

Segmentation of retinal fluid based on deep learning: application of three-dimensional fully convolutional neural networks in optical coherence tomography images

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Abstract

• **AIM:** To explore a segmentation algorithm based on deep learning to achieve accurate diagnosis and treatment of patients with retinal fluid.

• **METHODS:** A two-dimensional (2D) fully convolutional network for retinal segmentation was employed. In order to solve the category imbalance in retinal optical coherence tomography (OCT) images, the network parameters and loss function based on the 2D fully convolutional network were modified. For this network, the correlations of corresponding positions among adjacent images in space are ignored. Thus, we proposed a three-dimensional (3D) fully convolutional network for segmentation in the retinal OCT images.

• **RESULTS:** The algorithm was evaluated according to segmentation accuracy, Kappa coefficient, and F₁ score. For the 3D fully convolutional network proposed in this paper, the overall segmentation accuracy rate is 99.56%, Kappa coefficient is 98.47%, and F₁ score of retinal fluid is 95.50%.

• **CONCLUSION:** The OCT image segmentation algorithm based on deep learning is primarily founded on the 2D

convolutional network. The 3D network architecture proposed in this paper reduces the influence of category imbalance, realizes end-to-end segmentation of volume images, and achieves optimal segmentation results. The segmentation maps are practically the same as the manual annotations of doctors, and can provide doctors with more accurate diagnostic data.

• **KEYWORDS:** optical coherence tomography images; fluid segmentation; 2D fully convolutional network; 3D fully convolutional network

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INTRODUCTION

Retinal fluid, including sub-retinal fluid (SRF) and intra-retinal fluid (IRF), is a considerably common retinal ailment secondary to numerous diseases, which may cause severe vision loss. Therefore, a rapid and an accurate comprehensive view of retinal fluid may be of considerable significance in its diagnosis and treatment. Optical coherence tomography (OCT) technology, as a rapidly emerging type of medical imaging technology, offers various advantages and broad application prospects. It uses light instead of ultrasound to generate images. According to the backward ability or retroreflection of weakly coherent light, the biological tissue of different retina depths produces a cross-sectional image with high resolution and gray-light changes^[1]. This is beneficial for clearly visualizing various retinal layers in order to assess and quantify different pathological features of the retina qualitatively.

Presently, intelligent automation in the medical field is mainly used for research on the segmentation of magnetic resonance images and enhancement of retinal blood vessels. Imaging with the OCT is a new technology, and research on retinal OCT images is still in its early stage. In the study of retinal segmentation, semi-automatic methods were first used. For example, Kashani *et al*^[2] employed OCTOR software (Doheny

Eye Institute, Los Angeles, USA) for manual labeling; by manually clicking on the location of the fluid on each slice, Zheng *et al*^[3] obtained the fluid contour according to the algorithm. In order to reduce the workload of doctors, numerous researchers have also proposed automatic methods, such as segmentation methods based on the threshold and graph theories. The threshold-based segmentation algorithm mainly uses the characteristics of OCT images with evident gradient changes. Chen *et al*^[4] used the threshold-based segmentation to mark the retinal pigment epithelial (RPE) layer and determine the candidate region. However, the threshold-based segmentation algorithm requires high image quality; hence, it is not considerably adaptable to datasets with large quality variance among different images. Chen *et al*^[5] proposed the use of the graph search method for fluid segmentation. When macular holes and fluid coexist, the laboratory first removes the hole position; thereafter, the fluid segment is cut using the Adaboost classifier combined with a graph^[6]. Slokom *et al*^[7] and Fernandez^[8] used active contours to outline fluid regions. These traditional algorithms involve large amounts of mathematical calculations and a continuous iterative optimization process. Consequently, these methods will consume considerable amounts of time in actual testing that is not in line with actual application scenario requirements. With the development of deep learning, image features are automatically extracted by means of the convolutional network. It is observed that its effect is far superior than that of traditional algorithms.

In recent years, in the medical imaging field, deep learning methods have also been developed and continually applied. Long *et al*^[9] first proposed a fully convolutional network (FCN) for semantic segmentation, which achieved end-to-end image segmentation; it made pioneering progress in the application of deep learning in image segmentation. As a result, the algorithm quickly gained attention. The FCN has been applied to the segmentation of retinal fluid, and the conditional random field was used to fine-tune segmentation results^[10]. Subsequently, Ronneberger *et al*^[11] and Badrinarayanan *et al*^[12] proposed the U-Net and SegNet architectures, respectively, based on the FCN. The studies^[13-16] applied U-Net to the segmentation of OCT images. It has also been employed in the segmentation of drusen lesions^[13], and the effects of different image annotations on segmentation results have been compared. Moreover, it is reported that U-Net was applied to divide the IRF^[14], employed to segment the retina layers and fluid^[15], and modified the loss function. In another study^[16], two-stage FCNs were proposed based on U-Net. The first FCN was used to extract the retinal area, and the second FCN was used for fluid segmentation combined with the retinal information extracted in the previous stage. Although the retinal segmentation information can

be used to correct fluid segmentation, the network requires separate training at each stage. If retinal segmentation is wrong in the first stage because of large image noise, then the subsequent impact is extremely serious.

The development of deep networks has greatly improved the accuracy of image segmentation. However, based on the review of a substantial amount of literature, it was found that the networks used in each article differed; nevertheless, the reason for the selection of a specific network is not indicated. To resolve this problem, the effects of FCN, SegNet, and U-Net on retinal fluid segmentation are compared, and the appropriate network architecture is determined according to the results. In order to solve the category imbalance problem in retinal OCT images, the network parameters and loss function are modified based on the selected network. Considering that the OCT images are volume data, trend change information exists among adjacent images, and the two-dimensional (2D) fully convolutional network ignores the spatial information. Furthermore, if the network is trained in stages, then it is more difficult to utilize information. In order to solve this problem, the application of three-dimensional (3D) CNN in video segmentation^[17] is exploited. Therefore, we propose the construction of a 3D network structure for flexibly exploring the spatial association information to achieve improved segmentation results. Our research indicates that this present study is the first to utilize the 3D network architecture in the segmentation of retinal OCT images.

SUBJECTS AND METHODS

Ethical Approval The images used in the research were provided by Shanghai General Hospital. It was approved by the Medical Ethics Committee of Shanghai General Hospital Medical Science and was conducted in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants in this study. The labels for the experimental training data were annotated by the hospital's professional ophthalmologists.

Description of Project Objectives The overall process of the algorithm research presented in this paper is illustrated in Figure 1. It includes two stages: neural network training and testing.

The training process is depicted in Figure 1A. The input to the network structure is a set of OCT slice images corresponding to the retinal fundus image. The green line in this image indicates the scanning position of the corresponding OCT slice with a total of 19 scanning lines. However, the bright green line indicates the position of the current scanning line; the corresponding OCT slice is indicated by the blue arrow in the figure. The OCT slice images clearly depict the hierarchical structure of different retina locations. The output of the network structure is a set of manually labeled images.

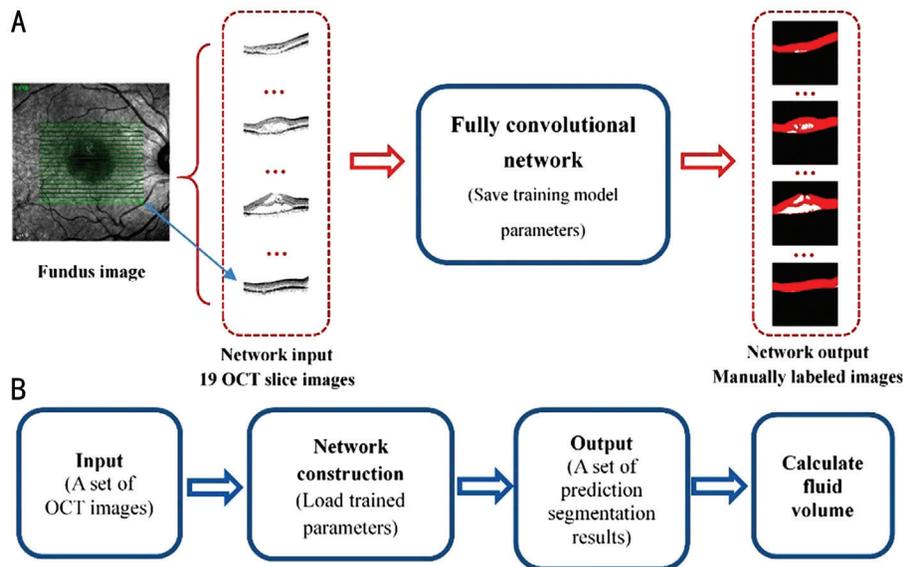


Figure 1 Overall flowchart of algorithm A: Training phase flowchart; B: Test phase flowchart.

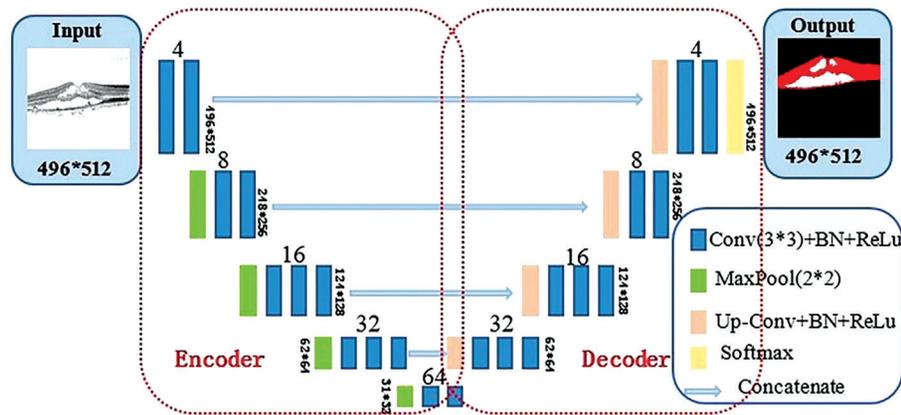


Figure 2 Improved 2D U-Net architecture diagram.

In this study, the label is divided into three categories: the background (black region), the tissue layer between the inner retina layer (ILM) and retinal pigment epithelial (RPE) layer [recorded as the ILM-RPE layer (red region)], and the lesion fluid area (white region). The testing process is illustrated in Figure 1B. The given set of a patient’s OCT images is inputted into the trained network; the network outputs the results after classifying each pixel. The fluid volume is calculated according to the segmentation result.

Retinal Fluid Segmentation Based on Improved 2D U-Net
Improved 2D U-Net After Long *et al*^[9] proposed the FCN, the image segmentation problem at the semantic level was solved, and an end-to-end pixel-to-pixel image segmentation was initially implemented. Since then, researchers have proposed various FCN-based network architectures to achieve more accurate segmentation effects. U-Net for biomedical image segmentation was proposed^[11]. In this study, in order to solve the category imbalance problem in retinal OCT images, an improved U-Net framework is proposed, which is illustrated in Figure 2. Each colored block in the figure represents the

operation performed on the image. The number above the colored blocks indicates the number of convolution kernels in the current layer, whereas the number on the side indicates the size of the current layer output.

Network structure layers Throughout the development of convolutional neural networks, it is evident that most of the proposed networks have been based on the modification of classic network architectures, such as AlexNet^[18], VGG-Net^[19], and GoogLeNet^[20]. The VGG-Net architecture proves that the convolutional layer of a small convolution kernel (with no pooling in the middle) is the same as the receptive field of a large convolution kernel; for example, two 3×3 convolutional layers have the same receptive field as a 5×5 convolutional layers. Moreover, it makes the decision function more discriminative; thus, the number of parameters can be significantly reduced. This method lays a theoretical foundation for the current network frame convolution kernel-size setting. Therefore, the basic modules of the three networks implemented in this study were constructed using the VGG-Net framework.

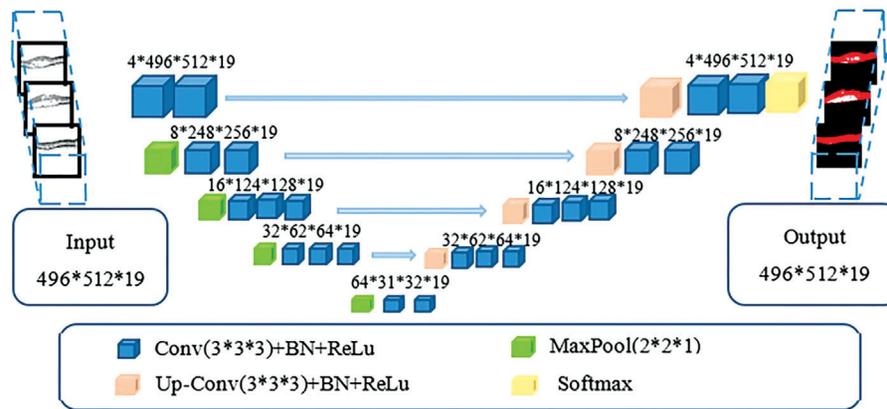


Figure 3 Improved 3D U-Net architecture.

Furthermore, because the deep neural network training process is prone to overfitting, the U-Net convolution block originally proposed in only uses the convolution (Conv)+ReLU operation and does not consider the overfitting phenomenon^[11]. Through the continuous innovations introduced by research scholars, it has been proposed that the aforementioned problem be solved by data augmentation or changing the network structure, such as increasing the regular term, dropout layer^[21], or batch normalization (BN) layer^[22]. The BN layer can improve the network gradient, considerably improve the training speed, and cause the training result to converge rapidly. Moreover, the addition of the BN layer can enable the network to reduce the use of the dropout layer and regular term as well as improve the network generalization ability. Therefore, each convolution block presented in this paper uses a combination of Conv+BN+ReLU.

Loss function An experimental comparison demonstrates that the weighted loss function can make the seven-layer retinal boundary segmentation more accurate and compensate for the imbalance between the background and other categories^[15]. In order to achieve the research objectives of this study, it is not necessary to stratify the retina; however, serious imbalances exist between the background, ILM-RPE layer, and fluid. The background pixels have the greatest influence and major contribution to the loss, such as leading the direction of the gradient update and masking important information.

Most pixels are simple and easy to divide; however, the characteristic information of pixels that are difficult to classify (such as edge pixels) cannot be fully learned. Therefore, the easy-to-classify pixels have a major contribution to the loss and dominate the gradient update direction. In order to solve this problem, the focal loss is proposed by Lin *et al*^[23] that involves solving the problem of unbalanced distribution in the target detection. Combining the ideas of previous two studies^[15,23], we propose an improved loss function, which is more suitable for network training of data sets in this paper.

Retinal Fluid Segmentation Based on Improved 3D U-Net

Because the 2D FCNs can only consider the neighborhood correlation of the image itself, the correlation of the spatial positions among images is ignored, and the OCT images consist of volume data with strong correlations among adjacent images. In actual cases, when the fluid in a single OCT image cannot be accurately determined, it is necessary for the ophthalmologist to combine the features of adjacent OCT images in order to perform segmentation annotation. Therefore, to consider the correlations among adjacent images, we propose the use of improved 3D U-Net, which is illustrated in Figure 3.

As illustrated in Figure 3, the entire network architecture is similar to that depicted in Figure 2, except that the input and output are changed from a 2D image to a volume image, and all convolution kernels in the network also become 3D structures. The numbers in the figure indicate the output shape of the current layer. For example, the input size is $496 \times 512 \times 19$, that is, 19 OCT scans of B-scan size 496×512 . The size $4 \times 496 \times 512 \times 19$ indicates that the number of convolution kernels is four, and the feature map shape following convolution is $496 \times 512 \times 19$.

In the experiment, a convolution kernel size of $3 \times 3 \times 3$ is used in the convolutional layer; this means that the single image is internally 3×3 convoluted, and spatial convolution is performed directly on three adjacent images. Moreover, the zero-padding operation is used. The ReLU activation function continues to be used in the hidden layer for nonlinear transformation. Finally, for multi-classification probability prediction, the softmax function is selected by the output layer activation function. Furthermore, in order to reduce overfitting, the BN layer is used in each coding or decoding block.

The pooling layer adopts maximum pooling; its convolution kernel size is $2 \times 2 \times 1$. This means that 2×2 maximum pooling is used in the single image, and the pooling operation is not performed between adjacent images in the space, which can consider additional neighborhood relationships among images.

RESULTS

Dataset Dataset size: There were 75 OCT volumes from 42 patients; each volume has 19 OCT scans of B-scan size 496×512 (a total of 1425 B-scans). The ratio of training set (%) to test set (%) is 70:30. The training set has 53 OCT volumes (1007 B-scans) from 31 patients. The test set has 22 OCT volumes (418 B-scans) from 20 patients.

Because the training dataset is limited, and fluid distribution is not balanced, a data augmentation strategy is applied to expand the training dataset for small samples to improve the robustness of the network. The following data augmentations are randomly applied to small samples for training: 1) Randomly rotated between 0 and 15°; 2) Randomly shifted horizontally within 20% of the image width; 3) Randomly shifted vertically within 20% of the image height; 4) Randomly sheared between 0 and 0.2 scale; 5) Randomly flipped.

Eventually, the training set was extended to 153 OCT volumes (2907 B-scans).

Experimental platform: The experiment was run on a workstation with CPU Intel Core i7-7700K@4.20Hz quad-core, 64-GB memory, 1024-GB disk, and two GPUs Nvidia GeForce GTX 1080 (each 8 GB). The experimental environment is the Ubuntu system.

Result Evaluation Metrics The network performance of the results of training and test datasets is evaluated. For the training dataset, the segmentation effect and network convergence are observed according to the accuracy rate of the dataset and loss trend during the training process. For the test dataset, the segmentation accuracy, F₁ score, and Kappa coefficient are computed according to the prediction results of this dataset in order to analyze the network generalization ability. The definitions of each evaluation metric are as follows: 1) Accuracy: This reflects the network ability to determine the entire dataset. The overall accuracy and the accuracy of each class are analyzed. 2) F₁ score^[24]: The harmonic mean of precision and recall, also known as the Dice coefficient^[25]. 3) Kappa coefficient^[26]: Kappa is a statistic that measures inter-rater agreement for qualitative (categorical) items. It is generally assumed to be a more robust measure than a simple percentage agreement calculation because it considers the possibility of the agreement occurring by chance.

Comparison and Analysis

Comparison results between 2D FCN (FCN8/FCN16), SegNet, and U-Net Figure 4 illustrates the accuracy and loss curves for the training dataset of all 2D convolutional networks. The abscissa is the number of iterations, which is recorded when the entire dataset is trained once. The ordinate is the accuracy (or loss). It should be noted that the four networks in the figure do not have a BN layer, and the result is obtained from the network trained with the cross entropy

Table 1 Results of evaluation metrics of all classes in test set

Metrics	FCN8	FCN16	SegNet	U-Net
ACC _{overall}	0.9854	0.9828	0.9856	0.9908
Kappa	0.9507	0.9411	0.9515	0.9692

Table 2 Results of evaluation metrics of each class in test set

Metrics	Labels ^a	FCN8	FCN16	SegNet	U-Net
ACC	0	0.9891	0.9863	0.9891	0.9934
	1	0.9858	0.9833	0.9858	0.9910
	2	0.9959	0.9960	0.9962	0.9973
F ₁ score	0	0.9934	0.9917	0.9934	0.9960
	1	0.9578	0.9492	0.9581	0.9731
	2	0.7903	0.8074	0.8135	0.8785

^aLabel 0 indicates background, label 1 indicates ILM-RPE layer, and label 2 indicates fluid area.

Table 3 Scores of evaluation metrics in test set

Metrics	2D U-Net	Improved 2D U-Net	Improved 3D U-Net
ACC _{overall}	0.9908	0.9917	0.9956
Kappa	0.9692	0.9725	0.9847

as a loss function. In Figure 4A, it can be observed that the U-Net accuracy curve is significantly higher than those of the other networks. Moreover, the U-Net loss curve in Figure 4B is closest to zero and decreases the fastest; this illustrates that it converges most easily. Based on the comparison of training results, the U-Net is clearly more suitable for achieving the research objective.

In order to prove that U-Net provides superior generalization ability, each network is evaluated on the test dataset; Tables 1 and 2 summarize the test results. The list in Table 1 indicates the scores of the evaluation metrics of the overall classes of each network on the test dataset. It can be observed that the ACC_{overall} and kappa values between FCN8, FCN16, and SegNet exhibit slight differences; U-Net is observed to be significantly superior to these other networks. The list in Table 2 provides the scores of each class of the evaluation metrics on the test dataset; U-Net also achieves the best results in all metrics in each class. Accordingly, based on the above results, U-Net is finally selected.

Comparison Results between Improved 3D U-Net, Improved 2D U-Net, and 2D U-Net

Table 3 summarizes the scores of the overall evaluation metrics of the three networks on the test dataset. According to the list, improved 3D U-Net achieves superior results for all metrics; this indicates that the proposed 3D U-Net exhibits the highest segmentation accuracy. Table 4 lists the evaluation scores of each class of the three networks on the test dataset. Because our focus is on the retinal fluid, it can be observed in the list that the proposed 3D U-Net achieves the best performance in all metrics for the retinal fluid segmentation (label 2).

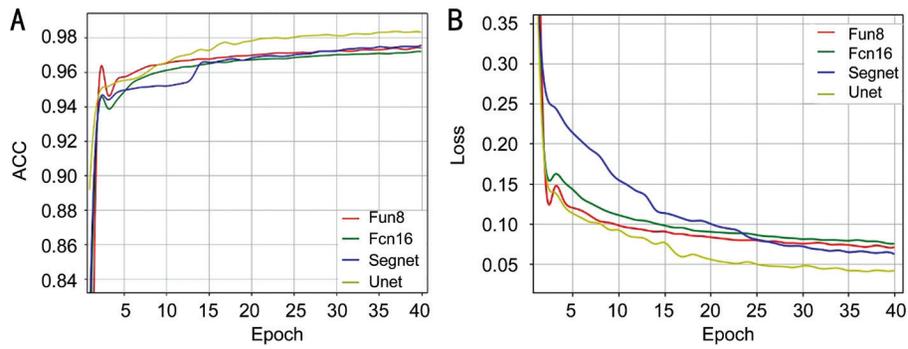


Figure 4 2D FCN training results A: Training accuracy curve; B: Training loss curve.

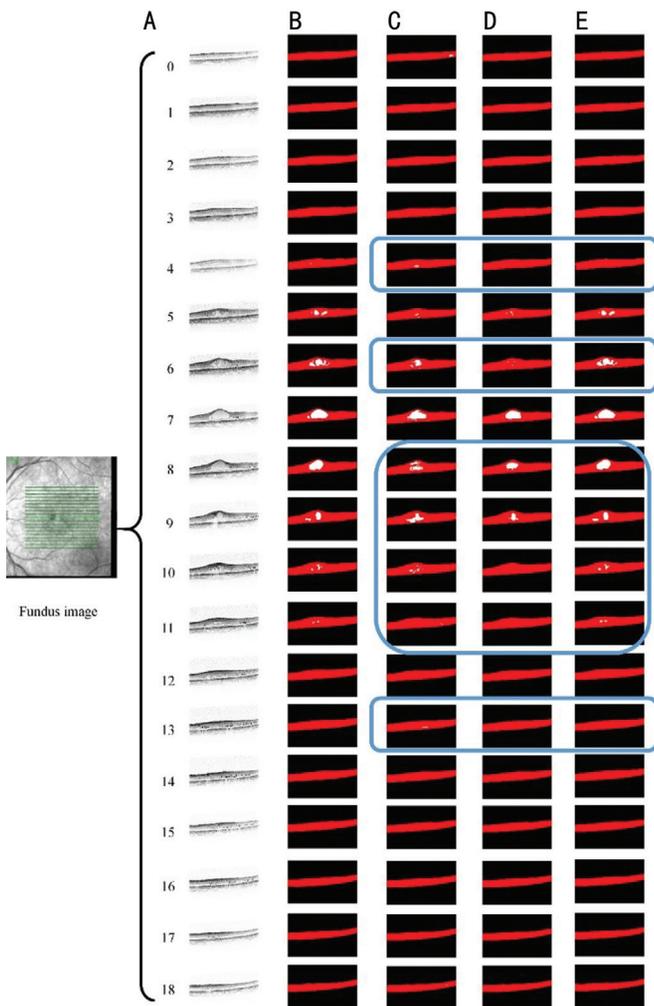


Figure 5 Segmentation results of OCT images with IRF A: 19 OCT images; B: Manually labelled annotations of ophthalmologists; C: Results of original 2D U-Net; D: Results of the improved 2D U-Net; E: Results of the improved 3D U-Net.

In order to understand the segmentation effect intuitively, the segmentation results are used as example. Figure 5 displays the results of a set of OCT images with the IRF. Figure 5A presents 19 OCT images, whereas Figure 5B provides manually labeled annotations of ophthalmologists. Figure 5C-5E illustrate the results of the original 2D U-Net, improved 2D U-Net, and improved 3D U-Net, respectively. In the figure, it can be observed from the images enclosed in blue that the original 2D

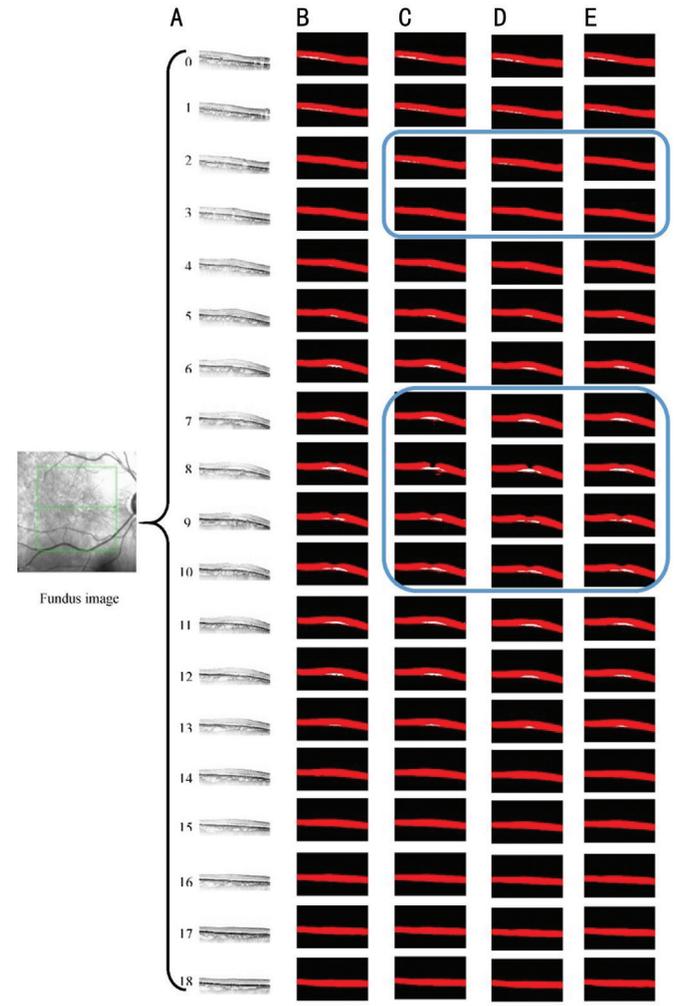


Figure 6 Segmentation results of OCT images with SRF A: 19 OCT images; B: Manually labelled annotations of ophthalmologists; C: Results of original 2D U-Net; D: Results of improved 2D U-Net; E: Results of improved 3D U-Net.

U-Net and improved 2D U-Net segmentation results contain several errors. Although the proposed 3D U-Net misses certain small areas, it corrects evident errors; visually, there is no significant difference, and the segmentation result is relatively accurate.

Figure 6 illustrates the segmentation results of a set of OCT images containing the SRF. It can be intuitively observed that the overall segmentation results of the proposed 3D U-Net are

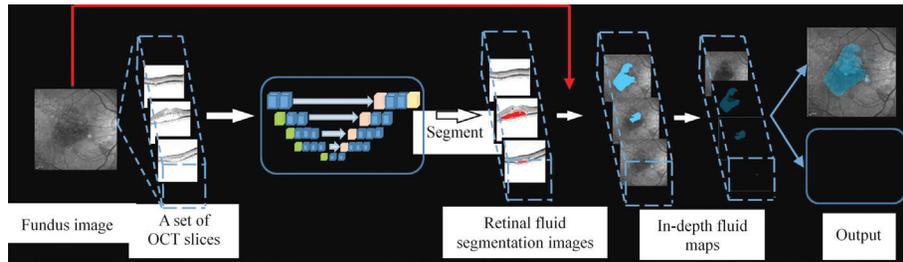


Figure 7 Overall process structure.

Table 4 Scores of evaluation metrics of each class in test set

Metrics	Labels ^a	2D U-Net	Improved 2D U-Net	Improved 3D U-Net
ACC	0	0.9934	0.9938	0.9970
	1	0.9910	0.9918	0.9956
	2	0.9973	0.9980	0.9986
F ₁ score	0	0.9960	0.9962	0.9982
	1	0.9731	0.9758	0.9860
	2	0.8785	0.9109	0.9550

^aLabel 0 indicates background, label 1 indicates ILM-RPE layer, and label 2 indicates fluid area.

practically the same as the manually labeled results. As can be observed from the images enclosed in blue, the segmentation results of 2D U-Net and improved 2D U-Net are evidently misclassified.

Overall Process Framework In order to provide doctors with an improved visual experience, the OCT images of patients are integrated into the original fundus map to illustrate the fluid contour; accordingly, the doctor can view the fluid shape more intuitively. The overall framework of this study based on the proposed 3D U-Net above is illustrated in Figure 7.

DISCUSSION

OCT images have high resolutions, and they distinctly display retinal tissue layers. When retinal fluid is present, the retina shape changes. Accordingly, the analysis of retinal fluid based on OCT images has become one of the most popular methods for clinical diagnosis. However, the OCT technique acquires numerous scanned slice images, and the retinal fluid shape and amount are uncertain. Moreover, it is time-consuming and cumbersome to analyze these images only by visual observation and perform manual segmentation. In order to realize intelligent medicine, deep learning algorithms have been continuously applied. In relation to this, to facilitate the pixel-level segmentation of images, the fully convolutional network^[9] has been proposed; accordingly, such a network has become a potential solution to problems involving medical image segmentation^[10,13-15].

In this study, the proposed 3D U-Net framework, which is found to be superior to other methods of comparison, achieves a 99.56% accuracy; the Kappa coefficient and F₁ score of retinal fluid achieved 98.47% and 95.50%, respectively. The segmentation results of our proposed algorithm are considerably similar to the annotations of professional doctors.

All of the foregoing demonstrate that the proposed algorithm has accurate segmentation ability; it is an effective and significant guide in practical applications.

In this study, although the input images are decentralized, they contain substantial amounts of speckle noise. In fact, the noise characteristics are considerably different from the target features; hence, whether noise improves or reduces performance is uncertain. To remove speckle noise, different algorithms (such as non-local mean filtering^[27] and algorithms based on sparsity de-noising^[28]) will be tested, and the effect of noise on segmentation results through experiments will be compared. The current training dataset is relatively small, and the types of retinal fluid images are limited. If the images contain several complicated diseases, then it is necessary to improve the segmentation ability of the network. If significant amounts of data can be collected in the future, the impact of this problem can be reduced. Different types of retinal fluid can be classified such that the network can distinguish the type of retinal fluid and calculate the corresponding volume; as a result, this will make it possible to provide more detailed information to the doctor. As for the problem that the medical images are relatively few, adversarial networks may be a solution^[29]. In the future work, adversarial networks will be tested based on the framework proposed in this paper. It is anticipated that the segmentation performance of the network can be improved even in the case of fewer samples.

The novel method can demonstrate retinal fluid and calculate the volume of them, which can help ophthalmologists comprehensively grasp the extent of a patient’s macular edema. At present, central retinal thickness (CRT) is usually used to evaluate the macular anatomy in patients with fluid before and after treatment^[30]. However, whereas CRT is a 2D

index, the volume of fluid is 3D. As a result, although CRT is somewhat useful in gauging the extent of retinal fluid, it has limited utility in the overall assessment of the resolution of fluid. Under these circumstances, OCT images have the potential to provide a more comprehensive clinical picture of a patient's macular edema. More specifically, identification of the volume of IRF and SRF allows ophthalmologists to intuitively and meaningfully analyze the extent of edema and its resolution over time^[31]. For many patients, it is difficult to detect changes in the location and volume of edema without objective data. Therefore, we believe it is necessary to use such data to gauge the regression of edema, which will contribute to the adjustment of follow-up treatment measures.

In this study, a segmentation algorithm framework based on 3D neural networks is proposed; the framework is aimed at resolving the problem of retinal fluid segmentation in retinal OCT images. Compared with other methods, the proposed 3D U-Net network is more aligned with the human working mode under real conditions. The network performs fluid segmentation by combining the spatial temporal correlations among images; thereby, more reasonable results are obtained. Moreover, the evaluation coefficients demonstrate that the proposed 3D U-Net architecture exhibits superior performance, and the fluid segmentation accuracy is higher. It is illustrated that the shape, distribution and the volume calculation of the retinal fluid can provide doctors with a more intuitive visual experience, which is highly significant in monitoring disease development and drug efficacy tracking.

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