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A novel method for dendritic spines detection based on directional morphological filter and shortest path

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ABSTRACT

Dendritic spines are tiny membranous protrusions from neuron's dendrites. They play a very important role in the nervous system. A number of mental diseases such as Alzheimer's disease and mental retardation are revealed to have close relations with spine morphologies or spine number changes. Spines have various shapes, and spine images are often not of good quality; hence it is very challenging to detect spines in neuron images. This paper presents a novel pipeline to detect dendritic spines in 2D maximum intensity projection (MIP) images and a new dendrite backbone extraction method is developed in the pipeline. The strategy for the backbone extraction approach is that it iteratively refines the extraction result based on directional morphological filtering and improved Hessian filtering until a satisfactory extraction result is obtained. A shortest path method is applied along a backbone to extract the boundary of the dendrites. Spines are then segmented from the dendrites outside the extracted boundary. Touching spines will be split using a marker-controlled watershed algorithm. We present the results of our algorithm on real images and compare our algorithm with two other spine detection methods. The results show that the proposed approach can detect dendrites and spines more accurately. Measurements and classification of spines are also made in this paper.

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1. Introduction

Dendritic spines are small protrusions from neuron's dendrites. They have the function of receiving excitatory inputs and transmitting them to cell bodies. Normally, the dendrites of a single neuron can contain hundreds or thousands of spines. Spines typically have a large spine head, which connects to the dendrites via a membranous neck. According to their shapes, spines could be classified as stubby, mushroom or thin [1]. The variable spine shape and volume is thought to be correlated with the strength and maturity of each spine-synapse.

Studies in the past several decades have shown that the structural and electrical properties of dendritic spines are critical for local signal integration and molecular compartmentalization [2–4]. The motility, the changes of morphology and the number of spines have a great influence on brain function and development of human beings in motivation, learning, and memory [5,6]. For instance, schizophrenia and mental retardation are related to alterations of spine's morphology or density [7,8]; ischemia, trauma or epilepsy may all cause the increase in spines plasticity [9,10]; after a severe stroke, a rapid loss of spines and dendritic swelling is observed [4,11]. Analyzing the spines is helpful for diagnosing disease and developing drugs to treat or slow down these diseases.

Automatic detection of spines in images is very important, because it helps release biologists from the heavy burden of manual spines detection process. Through the analysis of dendritic spines images, spine shape and spine parameters are obtained, which can then be used for further biomedical research. In this paper, we propose a novel pipeline for the detection and measurement of dendrites and spines on the maximum intensity projection (MIP) images. We develop a new backbone extraction approach and apply a shortest path method to detect dendrite boundaries and isolate dendritic spines. A backbone is the centerline of the dendrite structure. The novelty of our backbone extraction approach is that it uses an iterative process which can smooth the dendrites and

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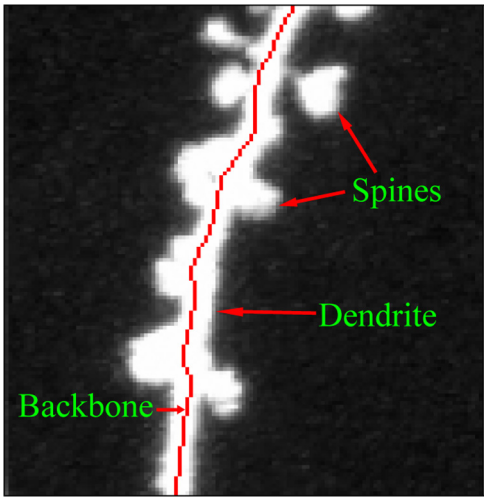

Fig. 1. An example showing spines, dendrites and backbone. This is the MIP image condensed from a 3D stack.

refine the backbone extraction results until satisfactory results are obtained. The backbone extraction of the dendrites is a key step for spines detection as dendrites are the trunk where spines attach to. However, backbone extraction is always affected by the huge number of small spines which usually disturb the backbone detection. Besides, a normal thinning algorithm is usually conducted on binary images, which depend heavily on thresholding algorithms. A simple thresholding algorithm may make a backbone disconnected. Our backbone extraction approach can iteratively remove the small spines from the dendrites, making the backbone extraction result better and re-connect any broken parts on the backbone. Moreover, touching spines can also be split through the proposed methods. Convincing results are obtained using our method. The spines, dendrites and backbone of dendrite are shown in Fig. 1. We will give a brief review of the existing spine detection methods in Section 2. The backbone extraction, boundary detection and spines extraction algorithms will be described in Sections 4 and 5. We show the experimental results in Section 6, followed by the discussion and conclusion of our work.

2. Related work

Great effort has been devoted to the automatic detection of spines in previous studies. In 1995, Watzel et al. proposed a spine detection approach which was based on the premise that only one dendrite was in the image [12]. Spines were extracted according to the medial axis spurs attached to the dendrites. This method cannot provide good results if multiple dendrites exist. Rusakov and Stewart described a method for quantification of spine length and distribution in [13]. Through binarization and skeletonization, lengths were computed through measuring skeletal branch lengths. Koh et al. detected spines based on their morphology [14]. The global thresholding method might lose many spines in the detection process. Weaver et al. further refined Koh et al.'s work in [15]. Xu et al. detected spines through two grassfire transforms to find the tips of spines and locate the boundary between spines and dendrites [16]. The adaptive local thresholding, voxel clustering and Rayburst sampling was used to analyze spines [17,18]. The NeuronStudio is a software which can detect dendrites and spines [18,19]. A sampling core which can be used for the determination of the radial distance in each direction was generated through a Rayburst sampling algorithm. Zhou et al. reconstructed the dendrite with the representation of neuron surface [20]. In this method, the level set algorithm was used to segment dendrites. Then spines were detected through a label-based thinning approach. Cheng et al. applied adaptive thresholding, SNR based method and morphology analysis to separate spines [21]. Attached spines and detached spines were detected separately. Bai et al. segmented the spines according to width-based criteria [22]. Spines were merged according to the distance and the orientation of spine head and base. They might not have a smooth backbone result by only using the thinning algorithm because spines in the binary image will affect the detection result. Fan et al. use a curvilinear structure detector to calculate the medial axis and maximum likelihood estimation was used to track spines [23]. Zhang et al. also used the curvilinear structure detector to extract the backbone and the boundary and used the linear discriminate analysis (LDA) classifier to further detect spines [24]. Janoos et al. reconstructed spines using surface representation and extracted skeletons based on the medial geodesic function [25]. Large spines were likely to be lost and spines shape was not well presented in these methods. They adopted another method which used local binary fitting (LBF) energy level set model with adaptive variances for the Gaussian kernel of each pixel to segment spines [26]. Lang et al. reconstructed neuron branches with detailed representation of spines from large-scale serial block-face scanning electron microscopy dataset [27]. Mukai et al. developed a novel method to extract spines based on their geometrical features and demonstrated the success of their method by analyzing effects elicited by androgen and estrogen on spinogenesis of hippocampal neurons [28].

3. Image acquisition

In our study, stimulated emission depletion (STED) microscope technique is used to image 3D dendritic spines of YFP-positive CA1 pyramidal neurons in living organotypic hippocampal slices, with spanning 140 μm in x, 140 μm in y, and 25–40 μm in z. There are 1024×1024 pixels in xy and 0.5 μm step size in z to ensure that the significant parts of the dendrites are contained in the image stack. The images are acquired in the range of 0-10 μm above the surface of the coverslip without showing any decrease in resolution as may have been expected for STED imaging in optically dense tissue. The detailed information of the dataset can be found in [29]. Our experiments are conducted on 2D images condensed from 3D image stacks through a maximum intensity projection (MIP) process.

4. Dendrites backbone extraction

4.1. Preprocessing

To improve the extraction results, we first use a median filter with a small window size (usually 3×3) to reduce noise. Then to deal with spines that are too close to each other, which often become connected after later operations such as the Hessian filter, we compute the gradient of the image, normalize the gradient magnitude to the range from 0 to 255, and use the difference between the image intensity and normalized gradient value to build a new image, denoted by I_l, which is obtained by

$$I_l = I - \frac{I_g \cdot 255}{I_{g\max} - I_{g\min}} \quad (1)$$

where I_g is the gradient image; $I_{g\max}$ and $I_{g\min}$ are the maximum and minimum gradient values. We show the input image and I_l in Fig. 2. From the images, some structures that are almost touching become separated (as indicated by the red circles in the figure), because this operation will reduce the effect of structures based on their directional change of magnitude in the intensity. The boundary has a larger gradient magnitude so its intensity values will be reduced

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