. *Bioinformatics*, 18(7):996–1003, 2002.

[14] R. Diestel. *Graph Theory*. Springer Berlin Heidelberg, 2005.

[15] N. Gehlenborg, S. O'Donoghue, N. Baliga, A. Goesmann, M. Hibbs, H. Kitano, O. Kohlbacher, H. Neuweger, R. Schneider, D. Tenenbaum, and A. Gavin. Visualization of Omics Data for Systems Biology. *Nature methods*, 7(3 Suppl):56–68, Mar. 2010.

[16] Z. Hu, J. Hung, Y. Wang, Y. Chang, C. Huang, M. Huyck, and C. DeLisi. VisANT 3.5: Multi-Scale Network Visualization, Analysis and Inference Based on the Gene Ontology. *Nucleic Acids Research*, 37(suppl 2):W115–W121, 2009.

[17] A. Irimia, M. Chambers, C. Torgerson, and J. Van Horn. Circular Representation of Human Cortical Networks for Subject and Population-Level Connectomic Visualization. *NeuroImage*, 60:1340–1351, 2012.

[18] M. Ito, N. Masuda, K. Shinomiya, K. Endo, and K. Ito. Systematic Analysis of Neural Projections Reveals Clonal Composition of the Drosophila Brain. *Current Biology*, 23(8):644 –655, March 2013.

[19] R. Jianu, C. Demiralp, and D. Laidlaw. Exploring Brain Connectivity with Two-Dimensional Neural Maps. *IEEE Transactions on Visualization and Computer Graphics*, 18:978–987, 2012.

[20] K. Li, L. Guo, C. Faraco, H. Zhu, D. andChen, Y. Yuan, J. Lv, F. Deng, X. Jiang, T. Zhang, X. Hu, D. Zhang, and T. Miller, L.S.and Liu. Visual Analytics of Brain Networks. *NeuroImage*, 61(1):82–97, 2012.

[21] C. Lin, K. Tsai, S. Wang, C. Hsieh, H. Chang, and A. Chiang. The Neuron Navigator: Exploring the Information Pathway Through the Neural Maze. *Visualization Symposium, IEEE Pacific*, 0:35–42, 2011.

[22] N. Milyaev, D. Osumi-Sutherland, S. Reeve, N. Burton, R. Baldock, and J. Armstrong. The Virtual Fly Brain Browser and Query Interface. *Bioinformatics*, 28(3):411–415, 2012.

[23] B. Mlecnik, M. Scheideler, H. Hackl, J. Hartler, F. Sanchez-Cabo, and Z. Trajanoski. PathwayExplorer: Web Service for Visualizing High-Throughput Expression Data on Biological Pathways. *Nucleic Acids Research*, 33(suppl 2):W633–W637, 2005.

[24] T. Munzner. A Nested Model for Visualization Design and Validation. *IEEE Transactions on Visualization and Computer Graphics*, 15(6):921–928, nov.-dec. 2009.

[25] S. R. Olsen and R. I. Wilson. Cracking neural circuits in a tiny brain: new approaches for understanding the neural circuitry of drosophila. *Trends in Neurosciences*, 31(10):512 – 520, 2008.

[26] G. Pavlopoulos, A. Wegener, and R. Schneider. A Survey of Visualization Tools for Biological Network Analysis. *BioData Mining*, 1(1):1–12, 2008.

[27] T. Rohlfing and C. Maurer Jr. Nonrigid Image Registration in Shared-Memory Multiprocessor Environments with Application to Brains, Breasts, and Bees. *IEEE Transactions on Information Technology in Biomedicine*, 7(1):16–25, 2003.

[28] G. Shepherd, A. Stepanyants, I. Bureau, D. Chklovskii, and K. Svoboda. Geometric and Functional Organization of Cortical Circuits. *Nature neuroscience*, 8(6):782–790, 2005.

[29] J. H. Simpson. Mapping and manipulating neural circuits in the fly brain. In S. F. Goodwin, editor, *Genetic Dissection of Neural Circuits and Behavior*, volume 65 of *Advances in Genetics*, pages 79 – 143. Academic Press, 2009.

[30] M. Smoot, K. Ono, J. Ruscheinski, P. Wang, and T. Ideker. Cytoscape 2.8: New Features for Data Integration and Network Visualization. *Bioinformatics*, 27(3):431–432, 2011.

[31] D. Stalling, M. Westerhoff, and H. Hege. Amira: A Highly Interactive System for Visual Data Analysis. In *The Visualization Handbook*, pages 749–767. Elsevier, 2005.

[32] C. Von Mering, M. Huynen, D. Jaeggi, S. Schmidt, P. Bork, and B. Snel. String: a database of predicted functional associations between proteins. *Nucleic acids research*, 31(1):258–261, 2003.

[33] M. Ward, G. Grinstein, and D. Keim. *Interactive Data Visualization: Foundations, Techniques, and Applications*. A. K. Peters, Ltd., Natick, MA, USA, 2010.

[34] R. Wiese, M. Eiglsperger, and M. Kaufmann. yFiles - Visualization and Automatic Layout of Graphs. In *Graph Drawing Software*, pages 173–191. Springer Berlin Heidelberg, 2004.

[35] H. Yu, T. Awasaki, M. Schroeder, F. Long, J. Yang, Y. He, P. Ding, J. Kao, G. Wu, H. Peng, G. Myers, and T. Lee. Clonal Development and Organization of the Adult Drosophila Central Brain. *Current Biology*, 23(8):633 –643, March 2013.

[36] J. Yu, M. Kanai, E. Demir, G. Jefferis, and B. Dickson. Cellular Organization of the Neural Circuit that Drives Drosophila Courtship Behavior. *Current Biology*, 20(18):1602–1614, 2010.