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3D-Reconstruction of Synapses with deep learning Based on EM Images

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ABSTRACT

Recently, due to the rapid development of electron microscope (EM) with its high resolution, stacks delivered by EM can be used to analyze a variety of components that are critical to understand brain function. Since synaptic study is essential in neurobiology and can be analyzed by EM stacks, the automated routines for reconstruction of synapses based on EM Images can become a very useful tool for analyzing large volumes of brain tissue and providing the ability to understand the mechanism of brain.

In this article, we propose a novel automated method to realize 3D reconstruction of synapses for Automated Tape-collecting Ultra Microtome Scanning Electron Microscopy (ATUM-SEM) with deep learning. Being different from other reconstruction algorithms, which employ classifier to segment synaptic clefts directly. We utilize deep learning method and segmentation algorithm to obtain synaptic clefts as well as promote the accuracy of reconstruction. The proposed method contains five parts: (1) using modified Moving Least Square (MLS) deformation algorithm and Scale Invariant Feature Transform (SIFT) features to register adjacent sections, (2) adopting Faster Region Convolutional Neural Networks (Faster R-CNN) algorithm to detect synapses, (3) utilizing screening method which takes context cues of synapses into consideration to reduce the false positive rate, (4) combining a practical morphology algorithm with a suitable fitting function to segment synaptic clefts and optimize the shape of them, (5) applying the plugin in FIJI to show the final 3D visualization of synapses. Experimental results on ATUM-SEM images demonstrate the effectiveness of our proposed method.

Keywords: Scanning electron microscope, Deep learning, 3D reconstruction of synapses

1. INTRODUCTION

It is generally known that synapse is one of the most important organelle in neurons and it plays a significant role in neural function. In order to study the correlation between synaptic growth and plasticity as well as understand the specific structure of synapses, it is necessary to obtain the 3D reconstruction of synapses. Although reconstruction algorithms [1] [2] focus on synaptic clefts segmentation directly and adopt stacks delivered by Focus Ion Beam Scanning Electron Microscopy (FIB-SEM), they are limited to small volumes and likely to be disturbed by membrane. By comparison, our method is applied to ATUM-SEM which can deal with large area sections and even reconstruct the synapses of a single mouse cortical column [3]. To avoid false distinction between synaptic cleft and membrane, we take presynaptic, synaptic cleft and postsynaptic as a whole, and then detect and segment synapses successively. In order to reconstruct synapses precisely, we adopt an effective detector to get the accurate localization of synapses and utilize a practical segmentation method to obtain the synaptic clefts.

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In this paper, we introduce an automated method to realize 3D reconstruction of synapses for ATUM-SEM by combining a series of effective methods in registration, detection and segmentation.

2. METHODS

As shown in Figure 1, the proposed 3D automated synapses reconstruction method for serial sections of biological tissue could be divided into five parts, which are corresponding Image registration, synapses detection with deep learning, selection with context cues, synapses segmentation and 3D reconstruction. In this paper, we focus on the middle three steps.

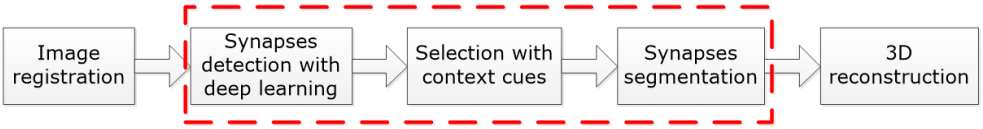

Figure 1. The workflow of the proposed method.

2.1 Image Registration

We employ the registration method proposed in [4], which registers adjacent sections with MLS deformation algorithm and utilizes SIFT features to detect corresponding landmarks across adjacent sections. This algorithm not only reflects the discontinuity around wrinkle areas but also keeps the smoothness in other regions, which provides a stable foundation for the follow-up works.

2.2 Synapses Detection with Deep Learning

In this part, Faster R-CNN [5] is adopted to detect the synapses in each microscopic neural image. Its core task is to design and train the Region Proposal Network (RPN) which shares full-image convolutional features with the detection networks. As a consequence, the four basic steps of target detection: region proposal, feature extraction, object proposals classification and bounding-box regression are unified to a deep-learning-based object detection system. Finally, Faster R-CNN turns out to be able to guarantee both of the overall detection accuracy and operation speed.

To avoid the out of memory error of GPU, small images are proposed to train Faster R-CNN. To be specific, we divide the original image (size of 7k x 8k) into 56 small images (size of 1k x 1k) and apply the plugin of training Image Labeler to label synapses, then flip these images and assure that the training samples are close to 10000. After that, we train Faster R-CNN to detect synapses in small images and use an effective stitching method to obtain the detection results of original image.

2.3 Selection with Context Cues

In order to promote the accuracy of detection, we take the spatial context containing multi-layer information into account for reducing the false positive rate. The main principle is summarized as follows. Since the synapse is a spatial structure with the size of nearly 400nm whereas the distance between adjacent layers is only 50nm, it can be speculated that the real synapse is able to arise in continuous layers. Thus we utilize the location information to delete the false results that there won't be any disturbances in adjacent layer. After being filtered through context cues, most false positives are removed while promoting the overall synapses detection accuracy.

2.4 Synapses Segmentation

According to the fact that synaptic clefts with 20nm width are wider than other dark regions around in the detected boxes obtained above, synapses can be segmented easily in serial sections by means of morphological processing method [6]. First, we use threshold method to convert the original synapse image to binary image, after that, erode and open operation are employed to eliminate boundary and get synaptic clefts.

After morphological processing, synaptic clefts can be formed roughly. To get more smooth synaptic clefts, suitable fitting curve is proposed to optimize the structure of the synaptic clefts. Since most shapes of synaptic clefts are similar to quadratic curve, we adopt a quadratic curve for each synaptic cleft. In order to obtain data used to be fitted, m pairs of points $P(x_i, y_i)$ $(1 < i \leq m)$ are selected randomly from the region which is segmented by morphological method. Then we utilize quadratic curve to optimize the shape of synaptic clefts, and curve can be described as $y_i = \mathrm{a}x_i^2 + bx_i + c, i = 1,2, \dots, m$. As a result, series of curves are obtained as synaptic clefts.

3. EXPERIMENT AND RESULTS

We now implement our method and compare its performance to that of [6]. The biological specimens used in this paper are taken from the cerebral cortex of mouse. The training dataset consists of 178 ATUM-SEM serial scans of size 7616 x 8576, with the thickness of 50nm and the resolution of 2nm per pixel. The testing dataset is obtained from a different part of the same stack.

In our work, we adopt precision-recall (PR) curves to evaluate the performance of our detection and segmentation methods. Furthermore, we use mean Average Precision (mAP) as well as Intersection-over-Union (IoU) for quantitative analysis.

3.1 Detection Results

Table 1 presents the training and testing results of Faster R-CNN on a TITAN X GPU. In table 1, ZF [7] and VGG16 [8] are deep neural networks with different layers and structure, the rate shows the running time of different models on training images (size of 1k x 1k). Using RPN+VGG16, the mAP is 83.4% for shared features, slightly higher than RPN+ZF. Therefore, we exploit VGG16 networks to detect synapses.

Table 1. Training and testing results of Faster R-CNN on a TITAN X GPU.

method	proposals	data	mAP (%)	rate
RPN + ZF, shared	300	10000 samples	82.1	9 fps
RPN + VGG16, shared	300	10000 samples	83.4	3 fps

Figure 2 shows the detection results of original images as well as presents conv5_3 features maps extracted from the Faster R-CNN model. These visualizations indicate that, neurons in the convolutional layer react to the visual patterns of synapses positively. Figure 3 displays the detection results of AdaBoost and Faster R-CNN which are screened by context cues, while the rectangles in red indicate the Faster R-CNN detection results and rectangles in blue present AdaBoost. This turns out to be a promising result, since it demonstrates that the detection accuracy of Faster R-CNN is more effective than AdaBoost.

We plot the precision-recall curves in Figure 5. According to the property of precision-recall plots, it can be seen that the approach which adopts context information perform further better than the version which ignores the context. It also leads

to the undoubted conclusion that the results of our full approach are much better than others. As shown in Table 2, our approach behaves gracefully in detection quantitative analysis. The mAP and IoU of our full approach is respectively 89.2 and 82.0, which is the best performance out of the four methods.

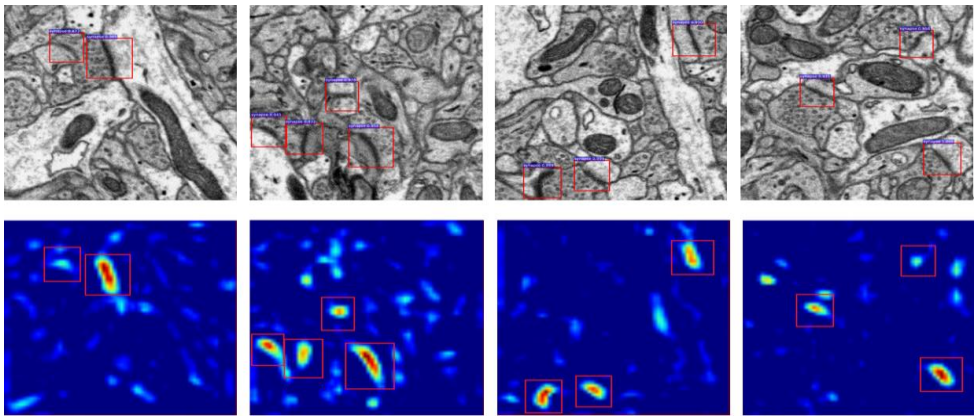

Figure 2. Top: Detection results of original images. Bottom: Thermographies corresponding to detection results.

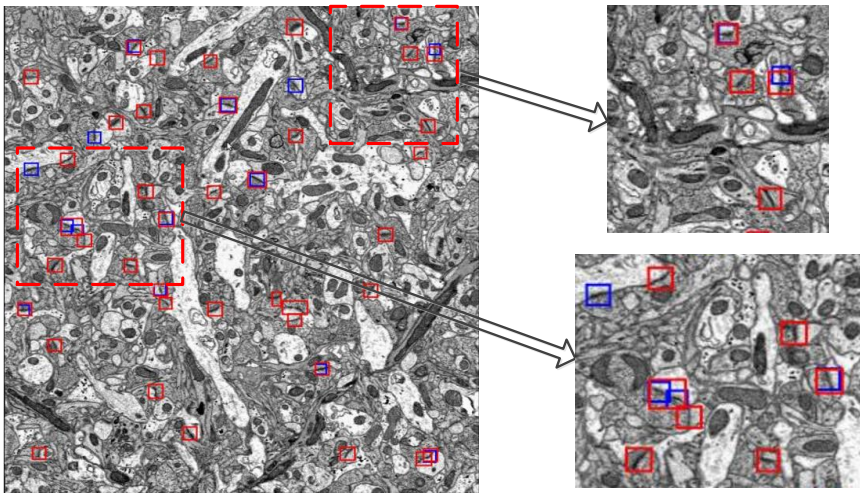

Figure 3. Detection results from Faster R-CNN (red) and AdaBoost (blue) after screening with context cues. Left: whole results. Right: local results.

3.2 Segmentation Results

The Segmentation results of synaptic clefts are shown in Figure 4, we can easily draw the conclusion that our method achieves satisfactory results. Most of the synaptic clefts are segmented correctly from the original images. It provides information on spatial distribution and statistical of synapses, which is significant for synapses researching. As shown in Figure 5 and Table 2, the performance of our segmentation approach in quantitative analysis is better than other methods. Figure 6 displays the visualization of synaptic 3D reconstruction through FIJI software.

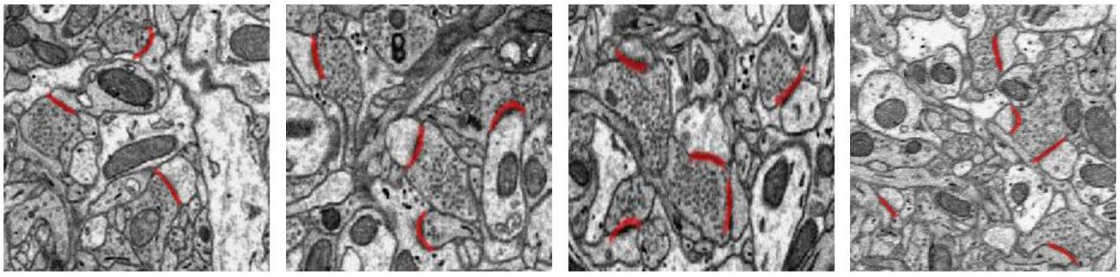

Figure 4. Segmentation results of synaptic clefts (the red parts are synaptic clefts).

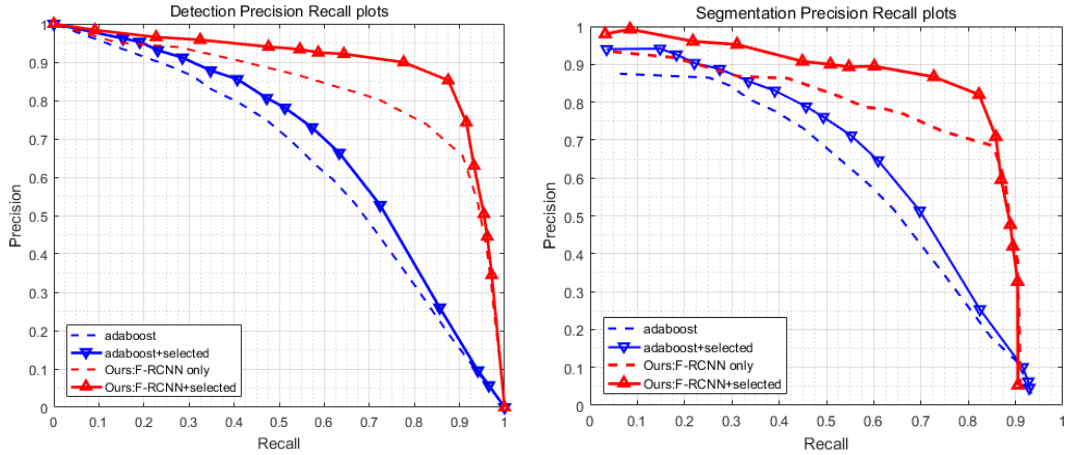

Figure 5. Precision-recall curves of detection (left) and segmentation (right). Our approach always perform better than the baseline of [6].

Table 2. The quantitative evaluation results of detection and segmentation. The best two results are shown in red and blue fronts.

method	detection		segmentation	
	mAP (%)	IoU (%)	mAP (%)	IoU(%)
Adaboost	63.4	56.1	55.4	47.8
Adaboost + selected	67.9	62.3	59.2	55.6
Faster Rcnn	83.4	75.6	70.0	65.5
Faster Rcnn + selected	89.2	82.0	78.2	75.5

4. CONCLUSION

In this paper, we present a novel approach to reconstruct synapses based on deep learning. Our strategy is to utilize Faster R-CNN to locate the regions of synapses, and then employ context cues to reduce false positives. Subsequently, morphology method and fitting function are proposed to get the synaptic clefts. At last, we use the dataset consisted of 178 ATUM-SEM serial scans to implement 3D reconstruction of synapses, experimental results demonstrate that our algorithm promotes the precision of detection and guarantees the accuracy of reconstruction.

We adopt deep learning model to detect synapses and achieve a promising result, while the efficiency of traditional segmentation algorithm is still able to be increased. Our next task is to propose deep neural networks to realize both detection and segmentation, which will enhance speed and accuracy for reconstruction algorithm.

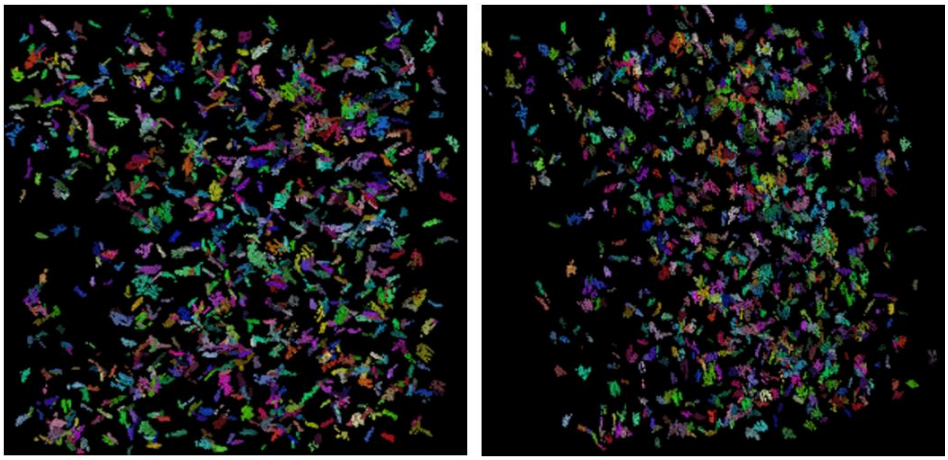

Figure 6. 3D-Retronstruction of synapses on a mouse cortex volume of 15.2 x 17.2 x 8.9μm^3. Left: 3D Visualization shown in front face. Right: 3D Visualization shown in side face.

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