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NeuroScheme: Efficient multiscale representations for the visual exploration of morphological data in the human brain neocortex

L. Pastor[1], S. Mata[† 1], P. Toharia[1], S. Bayona[1], J. P. Brito [1], J. J. Garcia-Cantero[1],

[1]Universidad Rey Juan Carlos, Spain

Abstract

The analysis of data sets from such a complex domain as neuroscience is severely hampered by the brain complexity and by the huge amount of data originated in current experiments and simulations. The complexity of the brain stems not only from the enormous number of relevant entities that integrate it (for example, around 10^{15} *synapses), but also from the complex interrelations among brain structures, which have to be analyzed at the many different organizational levels of the brain.*

Visualization techniques have proven to be valuable in order to explore and analyze complex systems from a wide variety of areas. Nevertheless, their application to the field of neuroscience must face some domain specific difficulties. In particular, the overwhelming amount of data poses a challenge to the current storage and processing capabilities, calling for compact data descriptions. Furthermore, the visual analysis of neural scenes requires the design of novel visual representations and techniques that help experts in their data exploration and interpretation activities, assisting them in fighting complexity.

In this paper we propose a visual exploratory framework that facilitates the process of knowledge extraction from complex neural scenes. This framework contains a multilevel structure, following the different organizational levels of the brain. Schematic or iconic symbols have been designed to portray the entities at each level, providing graphical representations that emphasize relevant features while hiding less important information. These schematic views, together with a multilevel organization, allow the exploration of the brain at different scales, combining in the same view different levels of abstraction whose entities can be either schematically represented (at different abstraction levels) or geometrically depicted at the finest level of detail. The fact that users can choose high geometric detail for just a fraction of brain structures results in a dramatic reduction of visual clutter, decreasing the difficulty of the visual exploration and interpretation task. The complexity due to sheer data size can be also reduced by generating the visual representations on the fly from compact data representations.

This work presents a first implementation of this framework, focused on the representation of the morphological aspects of the brain cortex. The underlying multilevel structure and the design of the graphical schematic representations constitute an approach that provides organized and uncluttered views that facilitate visual analysis, a task much more difficult (even unapproachable) if all brain structures were depicted at full geometric detail.

Categories and Subject Descriptors (according to ACM CCS): I.3.3 [Computer Graphics]: una categoria—otra categoria

1. Introduction

Understanding the human brain is currently one of the greatest scientific challenges. Despite the important advances of the last decades on specific aspects of neuroscience, there is still a lack of understanding of the brain functioning as a unified system that spans multiple levels of organization (such as genes, proteins, synapses, cells, microcircuits or brain regions). The overwhelming complexity of the brain comes

† susana.mata@urjc.es

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from the combination of a set of factors that increases the difficulty to gain insight into the neural system.

The amount of data to be analyzed is intrinsically huge (around 10^{11} neurons and 10^{15} synapses in the human brain [OGR05]. The experimental data gathered is currently growing at exponential rates: The availability of powerful microscopes using technologies such as the FIB-SEM CrossBeam workstations [CG09], makes it possible to gather in a few hours what previously required months of work. In addition to these technological advances, the support provided by ambitious research programs such as the Blue Brain [Mar06], the BRAIN initiative [Wol13] or the Human Brain Project HBP [McA12] is boosting the research activity of different teams from different disciplines.

The human brain can be seen as a complex processing system structured into **different organizational levels** that are studied at **very different scales**. This approach has provided a good knowledge of the individual levels but there is still a lack of understanding about the interactions and causal chain of events among the different levels of the hierarchy to achieve cognitive and behavioral processes.

Neuroscience addresses the study of the brain not only at different scales, but also from **different sub-domains** (morphology, electrophysiology, etc.). In consequence, the amount of variables under study and their different nature makes it unaffordable to analyze them all at a time. In fact, neuroscience itself can be seen as a set of sub-disciplines, each of them focusing on different scales, different entities and different sub-domains.

The extreme complexity of the human brain poses a challenge that requires the collaborative effort of multidisciplinary teams that integrate knowledge from a wide variety of fields. In this sense, information technologies provide valuable solutions for the storage, transmission and processing of vast amounts of data. However, the final interpretation and knowledge extraction must be done by human experts; therefore there is a need for innovative techniques that allow presenting the information of such a complex system in a way that facilitates its analysis and interpretation by human users.

This work presents a framework for the visual exploration of neuroscience data, tightly coupled to the brain organizational levels, which uses also novel schematic visual representations that increase the interpretability of the data. Specifically, this framework presents the following features:

- **Domain-driven organization of the data** that allows identifying different levels of abstraction and the entities belonging to each of these levels. Each entity will be described by a set of properties that will be structured according to their relevance and nature. Higher levels of abstraction encapsulate the details of lower levels, providing this way a visual reduction on the number of elements and in the number of variables to be observed.
- **User-centered graphical representations** of the entities, focused on emphasizing the most relevant features at each level of abstraction, while fading out the less important details. Consequently, the user can toggle between geometrical representations of the entities or schematic representations that will not necessarily resemble their real shape, but will provide a schematic view that helps in the understanding of the system.
- **Relation-driven navigation**. The domain is not only composed of entities, but also of relations among them. These relations could be graphically presented but they can also be used to drive the navigation, allowing the exploration of the system in an organized way.
- **Multi-scale presentation of the data**. This framework allows combining different levels of abstraction in the same view, allowing the user to choose the degree of detail to be presented and to observe the system at different scales simultaneously.
- **User-driven exploration of the data**, letting the user decide the level of abstraction at which each data set will be presented. Additionally, the user can establish filtering criteria and sorting operations to refine which elements will be displayed, combining also schematic representations with other standard realistic depictions of the data.

This framework addresses the main factors responsible for the extremely high complexity of the brain and proposes a visual approach to help in the exploration and understanding of our neural system. A preliminary implementation of NeuroScheme is also presented, focused on the morphological aspects of the brain cortex.

2. Related Work

Visualization is the process of using computer graphics to transform numerical data into meaningful imagery that should be driven by the underlying scientific applications [GLJ*10], [MM15]. Visualization techniques can facilitate the human cognitive processing, since it is more efficient to spot relevant elements or to detect patterns from graphical representations than when the information is presented using numerical or tabular representations [Chi01], [TM04]. Cockburn et al. in [CKB09] present a complete state of the art of interactive visualization through interfaces in which it is possible to have an overview and also detailed views, to zoom, and to use focus+context techniques. They affirm "The question then becomes which style of interface, or which combination of styles, offers the greatest performance advantages, for what tasks, and under what conditions? The current state of research fails to provide clear guidelines, despite a recent surge in empirical analysis of the techniques' effectiveness. Results to date have revealed that the efficiency of different techniques is dependent on many factors, particularly the nature of the users' task" [CKB09].

In the domain of neuron morphology, there are a variety of tasks for which software tools provide help. For instance, for segmentation and tracing there are tools such as Imaris [ima] or Neurolucida [GG90]. For reconstruction, visualization or simulation, NeuroConstruct [GSS07], Neuronize [BMB*13], or RTNeuron [HSMdM08] can be cited. However, most of these tools are based on graphical representations, depicting the complex geometrical shape of the neurons.

As mentioned, symbolic or abstract representations can be useful for representing complex data. Abstract representations have been applied to neural circuits and electrical models [DA92], [BB95], [GS96], [PC98], [KKRA07] or [Reb10]. Nonetheless, in the majority of cases, these representations do not include morphological information, or only in a very simplified manner.

In different domains iconic-based visualization techniques have been applied to relate each multidimensional data item to a graphic icon or a glyph. Glyphs are graphical entities that convey one or more data values via attributes such as shape, size, color, and position [War02]. The glyphs features will vary depending on the data variable values [dOL03]. Borgo et al. in [BKC*13] explain the foundations and review different techniques and applications of glyphs. One of the main advantages of glyphs is that in glyphs, some features are more salient than others [dOL03], allowing to highlight some variables over others.

The problem is that traditional multivariate visualization techniques typically do not scale well to large multivariate datasets. Hierarchical Visualization Techniques, such as dimensional stacking [LWW90], worlds-within-worlds [FB90], tree-maps [Shn09], [JS91] or cone trees [RMC91] base the visualization of the data on a hierarchical partitioning into subspaces. Yang et al. in [YPWR03] proposed hierarchical variations of traditional multivariate visualization techniques. A novel feature of the work presented here is the hierarchy proposed is based on the data's own, inherent levels of abstraction, having the particularity that apart from being possible to navigate through the different levels in the hierarchy, these levels are related and the user can easily explore those relationships within the interactive visualization process

Last, this paper presents the design of a number of glyphs that are well adapted to the task of representing neuron morphological data, given the evidences that their semantic relation to the task has significant impact on their perceptive effectiveness [Spe01].

3. Framework description

As previously stated, the proposed visualization approach relies on the structural organization of the domain to be represented. Therefore, the first stage of the system design is devoted to the understanding of the neural system structure, in order to identify the set of relevant entities and the relations among them. It is needless to remark the extreme complexity of the neural system and the fact that there are still many unsolved questions that give place to different hypothesis that remain neither rejected nor completely proved.

The two main approaches in the structural organization of the brain cortex are the so called "horizontal organization" and the "vertical organization" [ADPJ04]. The horizontal pattern of organization refers to the arrangement in layers parallel to the cortical surface (6 layers), while the vertical pattern describes clusters of cells grouped perpendicularly to the cortex surface, running across multiple layers. Those arrangements are called columns and have been considered to be the minimal processing unit in the brain cortex. Each column is composed by a number of microcolumns (around 100 microcolumns per column) that are considered to be the basic operational unit of the brain. Each microcolumn (also called minicolumn) contains a variable number of cells (between 80 and 100) of different types and in different proportions, depending on the region where they are located. In general terms, the brain cortex is formed by a numerous population of principal neurons (pyramidal cells) and a lower number of inhibitory neurons (interneurons) that connect to each other by means of synapses. Interneurons can be further classified into different sub-types, according to their axon morphology. Besides neurons, there are also other types of cells such as glia cells, but neurons are regarded as the most relevant elements of our cognitive abilities, from the functional point of view.

The anatomy of the brain and its components is essential for understanding its functional behavior [GSS07]. The basic morphology of a neuron consists of three main parts: The soma (that contains the cell nucleus), the axon (a cable-like projection from the soma which propagates signals to other cells) and the dendrites (prolongations from the soma that receive signals from other neurons). Axon and dendrites are also referred to as neurites and present a branching pattern that allows them to extend across space. Pyramidal neurons present a so called apical dendrite, that emerges from the apex of the soma. The rest of the dendrites in pyramidal cells are known as basal dendrites and are similar to those in interneurons [She04].

This brief and simplified description of the brain anatomy leads to the definition of a set of entities that will give place to the hierarchy of abstraction levels in our visual framework. Specifically, the following ones, from the highest to the lowest, have been defined: Column, microcolumn, neuron, neurite and branch. Each abstraction level is composed of entities of the lower abstraction level. There are many morphological properties that can be studied for these elements, but as a first approach, a subset of the most relevant ones were chosen to be represented in the schematic views: Element volume and area, and the number of relevant features for that element, such as branches, dendrites or neurons, depending on the element and scale under consideration. For the representations, each of these entities is given an iconic representation in Neuroscheme that will denote each relevant property by means of a graphical resource. The following section gives a detailed explanation of the graphical representations proposed here.

Regarding relations among entities, since this work is focused on anatomical morphology and structure, the basic one is the "is composed of" relation. This relation will be used to drive the navigation through the different levels of abstraction, allowing expanding an entity into all its components of lower level of abstraction, or collapsing a set of entities into a higher level one. This change of level of abstraction can be selectively performed, making it possible the combination of multiple scales into the same view. The incorporation of filtering, sorting and interaction capabilities will enrich the navigation, providing useful resources for the visual exploration of the system.

4. NeuroScheme

This section describes the glyphs designed for each of the abstraction levels identified in the previous section. The schematic depictions are intended to be easy to interpret and to represent the main morphological features of the entities at a glance.

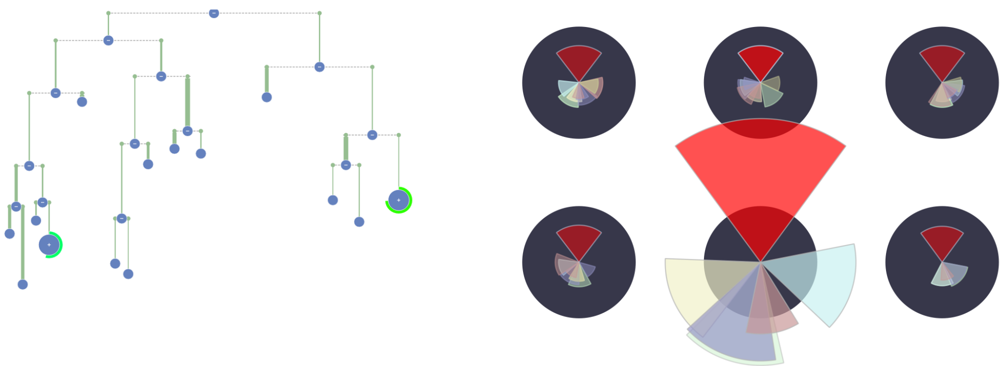
The lower level of abstraction represents the **branch entity**. In this level, all the dendritic arbors in a tree are displayed in detail, so that the branching structure and the bifurcations can be directly observed. This tree can be interactively compressed or expanded under user control (see figure 1(a)). When a node is compressed, its representation depicts information summarizing its hidden branches.

The second level corresponds to the **neurite entity**, and represents morphological variables for each dendrite or axon. Neurites belonging to a neuron are enclosed in a blue circle, in which each different colored sector represents a different neuritic arbor. The radius of the sector represents the volume covered by the dendritic or axonal arbor, whereas the sector angle corresponds to the area of that arbor. This icon allows to be interactively expanded for a zoomed-in view (see figure 1(b). In cases where an apical dendritic arbor exists, it will be colored in red. The rest of the arbors are differently colored to facilitate the visual discrimination between them.

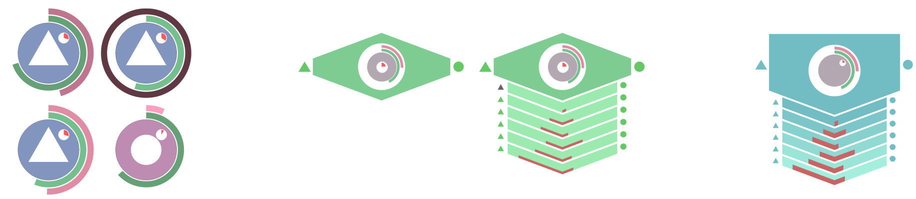
The third level of abstraction depicts the **neuron entity** (see figure 1(c)). The type of neuron is presented by means of colors and shapes. Pyramidal neurons are drawn as a blue circle with a triangular shape inside it. Interneurons are drawn as a purple circle with a circular shape inside it. In future versions of Neuroscheme, the shape can be used to represent the different subtypes of interneurons, while the color will still provide information about the general type of neuron.On the right upper side, a smaller white circle containing a red sector represents the number of bifurcations: A wider red sector denotes a higher number of dendritic bifurcations. Then, around the main circle containing the type of the neuron, there are two arcs. The inner arc (the one closer to the circle) corresponds to information related to the soma. The green color represents the volume of the soma; the darker the green, the more volume the soma has. The length of this closer arc represents the soma area. The longer the arc, the more area the soma surface has. The second arc corresponds to dendritic information. The pink color corresponds to the volume of the dendrites. The darker the pink color (tending to purple color), the highest the volume. The length of the outer arc represents the dendritic length. The longer this arc, the greater dendritic length.

The **microcolumn entity** representation consists of green rhomboidal shapes, in which a circle represents the average neuron of those conforming that microcolumn (see figure 1(d)). This circle is surrounded by two arcs. Just like for the neuron level, the inner arc corresponds to (average) information from the soma, whereas the outer arc represents dendritic information. This microcolumn level can additionally be expanded, showing information of the different layers in the microcolumn. When expanded, six new arrow-like shapes (one per layer) appear. The upper green arrow corresponds to the first layer, whereas the bottom green one corresponds to the sixth layer. Each arrow contains information of the number of cells; the number of pyramidal cells in a particular layer are represented by a red line on the left side of the arrow corresponding to that layer. The longer this red line, the greater number of cells. Analogously, the red line on the right side of each layer arrow represents the number of interneuron cells in that layer. Next to the green shape representing the microcolumn or each arrow representing a layer (when this microcolumn representation is expanded), there is a triangle that can be selected so that only the information corresponding to the pyramidal cells is displayed; and a green circle, which if selected, makes that only interneuron information is presented

The highest level of abstraction supported so far corresponds to the **column entity** (see figure 1(e) and is represented by a blue pentagonal shape, containing also a circle. In a similar way as in the microcolumn level, this circle depicts information of the average neuron of the column (the soma and dendritic information). Again, the column can be expanded, so that the information can be seen separated into the six different layers (each layer represented with a blue arrow). The length of the red line on the left of each layer arrow, corresponds to the number of pyramidal cells contained in that column layer, whereas the length of the red line on the right corresponds to the number of interneuron cells. As it happened into the microcolumn level, next to the blue shape representing the microcolumn, and to each blue arrow representing a layer (when this column representation is expanded), there is a blue triangle that can be selected so that only the information corresponding to the pyramidal cells is displayed, and a blue circle which, when selected, makes

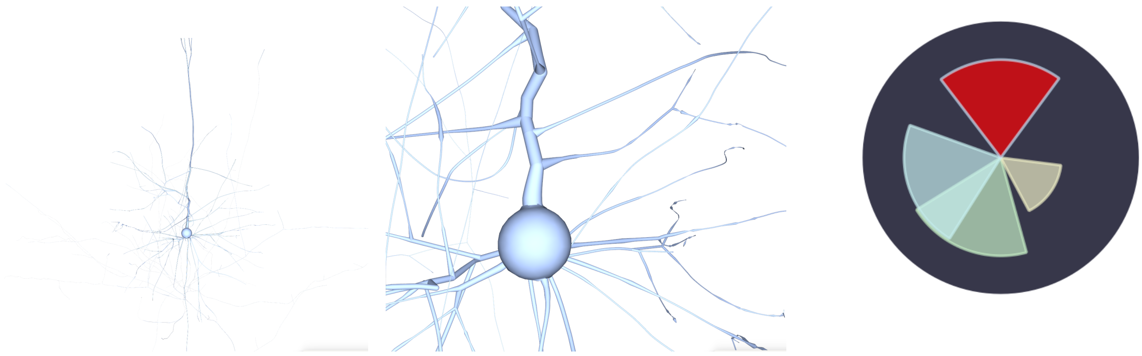


(a) Branch entity with collapsed sub-branches (b) Neurite entity with an example of an expanded tree



(c) Neuron entity (d) Microcolumn entity (e) Column entity

Figure 1: *Different icons and abstraction levels used in NeuroScheme.*



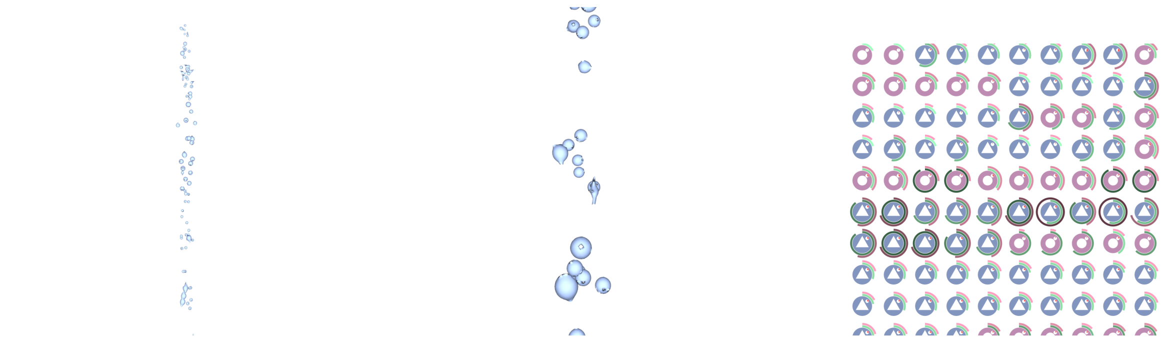
(a) Realistic representation: far view (b) Realistic representation: closeup view (c) Abstract representation

Figure 2: *Neuron geometrically represented and its schematic depiction at neurite level of abstraction*

that only the information corresponding to interneurons is depicted.

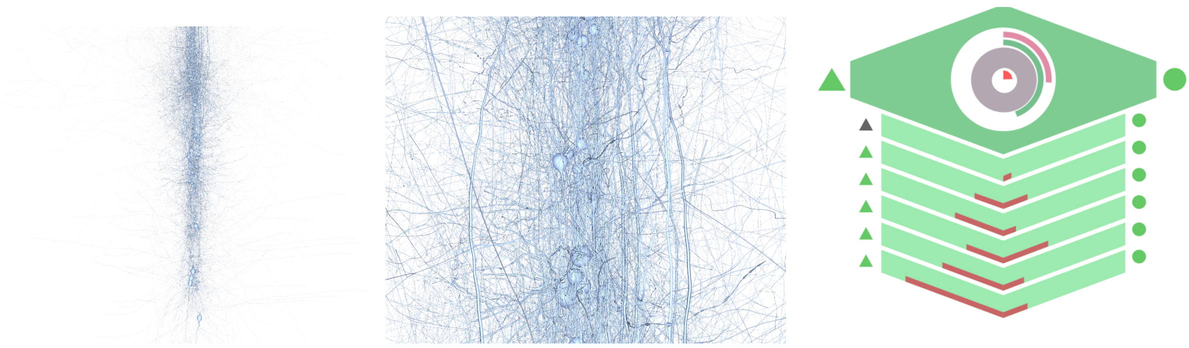
The framework also allows to display some elements at one abstraction level and others at a different abstraction level. For instance, we can display some neurons of interest at the second level and the rest of the neurons at the third level.

By means of the relation "is composed of", Neuroscheme keeps track of the hierarchical organization of the abstraction levels, allowing the user to expand higher level entities into the lower level ones and collapsing lower level entities into higher level ones. This can be selectively performed, making it possible to select a neuron of a column and keep it at its branching level while the rest of the neurons of the column are collapsed into a higher level of abstraction. Selection at higher levels of abstraction implies the selection of all their lower level entities; this way, selection of a layer in



(a) Realistic depiction of somas: far view (b) Realistic depiction of somas: closeup view (c) Abstract representation

Figure 3: *Realistic and abstract depictions of a set of neurons*



(a) Realistic representation: far view (b) Realistic representation: closeup view (c) Abstract representation

Figure 4: *Visualization of a microcolumn*

a microcolumn will select all the neurons belonging to that layer.

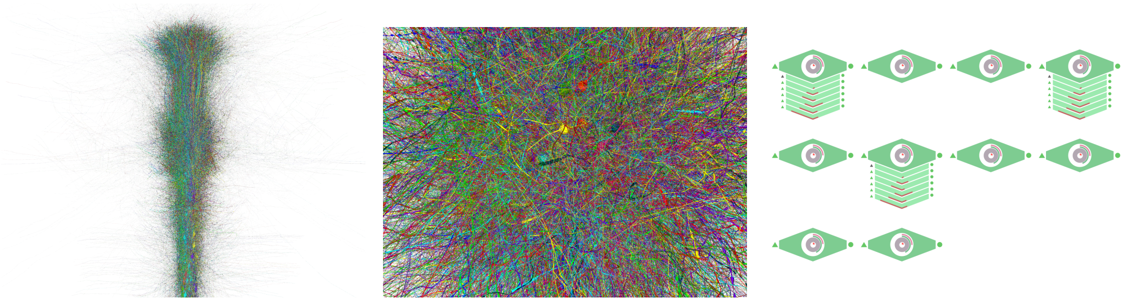
Also, selection of elements is allowed at all times in the visualization, allowing to apply filters and hide the information less relevant at a particular moment.

The position and the order of the graphical representations can also be parameterized. This way, for example, neurons can be represented in their original positions, or ordered into a grid according to a particular criterion in order to make visual analysis or comparisons.

5. Results

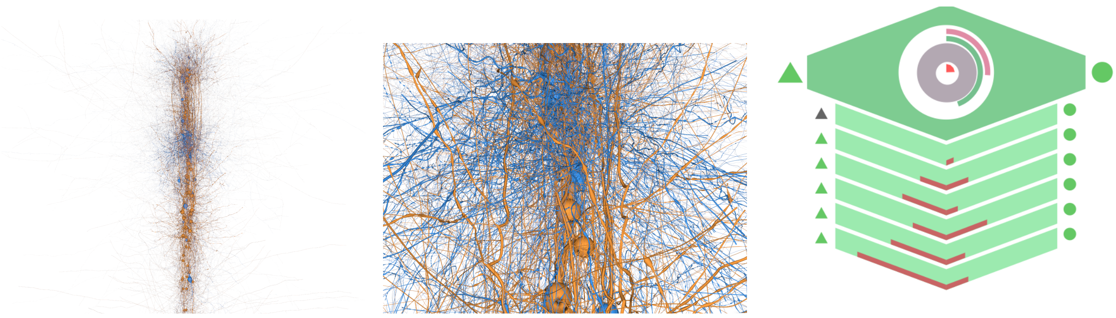
This section shows some examples that illustrate the utility of the proposed framework. The data used in these examples comes from the Blue Brain Project [Mar06] and represents a synthetic microcircuit from the cortex area of the brain. This microcircuit has one column which is composed of 10 minicolumns and each minicolumn is composed of 100 neurons. Since the data has been synthetically generated, there are only 50 different morphologies that appear replicated in different positions and orientations. The geometrical depictions of neurons rely on the generation of polygonal meshes that approximate their geometry. The optimization of the mesh generation in order to achieve interactive rates is an ongoing work, but this does not interfere with the main goal of this framework that if focused on increasing the interpretability of the neural scenes. The schematic representation has been generated with Neuroscheme, following the designs previously discussed. All demos presented below have been run on an Intel i7 4820K processor at 3.7GHz with 16GB DDR3 RAM and an nVIDIA 770 GTX with 2GB of memory.

Figure 2 shows an example of a neuron represented at the *neurite* level of abstraction. It can be appreciated that the neuron has an apical dendritic arbor (represented with the upper red sector) and basal dendritic arbors. As the blue sector has a greater radius and angle that the beige sector, in a glimpse we know that its dendritic arbor has greater volume and area. Using the geometric representation (see figures 2(a), 2(b)) it is far more difficult to distinguish between the different dendritic arbors and hence, to appreciate that difference both in volume and area.



(a) Realistic representation: far view (b) Realistic representation: closeup view (c) Abstract representation

Figure 5: *Microcolumns in a column*



(a) Realistic representation: far view (b) Realistic representation: closeup view (c) Abstract representation

Figure 6: *Depiction of a microcolumn with the purpose of comparing the number of pyramidal neurons versus the number of interneurons*

Figure 3 corresponds to the *neuron* entity; in particular, we can observe the somas of the neurons composing a column. We will pay attention to the information related to the somas, reflected in the inner arc surrounding the big circle. The darker green color indicates that the soma volume of the highlighted neuron is greater than that of the neuron just below it. The length of the inner arc shows that the highlighted neuron also has a greater soma area. This fact is more difficult to appreciate with the geometrical representation.

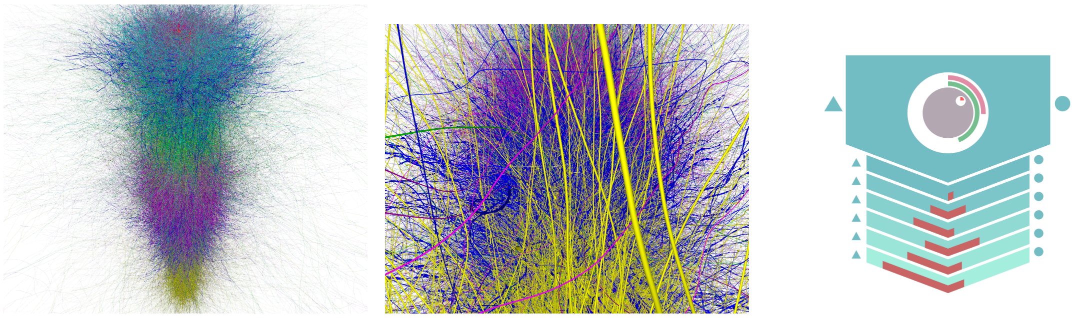
In figures 4(a) and 4(b) there is a plausible representation of a microcolumn. In figure 4(c), the same microcolumn is displayed at the neuron entity abstraction level. With the abstract representation, we quickly observe that some neurons seem to be replicated.

Figure 5(c) shows the different microcolumns in a column. In the geometric view (see figures 5(a) and 5(a)) each microcolumn has been rendered with a different color. Since the scene is complex, the visual exploration does not provide any outstanding information. However, the same scenario represented with Neuroscheme makes it evident that all the microcolumns of that column have exactly the same average neuron so they could even be composed by the same neurons.

A common task consists in counting the number of neurons present in a microcolumn. In the geometric representation (see figures 6(a) and 6(b)), even if pyramidal cells have been rendered in orange color and interneurons have been rendered in blue color, it is difficult to appreciate the difference between the number of pyramidal cells and the number of interneurons and to see how those numbers vary in the different layers. In the microcolumn abstract extended representation (see figure 6(c)), we can easily compare the number of pyramidal cells (the red line on the left side) with the number of interneurons (the red line on the right side) for each layer.

Figure 7(a) shows a column in which the neurons have been geometrically rendered applying a different color for each layer. We observe the whole column and in 7(b) a closeup view. Although the layer delimitation is clear, with this geometric representation it is still difficult to know, which layer (layer 5 or layer 6) has a greater number of cells. When taking a look to the extended abstract representation of the column entity (see figure 7(c), we can easily observe that the number of cells is smaller in layer 5 than in layer 6.

These few examples illustrate the potentiality of the proposed framework, presenting some situations in which the



(a) Realistic representation: far view (b) Realistic representation: closeup view (c) Abstract representation

Figure 7: *Depiction of a column with the purpose of comparing the number of neurons in the different layers*

use of Neuroscheme facilitates a first visual analysis of neural data. The different abstract representation levels facilitate spotting similarities and dissimilarities and help to provide an interactive exploration of the data.

6. Conclusions and future work

This paper has presented a general framework for the visual exploration of the nervous system, where the presence of the concept of abstraction is twofold. Firstly, the formalization of the application domain allows structuring the data into a set of levels composed of entities and relations among them. Higher level entities can be seen as "black boxes" with respect to lower level ones, providing encapsulation capabilities and preventing the system from displaying distracting lower level details when not needed. Secondly, the visualization based on schematic or iconic symbols, behaves itself as a visual abstraction means, where the most relevant features are metaphorically depicted, decoupled from the real appearance of the objects.

The multiscale nature of the neural system has been approached through the combination of different abstraction levels into the same view. The fact that entities at the whole range of scales can be visualized in the same image, together with the possibility of selecting between their schematic or geometrical depictions, provide a focus+context environment where the user can explore certain regions of the scene at the finest detail while keeping a general overview of the rest of the system. The additional filtering and sorting capabilities permit a user guided exploration of the brain where the organized and decluttered views increase the interpretability of dense neuronal scenes.

Computational complexity derived from the huge amount of data and the intricate geometry of the neurons is also addressed through the possibility of generating their visual representations on the fly, from compact descriptions of the cells that avoid the need of storing heavy geometrical descriptions based on common graphical models such as polygonal meshes.

Neuroscheme presents itself as a first prototype that illustrates the potential of the presented framework, oriented towards the visualization of morphological features of the brain cortex. The preliminary presented results show the advantages of the schematic multilevel visualization versus the geometrical depiction of the data, making Neuroscheme a promising tool that deserves further development.

Regarding future work, the extension of Neuroscheme to a wider range of abstraction levels and to other subdomains, besides the morphological one, is a straightforward path. The generalization of our framework to other complex systems from other domains different from neuroscience, presents itself as a challenging work that deserves to be explored. In this sense, the formalization of these domains plays a crucial role in the identification of entities and their structural organization, opening the way to address the visualization of unstructured domains where the definition of levels of abstraction is not obvious.

A rigorous validation study to evaluate the effectiveness of the presented visualization framework will allow a quantification of the improvement in terms of visual interpretability of the scenes. Improvements in the computational performance can also be achieved through the efficient implementation of the on the fly generation of the visual models, either schematic or geometrical.

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