Neurocomputing 438 (2021) 323–333

Contents lists available at ScienceDirect

Neurocomputing

journal homepage: www.elsevier.com/locate/neucom

Towards computational analytics of 3D neuron images using deep adversarial learning

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ARTICLE INFO

Article history:
Received 2 December 2019
Revised 21 February 2020
Accepted 7 March 2020
Available online 23 January 2021

Keywords:
Computational neuroscience
3D neuron image
Neuronal morphology
Generative adversarial networks
Large-scale retrieval

ABSTRACT

Benefited from advances of neuron tracing techniques, the ever-increasing number of digitally reconstructed 3D neuron images have greatly facilitated the research in neuromorphology. However, the sheer volume and the complexity of these 3D neuron data pose significant challenges for computational analytics, e.g., effectively finding neurons sharing similar morphologies, identifying neuron types, correlating neuron morphologies with properties, all of which require accurate measuring and fast indexing methods especially designed for the massive 3D neuronal images. In this paper, we present an accurate and efficient framework for the computational analytics of 3D neuronal structures based on advances of deep learning and data mining techniques. Particularly, unlike previous methods quantitatively describe neurons by measuring pre-defined metrics according to the tree-topological structures, we first develop a new method for the morphological feature representation by a proposed 3D neuron mapping and a modified generative adversarial networks (GANs). Subsequently, considering the computational complexity when retrieving large-scale neuron datasets, we integrate the neuron features with graph-based indexing, which can significantly improve the retrieval efficiency without losing accuracy. Experimental results show that our framework can effectively measure the similarity among massive neurons (e.g., 100,000 neurons), outperforming state-of-the-arts with more than 10% in accuracy and hundreds of times in efficiency improvements.

1. Introduction

Investigating neuronal morphology is an important topic in neuroscience and clinical diagnosis, since morphology plays a critical role in neuronal type identification, network connectivity, and thus functional property. Recent frontiers in microscopy imaging and neuron tracing have significantly improved the research of neuronal morphology [16], e.g., BigNeuron [30] and NeuroMorpho.Org projects [2], resulting in an increasing number of neuron images which are digitally reconstructed from soma to dendrite with fine-grained 3D structures. These large-scale datasets provide new opportunities for the analytics of neuronal morphology. For example, indexing neurons sharing similar morphologies, grouping neurons into biomedical meaningful clusters, exploring the relation between morphologies and functional properties with respect to their cell types, etc, all of these require computational modeling and mining of 3D neurons in currently large-scale datasets. Accordingly, the key step and the major challenge is the feature representation of 3D neuronal images, i.e., how to quantitatively represent and discriminate structures for various types of neurons.

In recent years, multiple methods and tools have been proposed for the neuronal feature representation. Especially, due to the tree-like characteristics of neurons, most efforts focused on computing neuroanatomical measurements of pre-defined metrics according to the tree structures, such as neuron's total length and width, soma surface, the angel of two compartments, and the order of the branch with respect to soma, etc. These pre-defined metrics are treated as the most representative measures for neuron morphology developed by domain experts. In addition to these specifically designed measurements, several works employed theories and methods in topology and geometry, to extract general features from the tree-structure, e.g., moments invariant [25], persistent homology [7], sholl analysis [21], etc. Moreover, for more accurate comparison of two or more neuronal structures, several works decomposed neurons into segments and then designed features

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https://doi.org/10.1016/j.neucom.2020.03.129
0925-2312/

using morphological statistics [3,13]. All these pre-defined measurements (i.e., "hand-crafted" features) have been achieved many successes in solving multiple challenges of neuron morphology analysis for certain species, brain regions, or cell types.

However, with the continuously expanding of digitally reconstructed neuron data, new challenges need to be considered when tackling the feature representation and indexing for large-scale neuron datasets. Firstly, massive 3D neurons can significantly increase the varieties of neuronal structures and categories of neuronal types, which makes neurons more difficult to differentiate, e.g., the difference of neurons belonging to different categories can be subtle (indicated small inter-class variances), while the difference of neurons belonging to same categories can be remarkable (indicated large intra-class variances). Traditional "hand-crafted" features cannot well consider and differentiate large-scale newly reconstructed neurons by pre-defined measurements. Secondly, the computational efficiency is another challenge when tackling large-scale neuron datasets. Current neuron datasets can include hundreds of thousands of neurons, e.g., the NeuroMorpho.Org dataset [29] already includes more than $100,000$ reconstructed neurons which is still fast growing. For the neuronal retrieval and clustering tasks, if every time we find similar neurons by exhaustive computing and searching in the whole database with hundreds to thousands dimensions of feature vectors, the whole process would be very time-consuming. Therefore, accurate and efficient methods should be developed for the representation and indexing of currently large-scale 3D neuron data. Additionally, as illustrated in Fig. 1, the specific structures of 3D neurons, i.e., complex tree topologies in 3D space, makes them even harder for unified modeling, in comparison with regular 2D images and 3D point sets.

In this paper, we develop a novel framework for effective feature representation and retrieval of 3D neuronal images by investigating recent advances in deep learning and computer vision, especially for recently fast-growing large-scale neuron datasets. Unlike previous methods that extract neuronal features based on the pre-defined measurements, our framework learns deep features through the proposed 3D neuronal mapping method with a modified Generative Adversarial Networks (GANs) [17], which is able to learn effective features for the representation of 3D neuron images. Particularly, the 3D neuronal mapping can transform 3D neurons into 2D images for convenient network training, as well as preserving spatial structures and tree-topologies. For the first time, the 3D neuron mapping utilizes all the information provided in the original SWC formatted files, including point coordinates, connections, radius, and structure identifiers, to preserve the spatial tree-topologies. The mapped 2D images are subsequently set as input for the training of GANs. Based on the newly designed features of neuron morphology, we further apply the features for the task of neuronal retrieval, to index and analyze neurons sharing similar morphologies. Considering the computational efficiency when comparing the neuronal similarity with high-dimensional features among large-scale datasets, we integrate the neuronal features with a graph-based indexing strategy, i.e., Hierarchical Navigable Small World graphs (HNSW) [26], for efficient retrieval with massive neuron data without losing accuracy. The proposed framework is evaluated in the tasks of feature representation and retrieval using NeuroMorpho with more than 99,000 neurons, which is currently the largest neuron dataset worldwide. In comparison with most recent advances in computational neuron morphology, the proposed framework can significantly improve both accuracy and efficiency for the feature representation and retrieval in large-scale 3D neuron dataset.

The remaining of this paper is organized as follows: Section 2 briefly introduces the backgrounds and related works of computational neuromorphology and deep feature representation. Section 3 provides technical details of 3D neuron mapping, feature learning, and efficient indexing. Followed experimental results and discussions in Section 4. Finally, Section 5 concludes this paper and discuss future works.

2. Related work

In this paper, we develop a computational method for the analytics of 3D neurons based on advances of deep learning and computer vision. Here, we first introduce technical backgrounds of unsupervised feature learning, then review related methods and tools for the analytics of neuronal morphology.

2.1. Unsupervised feature learning

Feature representation is one of the most fundamental tasks in machine learning and pattern recognition, which focuses on the learning of representations from the dataset that somehow makes it easier to extract useful information for varieties of analytical tasks, e.g., image classification, retrieval, recognition [4]. In most practical problems, it is labor intensive, expensive, and even impossible to access annotations for each image sample. To this end, unsupervised feature learning methods have been widely investigated which explore and learn representations from the data itself without corresponding labels. Autoencoder is one of the most popular deep models for unsupervised feature learning, which can encode the input into feature representation so that the input can be reconstructed from the representation [5]. Subsequently, many variants of autoencoder models have been proposed for more accurate and robust feature learning, e.g., denoising autoencoder [38], sparse autoencoder [40], and variational autoencoder [32]. In addition to these autoencoder based models, restrict Boltzmann machines (RBM) [1] and its variants, e.g., deep belief networks [18] and deep Boltzmann machines [35], are also popular methods for unsupervised deep feature learning.

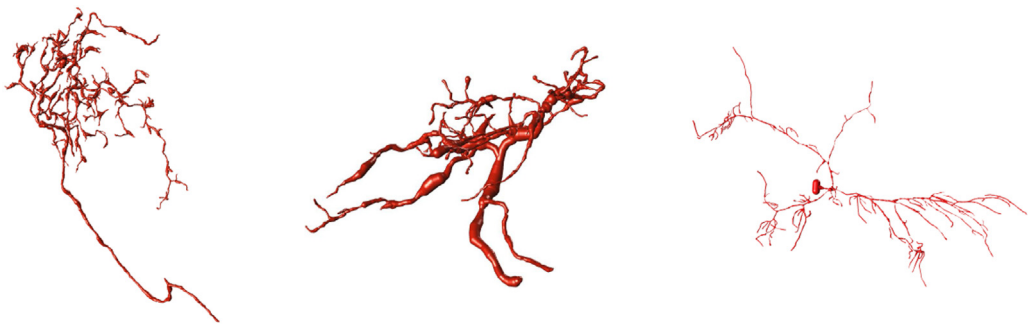

Fig. 1. Illustrating of some 3D neurons, showing complex spatial structures, which are quite different with traditional 2D images and 3D point sets.

More recently, Generative Adversarial Networks (GANs) [17] and its variants demonstrate excellent performance for image generation as well as unsupervised feature representation. Generally, GANs consist of two distinct networks, i.e., generator and discriminator, which learns to capture the data distribution and discriminate images generated from the generator and those from the training data respectively. Especially, among the variants of GANs, DCGANs [34], InfoGAN [8], and BiGANs [14] are the most widely used models for the feature learning of general image modalities. However, due to the specific 3D structures and the tree-like topologies, few methods focus on the unsupervised feature learning of 3D neuron morphological data so far.

2.2. Neuronal morphology

Due to the strong relevance between morphologies and functional properties (e.g., cell classes, development stages), neuronal morphology is a long-time and critical research topic in neuroscience. Especially in recent years, with the rapidly developing techniques of microscopy imaging and neuron tracing, neuronal morphology can be quantitatively explored from dendrite to axon in high precision. Currently, based on the well-reconstructed 3D neuron images, the research of neuronal morphology mainly focuses on two areas: (1) the quantitative representation of 3D neuronal structures, and (2) group analytics and exploration (e.g., retrieval, clustering) with numerous of neuron data. We briefly review related works in these two areas.

2.2.1. **Quantitative representation:** to quantitatively measure the morphology of 3D neuron data, multiple works have been proposed based on the computational modeling of tree-topological structures in recent years. Scorcioni et al. [37] first developed a freely available software tool for the quantitative characterization of neuronal morphology, namely *L-Measure*, which can compute tens of neuroanatomical parameters from 3D neuron data by predefined metrics. Costa et al. [12] proposed the concept of neuromorphological space as the multidimensional space defined by a set of morphological measurements for the representative set of almost 6,000 biological neurons. Subsequently, Langhammer et al. [21] employed sholl analysis to automatically explore the digitized neuronal morphology in both whole cell and arbor subregions. More recently, Li et al. [22] developed new computational metrics for comparing neuronal tree shapes based on the concept of topological persistence, which can vectorize each neuron structure into a simple yet informative summary. Kanari et al. [19] invented the Topological Morphological Descriptor (TMD) to encode the spatial structure of any tree as a "barcode", which couples the topology of the branches with their spatial extents by tracking their topological evolution in 3D space. Unlike these hand-crafted designed features, Li et al. [23] first employed deep learning method, i.e., stacked auto-encoder, to learn deep features for the 3D neurons. However, since the number of neurons in NeuroMorpho.Org dataset [29] has increased from 50,000 to 100,000 in recent two years, there are no related quantitative representation methods developed for such a large-scale neuron dataset.

2.2.2. **Neuronal exploration:** based on the quantitative representation of 3D neuron data, many computational methods and tools have been developed for the exploration of neuronal morphology. For example, Wan et al. [39] first developed *BlastNeuron*, which can automatically compare, retrieve, and cluster for more than 10,000 3D neuron data, based on the features of *L-Measure* [37] and moment invariants [25]. Costa et al. [13] developed an online tool for fast, sensitive neuron similarity search, i.e., *NBLAST*, which supports the pairwise comparison, and the search of databases of neurons, as well as hierarchical clustering. Moreover, considering the computational efficiency during the similarity search, Conjeti et al. [10,28] first employed hashing methods for large-scale neuron retrieval, and developed an Android App, i.e., *Neuron-Miner*, for fast retrieval over 31,266 neurons. More recently, Fulmer et al. [15] introduced augmented reality and mixed reality techniques for the visualization of 3D neuron morphologies (i.e., *ImWeb*), by the immersive web browsing with the Microsoft HoloLens headset. However, the above methods and tools can only support the retrieval and exploration of pre-stored neurons, i.e., the input is neuron id rather than the original morphological data, which cannot afford the requirements for the analytics of the ever-increasing number of digitally reconstructed neurons.

3. Methodology

In this section, we present methodological details of our proposed framework for the computational analytics of 3D neuron images, including 3D neuronal mapping, unsupervised deep feature learning, and graph-based neuronal indexing.

3.1. 3D Neuron Mapping

The 3D neuron morphological data are reconstructed from multiple microscopy slices through the neuron tracing techniques. Afterwards, the 3D neuron data are stored using the SWC format files, which is the standard version used in currently large-scale neuron datasets, such as NeuroMorpho.Org [29] and FlyCircuit [9]. For each SWC file, it includes hundreds to thousands of 3D points. Moreover, as illustrated in Table 1, each point includes 7 dimensional information to indicate the spatial structures of neuron morphology. The first dimension "Point Number" denotes the order of each point. The second dimension "Point Identifier" denotes the type of each point according to the structure of neuron cells, including soma, axon, dendrite, etc. The third, fourth, and fifth dimensions denote the 3D coordinates (X, Y, Z) of each point in micrometers. The sixth dimension denotes the radius of corresponding points in micrometers. Finally, the seventh dimension denotes the serial number of parent point, which can reveal the tree-topological structures of neuron morphology.

The 3D neuron data are quite different with most widely investigated 2D images and 3D point sets. Accordingly, it is hard to directly employ existed deep neural networks for the computational analytics of neuronal morphology. Especially, the 3D neuron data demonstrates complex spatial structures with tree-topologies, i.e., from soma to dendrite, which need to be considered in the feature learning. Besides the tree-topologies, the other biomedical information recorded in the SWC file also plays critical roles in the differentiation of neuron morphologies, e.g., "Point Identifier" and "Radius". For an accurate representation of 3D neurons, all these items should be involved during the feature learning of deep neural networks.

Here, we present 3D neuronal mapping, which can transform 3D neurons into 2D images for unsupervised deep feature learning, as well as preserving spatial structures and properties. Fig. 2 demonstrates the pipeline of our proposed 3D neuron mapping. Given an SWC format file, we first extract their 3D points coordinates and employ principal component analysis (PCA) to move neurons into a normalized axis, which is consistent with the previous method [23]. Afterwards, we map all the 3D points and their radius into 2D with three angles of view, i.e., three circles in X-Y, X-Z and Y-Z plane respectively for each point (Fig. 2(b)). Subsequently, each point is connected with its parent point, where the

Table 1
For each neuronal cell, the 7 dimensional information recorded in SWC format files.

1	2	3	4	5	6	7
Point Number	Point Identifier	X Position	Y Position	Z Position	Radius	Parent Point

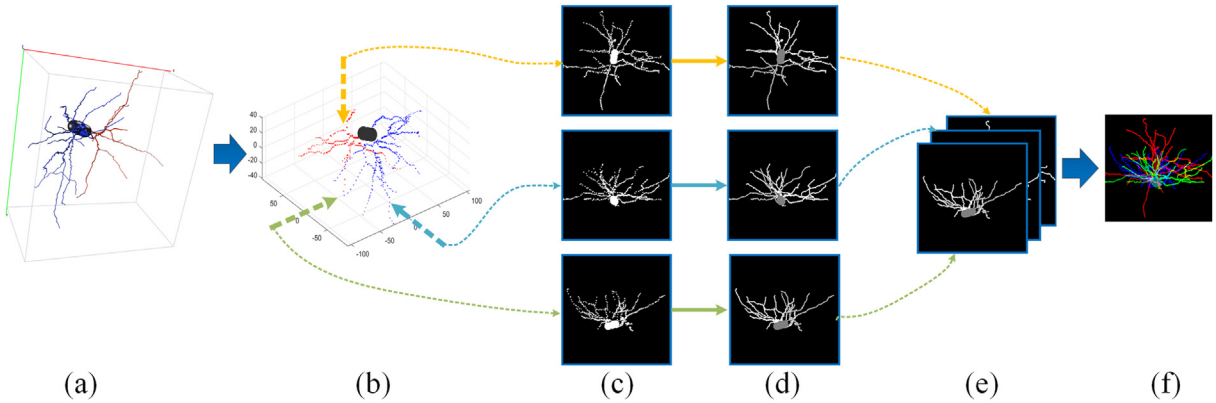

Fig. 2. The pipeline of our proposed 3D neuron mapping, which can map 3D neuron data into 2D images for convenient unsupervised deep feature learning, as well as preserving their spatial structures: (a) given an SWC formatted neuronal file, visualizing original 3D neuromorphological data using Vaa3D [31]; (b) plotting all points recorded in the SWC file in 3D space, different color indicates different point identifier; (c) orthogonally mapping all the points with corresponding radius in three angles of view, denoted as small solid circles; (d) connecting each circle with their parent circle using the index of parent point, then assigning each circle and their closest connection with corresponding gray-level according to their point identifier; (f) considering the three gray images to compose an RGB color image, where each gray image indicates a channel.

thickness of each line is determined by the radius of the corresponding point and their parent point, i.e., the tangents of two mapped circles (Fig. 2(c)). Unlike previous methods which only consider each point and its connections [23], we propose to fully explore the information provided in the SWC file. As the "Point Identifier" denotes the point type based on the structure of neuron cells, each point has different biomedical meanings in the representation of 3D neuronal structures. Therefore, the mapped circle and their connections cannot be treated as equal without discrimination. To this end, for the mapped circles and their connections, we propose to assign different gray levels according to the type of "Point Identifier". Especially, there are in total 8 point types, which can be normalized to gray levels from 0 to 255. The connected lines can be mapped to the gray level consistent with the point and its parent point, i.e., half of the line follows the gray level of current points, another half of the line follows the gray level of its parent point. Finally, for a 3D neuron data, it can be mapped into three gray images in 2D (Fig. 2(d)). For convenience, we store the three gray images as a tensor, then converting the tensor into color images with corresponding R, G, B channels (as illustrated in Fig. 2(e)(f)). The 3D neuron mapping strategy has fully utilized the information provided in the SWC files, preserving 3D structures and tree-topologies of neuron morphologies.

3.2. Unsupervised feature learning for 3D Neuron Data

Based on the 3D neuron mapping, each 3D neuron data can be transformed into 2D images for convenient training of deep neural networks. Despite varieties of deep neural networks have been designed in recent years, achieved many successes in the analytics of nature images and biomedical images, two challenges still need to be considered when applying deep learning techniques for currently neuron datasets. Firstly, existed neuron datasets lack sufficient annotations for supervised feature learning. Actually, it is still an open problem for the fine-grained classification of neuron cells, where existed neuron datasets only provide coarse cell types, brain regions, transmitters, without well-organized taxonomy. Secondly, the tree-topological structure in neuron morphology should be also taken into account, which plays critical roles in the determination of different neurons. More discriminative deep neural networks need to be designed for effective feature learning of neuron data.

We formulate the feature learning of 3D neuron data into an image generation problem and propose to use deep convolutional generative adversarial networks (DCGAN) in tackling the above challenges [34]. As shown in Fig. 3, we build a generator-discriminator network with convolutional stride and transposed convolution for the downsampling and the upsampling. In the generator network (denoted as G), a 128×128 sized image $G(z)$ can be generated from an uniformed noise distribution $p_z(z)$, to mimic the space of 2D neuron images. The generated images are labeled as fake, where x obtained from the neuron datasets are labeled as true. In the discriminator network (denoted as D), it tries to maximize the probability it correctly classifies real and fake images, while the generator network G tries to minimize the probability that the outputs of $D(G(z))$ are fake. Accordingly, to train the network, D and G play the following two-player minimax game with value function $V(D, G)$:

$$\min_G \max_D V(D,G) = E_{x\sim p_{data}(x)}[\log D(x)] + E_{z\sim p_z(z)}[\log(1 - D(G(z)))] \tag{1}$$

where the generator G tries to minimize the objective function while the discriminator D tries to maximize it.

For all layers in the generator network, we choose the *ReLU* as the activation function and apply batch normalization except the last layer, where we choose the *tanh* as the activation function. The dimension of the input noise vector is set to 100. All weights in the generator network are initialized from a zero-centered normal distribution with standard deviation 0.02. In the discriminator network, the *LeakyReLU* is employed as the activation function for each layer except the last layer, where we choose the *sigmoid* as the active function. In the *LeakyReLU*, the slope of the leak was set to 0.2 in all layers. Additionally, when training the discriminator net-

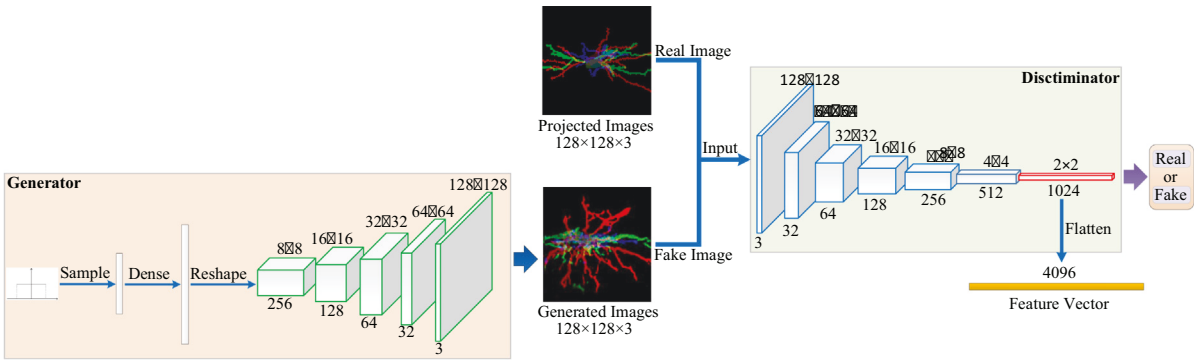

Fig. 3. The model architecture of our deep convolutional generative adversarial networks for the unsupervised feature learning of mapped neuronal images.

work, we set the learning rate as 0.0001, while using 0.0002 instead to train the generator network, leaving the momentum term β_1 with the value of 0.5. After the training of both generator and discriminator networks, each mapped neuron image can be set as input to the discriminator network, i.e., a classification neural network, where we extract feature vectors from the last layer. These feature vectors can be considered as the quantitative representation of each 3D neuron data.

In addition to the above unsupervised deep feature learning, previous works demonstrate that deep features are complementary with the traditional hand-crafted features, i.e., measurement-based features, in the representation of 3D neuron data [23]. Therefore, for more accurate neuron analytics, we further explore more types of measurement features and fuse them with deep features. Especially, due to the ever-increasing number of reconstructed 3D neurons in the public datasets, previously low-dimensional measurement features (e.g., dozens of measurements) cannot work well in the discrimination of large-scale neurons. Here, we introduce more measurements for the representation of 3D neuron data. Especially, the increased measurements can be reflected in two aspects:

1. We introduce new types of measurements: in addition to the most widely employed measurements in previous works, such as the number of branches, soma surface, etc, we adopt new types of measurements to make neuron features more discriminative. For example, for each bifurcation point, we adopt a new measurement, i.e., last parent diameter, which returns the diameter of the last bifurcation before the terminal tips. Most of these newly added measurements can help to represent 3D neurons in branch and bifurcation level.
2. We extend existed measurements with more metrics: previous low-dimensional measurements only employ one or two metrics for the representation of 3D neurons. For example, for the measurement of volume, previous methods only return the sum of the volume for all the compartments, which cannot well differentiate massive neuron data. As for the neurons with different morphologies, the sum of their compartment volume can be close. For these measurements, we further compute their minimum, average, and maximum for the neuron feature representation.

Based on the above two strategies for the extension of measurements, the dimension of hand-crafted features has increased from 38 to 169, which can well enlarge the representational power for massive 3D neurons.

After the computation of two kinds of improved neuron features, i.e., unsupervised deep features and extended hand-crafted features, we fuse these two kinds of features together as the representation of 3D neuron data. Since the dimensions of two kinds of features are not consistent, we employ the principal component analysis (PCA) algorithm to compact thousands dimensional deep features into hundreds dimensions. Then these two kinds of features can be combined together as the quantitative representation for large-scale 3D neurons.

3.3. Efficient and robust retrieval for large-scale neuron datasets

On the basis of unsupervised feature learning, each neuron can be quantitatively described through the fused features above. Afterwards, we employ these features for further neuron analysis and exploration. Among the analytical tasks for neuron morphology, retrieval is one of the most important and widely investigated tasks. Given a query neuron, neuromorphological retrieval can find neurons with similar morphologies in large-scale datasets, which are the basic step for further neuron comparison, type identification, group analysis, structure and functional property correlation, etc. However, the continuously expanded neuron datasets pose significant challenges for efficient neuron retrieval. For each retrieval task, if every time we exhaustively compute the Euclidean distance between each query neuron and all neurons in large-scale dataset, the whole process would be very time-consuming, which cannot afford the requirements for online neuron retrieval system. In recent years, multiple efforts have been made for efficient neuron retrieval, through the learning to hashing techniques [24,10]. This kind of method aims to learn effective hashing functions through the existed datasets, which can transform long neuronal feature vectors into short binary codes, preserving original neuronal similarities as much as possible in the meanwhile. Despite the hashing based methods can efficiently find similar neurons in large-scale dataset, they cannot achieve comparative performance with the exhaustive computation of Euclidean distance through feature vectors, due to the information loss when transforming feature vectors into binary codes, where these binary coding transformations are not one-to-one correspondences.

In order to remarkably improve the retrieval efficiency without losing precision, we introduce a fully graph-based approximate K-nearest neighbor search method through the navigable small world graphs with controllable hierarchy, i.e., Hierarchical Navigable Small World graphs, denoted as HNSW [26]. This search strategy is specially designed for the indexing of high-dimensional and large-scale datasets, which incrementally builds multi-layer graph structures for efficient and robust indexing. Fig. 4 presents the pipeline of our solution for the efficient and robust retrieval in large-scale neuron datasets using the HNSW indexing. In the phase of retrieval model construction, we first extract quantitatively morphological features for the representation of all 3D neuron data in the database, using the above proposed method, i.e., 3D neuron mapping, generative adversarial feature learning, and feature fusion. Subsequently, for efficient similarity search in massive neu-

rons, we consider each neuron feature as a node to construct the graph according to their Euclidean distance. We employ the method of HNSW for the construction of hierarchical graph, i.e., specially designed for the indexing of high-dimensional and large-scale datasets, which incrementally builds multi-layer graph structures for efficient and robust indexing.

The HNSW algorithm was originally from the Navigable Small World graphs (NSW) [20,6], a typical graph-based similarity searching strategy, which suffers from the polylogarithmic search complexity of the routing process. By extending the NSW graph into multiple layers, HNSW is similar to the well-known 1-D probabilistic skip list structure [33], where the major difference is that the HNSW can generalize the structure by replacing linked lists with proximity graphs. As illustrated in Fig. 4, when constructing the hierarchical graph, the HNSW algorithm separates the links according to their length scale into different layers. Afterwards, in the phase of online neuron query, given a query neuron, the quantitative features can be first extracted through the above proposed method. Then, the HNSW algorithm greedily traverses the multi-layer graph through the node (i.e., neuronal features in the database) from the top layer until a local minimum is reached. Then the search can be moved to the lower layer which has shorter links, restarting from the node which is the local minimum in the previous layer. The above process can be repeated to find the nearest neighbor. Since the maximum number of connections per node in all layers can be made constant, the HNSW can reach a logarithmic complexity scaling of routing in a navigable small world network. Accordingly, the query neuron can efficiently find its top similar neurons in the database through the indexing in the hierarchical NSW graph with the embedding of all neuron features.

In comparison with previous neuron morphological retrieval through learning to hashing, there are mainly two advantages when using HNSW for neuron retrieval. Firstly, the retrieval precision can be guaranteed, since the information in neuron features haven't been lost during the construction of hierarchical graphs. The graph-based strategy can generally achieve excellent performance in the approximate nearest neighbor search. Secondly, the efficiency of HNSW is comparable with hashing- based methods. The search complexity of HNSW is $O(\log(N))$, which is efficient enough in tackling the retrieval of the dataset with $100,000$ neurons. In addition, despite the hashing based methods can achieve theoretically $O(1)$ search complexity, re-ranking of tens to hundreds of top similar samples are generally required in practical cases, since the top similar samples can share the same binary codes, which need further ranking through the computation of their Euclidean distance. In the experiment, we will demonstrate the superiority of the HNSW for the retrieval of large-scale neuron datasets.

4. Experiments

In the experiment, we demonstrate the effectiveness of the proposed framework for the computational analytics of neuronal morphology, as well as the discussion of potential use cases.

4.1. Experimental Setting

In the experiment, we employ the publicly available largest neuron dataset, i.e., NeuroMorpho [29] for method evaluation and comparison. Especially, the NeuroMorpho [29] currently includes more than $100,000$ reconstructed 3D neurons collected from 545 labs worldwide, with the collection of neurons from 64 species, 317 brain regions, and 721 cell types. For the measurement-based features, we employ the L-Measure toolbox [37], extracting all the 43 types of quantitative morphological measurements, with the metrics computation of minimum, average, maximum, and sum. We finally employ the 169 dimensional measurement-based features, after the ignoring of redundant measurements. In our experiment, we consider all $99,453$ effective neurons in the NeuroMorpho dataset [29], which was accessed in February, 2019 with the version of $v7.6$, excluding neurons that cannot be processed by L-Measure toolbox [29].

For the 3D neuron mapping, we map all 3D neurons into 2D images with a size of 128×128. The whole network (including generator and discriminator) is trained end-to-end in 70 epochs with the learning rate of 0.0001 and 0.0002 for the generator and discriminator respectively. The learned deep features are 4096

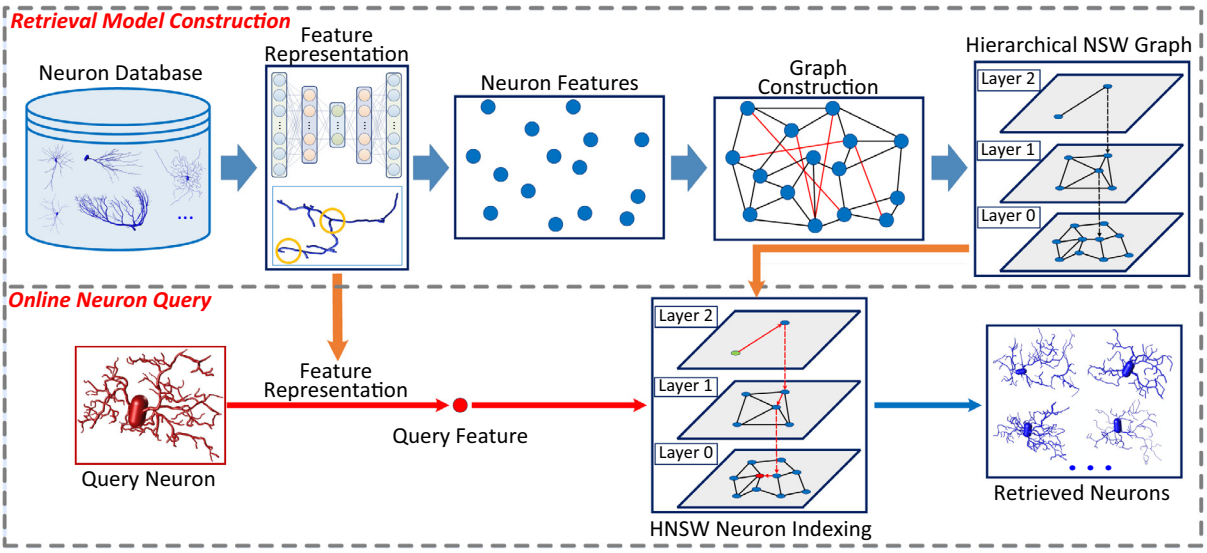

Fig. 4. The proposed pipeline for efficient and robust retrieval in large-scale neuron datasets, which includes two phases, i.e., retrieval model construction and online neuron query. In the phase of retrieval model construction, morphological features of all 3D neuron data from the database can be obtained through the above developed feature representation method, then each neuron can be considered as a node to construct the hierarchical navigable small world graphs for efficient indexing; In the phase of online neuron query, the feature of query neuron can be also first computed, then the neuron indexing can be treated as the greedily traverses from the entry point in top layer to the query point in the lower layer; the whole process can reach logarithmic complexity scaling of routing, achieving large-scale neuron retrieval in real-time.

dimensions. All experiments are processed on Python v3.6, and Keras with GEFORCE GTX TITAN GPUs.

4.2. Evaluation of unsupervised feature learning

We first evaluate the effectiveness of the proposed unsupervised feature learning method in the quantitative representation of 3D neuron morphologies. Especially, we evaluate neuron features through the neuron retrieval task, which is also the most widely investigated task in the neuromorphological analytics. For the fair comparison with related works, we also adopt the uPNs as query neurons, with the brain regions of the olfactory antennal lobe, glomerulus, and the cell classes of the principal cell, uniglomerular projection [39,23,13]. As the current neuron datasets haven't provided well-organized neuronal taxonomy, uPNs are one of the most fine-grained recognized neurons in the NeuroMorpho dataset [29]. Besides, for the evaluation metric, we evaluate the retrieval performance by the computing of average retrieval precision, which is defined as the ratio of retrieved uPNs among all retrieved top-K neurons after the indexing of in total 99,453 neuron cells. We adopt the retrieval precision for evaluation since neuroscientists usually need to compare the similarity between the query neuron and its retrieved top similar neurons.

In Table 2, we present the average retrieval precision of the proposed methods in comparison with other related methods, to evaluate the representational power especially for the 3D neuron morphological data. As demonstrated in Table 2, there are three groups of feature representation methods recorded: (1) features learned from unsupervised deep neural networks (i.e., Deep-DBM, Deep-VAE, Deep-SCAE, Deep-DCGAN); (2) features measured by multiple quantitative metrics (i.e., L-Measure38, L-Measure169); (3) features fused by both deep features and hand-crafted features (i.e., DCGAN-Fuse, SCAE-Fuse). Among of these methods, Deep-DCGAN, L-Measure169, and DCGAN-Fuse are the methods we presented in this paper. Particularly, Deep-DCGAN indicates the neuron features learned through the 3D neuronal mapping and unsupervised deep convolutional generative adversarial networks. L-Measure169 indicates the hand-crafted neuron features we extracted through 169 types of L-Measure metrics. DCGAN-Fuse indicates the feature fusion of Deep-DCGAN features and L-Measure169 introduced in Section 3.2. Considering the deep features generally have high-dimensional vectors in comparison with hand-crafted features, we uniformly compress all deep features into 130 dimensions for the feature fusion through principal component analysis (PCA), which consists with hand-crafted features. In addition to these proposed methods, we also introduce the competitive methods respectively:

1. Deep-DBM: Deep Boltzmann Machines (DBM) [36] is one of the most widely used deep neural networks for unsupervised feature learning. Here, we train the DBM networks from scratch, using the neuron images obtained from the 3D neuron mapping. We set the dimension in hidden layer as 512, which can achieve the best performance comparing with other parameters.
2. Deep-VAE: Variational Auto-Encoder (VAE) [32] has also been widely employed for the feature representation of varieties of image modalities. In the VAE model, we use the hidden vector that generates vectors of means and standard deviations as learnt features, which performs better than the latent vector.
3. Deep-SCAE: Stacked Convolutional Auto-Encoder (SCAE) [27] is a very popular network for unsupervised feature learning. More specifically, this is the first deep neural network that has been employed for the representation of neuromorphological data [23]. The parameter setting here is consistent with previous works [23].
4. L-Measure38: L-Measure is the most widely used toolbox for the measurement of neuron features [37]. Especially, multiple neuronal analytical works employed the 38 dimensional measurements for the representation of neuron morphologies [24,11,10].
5. SCAE-Fusion: this method fuses the features of Deep-SCAE and L-Measure38, which had achieved excellent performance for the retrieval of 50,000 neurons in previous works [23]. These feature fusion results are generally much better than both the results of deep features and the measure-based features.

According to Table 2, our proposed method DCGAN-Fuse can always achieve the best performance under different number of retrieved neurons from top-10 to top-100, with around 9% to 21% precision improvement compared with the second best method. These results validate the effectiveness of our proposed new framework for the quantitative description of large-scale 3D neuron data, demonstrating superior representational power in the discrimination of massive neurons. Besides, the corresponding two improved methods, i.e., Deep-DCGAN with 3D neuronal mapping and L-Measure169 with more types of measurements, also perform better in comparison with competitive deep features and hand-crafted features respectively. The retrieval precision has a significant improvement from L-Measure38 to L-Measure169, validating the fact that more types of effective measurements can boost the quantitative representation for large-scale datasets. Moreover, for the comparison of 4 deep learning based methods, Deep-DCGAN can achieve much better performance in comparison with Deep-DBM, Deep-VAE and Deep-SCAE. These superior results mainly benefited from the well-designed 3D neuronal mapping and the introduction of DCGAN. Specially, the 3D neuronal mapping preserved all dimensional information provided in the original SWC format files, including each point with its coordinates, connections, radius, and identifiers. For comparison, the Deep-SCAE only considered the projection of points and their connection. The introduced DCGAN also performs better in comparison with VAE and DBM for the feature representation of mapped 2D neuron images. In addition to the deep features and measurement features, i.e., Deep-DCGAN and L-

Table 2
Comparing the average retrieval precision of eight methods under different numbers of retrieved neurons.

Method	top10	top20	top30	top50	top100
Deep-DBM	0.5636	0.4510	0.3780	0.2890	0.1895
Deep-VAE	0.6259	0.5185	0.4522	0.3632	0.2367
Deep-SCAE	0.6305	0.5181	0.4533	0.3715	0.2530
Deep-DCGAN	0.7031	0.6041	0.5366	0.4459	0.3103
L-Measure38	0.7729	0.6802	0.6227	0.5391	0.3967
L-Measure169	0.8627	0.7852	0.7231	0.6343	0.4746
SCAE-Fuse	0.7928	0.6900	0.6198	0.5168	0.3512
DCGAN-Fuse	**0.9559**	**0.9311**	**0.9090**	**0.8533**	**0.6861**

Measure169, we find that measurement features can generally perform better than the deep features, since deep features are more likely to represent holistic structures of neuronal morphologies, while measurement features are more likely to represent fine-grained structures. Comprehensive feature representation from global to local is able to differentiate the difference among massive neurons. Accordingly, their combination can significantly improve the representation power for the 3D neuron data.

Besides the quantitative comparison of retrieval precision, we also randomly select five neurons in the NeuroMorpho [29] dataset and set them as query neurons. As demonstrated in Fig. 5, the left 5 neurons are queries. The corresponding neurons on the right are their top-5 most similar neurons by indexing all neurons in the dataset, through our proposed feature representation framework. According to Fig. 5, our proposed framework can indeed retrieve similar neurons from large-scale datasets, showing strong relevance between each query neuron and their retrieved neurons. Moreover, we also present related information for the above all neurons in Fig. 5, including neuron names, brain regions and cell classes provided in NeuroMorpho dataset [29]. We find that most retrieved neurons also share similar functional properties with each query neuron. More importantly, for some neurons where their properties are not well explored in the dataset, the corresponding retrieved similar neurons can help to infer the properties of the unknown neuron.

4.3. Evaluation of efficient retrieval

We further evaluate the effectiveness of the introduced graph-based nearest neighbor search for efficient and robust retrieval of massive neurons with hundreds of dimensional features. Especially, for the HNSW method [26], we set the parameter M as 16 (defined as the maximum number of outgoing connections in the graph), and the parameter *efConstruction* as 200 (controls speed/accuracy trade-off during the index construction). We compare the retrieval precision and efficiency with two typical methods:

1. Baseline: as described above, the DCGAN-Fuse includes 299 dimensional features fused by the measurement features and deep features, which achieves the best retrieval precision with state-of-the-arts. Here, we validate its retrieval efficiency through the exhaustive computing and ranking of their Euclidean distance, which can achieve the most reliable and accurate

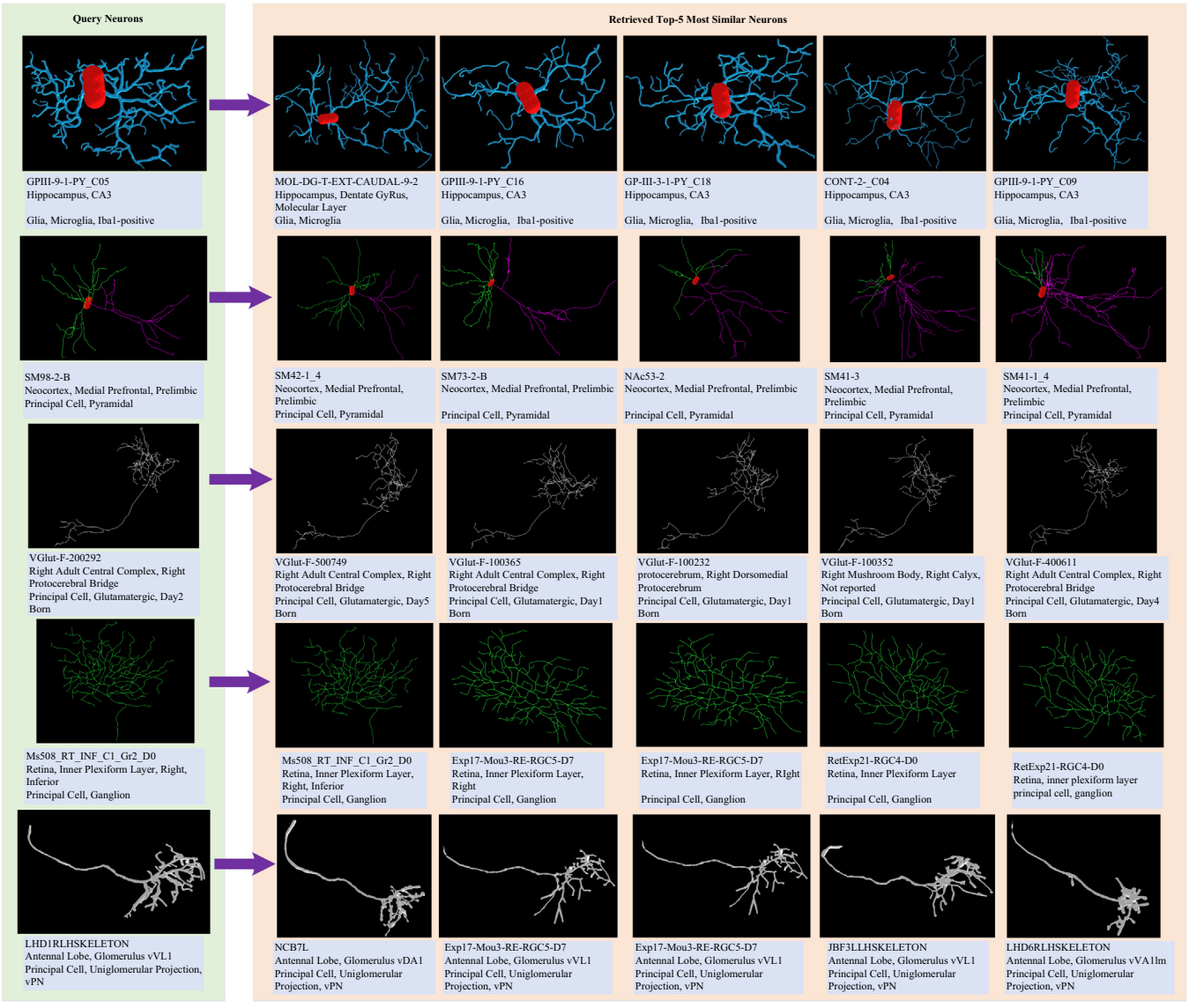

Fig. 5. Five randomly selected query neurons and their top-5 most similar neurons using the proposed method, as well as their neuron name, available brain regions and cell classes provided in the NeuroMorpho dataset [29].

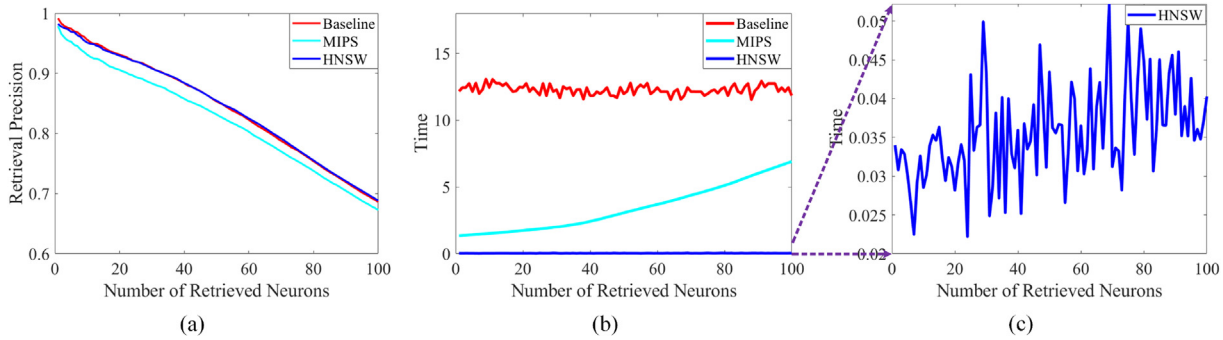

Fig. 6. Evaluation of the introduced HNSW method for the efficient neuron retrieval: (a) retrieval precision of three compared methods under the different number of retrieved neurons, (b) retrieval time comparison of three methods under the ranking of the different number of retrieved neurons (in second), (c) retrieval time of HNSW method under the ranking of the different number of retrieved neurons (in second).

retrieval results. This exhaustive computing and ranking can be treated as the baseline for the evaluation of neuron retrieval efficiency.

2. MIPS [24]: as one of the well investigated hashing methods, MIPS can effectively learn the hashing functions through the maximum inner product search. Moreover, MIPS has been applied for neuron morphological retrieval and achieved excellent performance.Fog. 6 records the retrieval precision and efficiency (in second) for the three compared methods, after the indexing from top-1 to top-100 most similar neurons in the NeuroMorpho dataset [29]. To overcome the randomness of these three methods, all the methods are run randomly 100 times to record their average precision and running time. The retrieval time is the accumulative running time by computing the top-K similar results for the indexing of all uPNs. According to the Fig. 6(a), the HNSW based retrieval can achieve almost similar retrieval precision in comparison with the baseline method, i.e., directly computing and ranking through the Euclidean distance for each neuron feature. Therefore, such graph-based indexing is reliable for the approximate nearest neighbor searching of large-scale neuron dataset. The hashing-based method, i.e., MIPS [24] cannot achieve comparable results, due to the information loss when transforming neuron features into binary codes. In the Fig. 6(b) and (c), HNSW based retrieval is the most efficient method for the large-scale neuron retrieval task, with hundreds of efficiency improvements in comparison with the baseline method. Theoretically, hashing-based methods can achieve efficient retrieval. However, for the retrieved top similar neurons, their hamming distance can be the same. Re-ranking top similar neurons through the computation of Euclidean distance is generally employed to guarantee the performance of hashing-based methods. Therefore, our introduced HNSW method [26] is efficient and robust for the retrieval of massive neuron data.

5. Conclusion

In this paper, we present a novel framework for the computational analytics of 3D neuron images, through a deep adversarial learning framework. Especially, to transform the specific 3D neuron data into an available modality for deep model training, we present a 3D neuron mapping method to transform 3D neurons into 2D images, as well as preserving their spatial structures. The deep neuron features can be then learnt through a well-designed deep convolutional generative adversarial networks. In addition, we explore more types of measurement features and fuse them with deep features for accurate neuron representation. To boost the computational efficiency without losing retrieval precision, we further introduce a graph-based searching strategy for the retrieval in large-scale neuron datasets. Experimental results validate the superiority of our proposed framework in comparison with state-of-the-arts. In the future, we will develop a comprehensive tool for neuron retrieval and computational analytics, based on the methods presented in this work.

CRediT authorship contribution statement

Zhongyu Li: Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Supervision. **Xiayue Fan:** Software, Data curation, Validation. **Zengyi Shang:** Software, Visualization. **Lina Zhang:** Resources, Validation. **Haotian Zhen:** Visualization. **Chaowei Fang:** Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This work is partially supported by the National Science Foundation of China under grant 61902310, the China Postdoctoral Science Foundation under grant 2019M663670, and the Natural Science Basic Research Program of Shaanxi under grant 2020JQ-030.

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