Ischemic Stroke Lesion Prediction in CT Perfusion Scans Using Multiple Parallel U-Nets Following by a Pixel-level Classifier

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***Abstract*—It is critical to know what brain regions are affected by an ischemic stroke, as this enables doctors to make more effective decisions about stroke patient therapy. These regions are often identified by segmenting computed tomography perfusion (CTP) images. Previously, this task has been done manually by an expert. However, manual segmentation is an extremely tedious and time-consuming process, that is not suitable for ischemic stroke lesion segmentation as it is highly time sensitive. In addition, these approaches require an expert to do the segmentation task, who may not be available and are prone to errors. Several automatic medical image analysis methods have been proposed for ischemic stroke lesion segmentation. These approaches, typically, use hand-crafted features that are predefined to represent the input data. However, because of the irregular and physiologically shapes, ischemic stroke lesions cannot be properly predicted, in an automatic way, using simple predefined features. In this work, we propose an automatic prediction algorithm that learns an effective model for segmenting the ischemic stroke lesion. This learned model first uses four 2D U-Nets to, separately, extract valuable information about the location of the stroke lesion from four CTP maps (CBV, CBF, MTT, Tmax). The model then combines the probability maps extracted by the U-Nets, to decide whether the pixels are either lesion or healthy tissues. This approach uses information about each pixel, as well as its neighborhood, to learn the stroke lesion, despite their varying shapes. The segmentation performance is evaluated using dice similarity coefficient (DSC), volume similarity (VS), and Recall. We have used this new algorithm on ISLES 2018 challenge dataset and found that our approach achieved results that are better than state-of-the-art approaches.**

***Index Terms*—Ischemic stroke, prediction, CT perfusion, Parallel U-Nets, Pixel-level classifier**

I. Introduction

One in six people worldwide will have a stroke in their lifetime. A total of 15 million people worldwide suffer a stroke each year and 5.8 million people die from it [1]. There are two main types of stroke: ischemic (clot and permanent occlusion of a blood vessel), and hemorrhagic (rupture or break of a blood vessel). Overall 80-85% of all strokes are ischemic stroke. Ischemic stroke occurs when there is a reduction in cerebral blood flow due to arterial occlusion [2]–[4]. Decreased cerebral blood flow, if it persists long enough, will result in irreversible infarction of brain tissue [5]–[7]. To halt infarct growth, the most effective therapy is the rapid recanalization of the occluded artery and reperfusion of ischemic brain tissue [8]. However, reperfusion must occur at a time point when there is still brain to salvage. This has led to the development of brain imaging methods, most notably CT perfusion (CTP), to identify the relative amounts of brain tissue that is irreversibly (ischemic core) and salvageable tissue at risk (penumbra). Recent clinical trials have shown that stroke patients that benefit most from reperfusion therapies are those with a large mismatch between the size of salvageable penumbra and core on CT perfusion [9]–[11].

CT perfusion is by far the most widely adopted method to identify ischemic stroke patients with salvageable penumbra. CT perfusion is a kinetic tracer technique which involves continuous imaging of a slab of brain tissue during the administration of a bolus of iodinated contrast agent. The first-pass arrival of contrast agent in the tissue results in a change in signal intensity that is used to calculate time-density curves for each voxel [12]. These time density curves are then processed with a temporal deconvolution algorithm and a known arterial input function to generate images of Cerebral Blood Volume (CBV), Cerebral Blood Flow (CBF), Mean Transit Time (MTT), and Time to peak (Tmax) [13]. In addition, CTP has some advantages compared to other medical imaging modalities, such as MRI, because of its lower cost, increased availability, and effectiveness [12], [14].

There are crucial challenges in the ischemic stroke lesion prediction, such as the lack of consistent location and appearance of the lesion and the varying size and shape of the lesion over time [15]. To address these challenges, several methods have been proposed in the past to detect ischemic stroke lesion. These methods can be classified into two types, manual, and automated [16]–[19]. Since manual approaches are an extremely tedious and time-consuming process, they are not suitable for ischemic stroke lesion segmentation where the treatment is highly time sensitive. In the previous research, several automatic medical image analysis methods and mathematical models have been proposed for ischemic stroke lesion segmentation [20]. These approaches typically used hand-crafted features that are predefined to represent the data. Because of the irregular and physiologically shapes of stroke lesion, they cannot be properly used to perform automatic segmentation.

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Neural networks, especially convolutional neural networks (CNN), have become a promising and popular technique to tackle image processing and computer vision tasks [21], [22]. Specifically, it has been used extensively in medical imaging applications–segmentation and classification [23]–[25]. One of the most popular network is U-Net which is a special case of a standard CNN [26], and have been used successfully for medical image segmentation tasks [15], [27].

In this paper, we propose a novel deep learning algorithm capable of processing pretreatment CT perfusion images in order to improve the identification of ischemic stroke lesion. The proposed algorithm consists of multiple parallel U-Nets followed by a pixel-level classifier. The main idea behind this algorithm is to combine valuable information extracted by the parallel U-Nets from CTP maps to achieve a higher probability of stroke lesion prediction. The proposed algorithm is evaluated against the ISLES 2018 challenge dataset [28] and compares favorably to the winners of the challenge [29], [30].

The remainder of the paper is organized as follows: First, a brief review of image analysis for ischemic stroke lesion prediction is presented. Then the proposed stroke lesion prediction model is explained. In the third section, the experiments and results are presented. Finally, we conclude by presenting the pros and cons of our approach.

II. Image Analysis for Ischemic Stroke Identification

Today, determining which parts of the brain have already been damaged is done by simple thresholding the CTP images [31]. To assist clinicians in making rapid treatment decisions in acute stroke, a commercial software has been developed to process the CT perfusion source data to generate the CBF, CBV and delay time images and quickly estimate core and penumbral sizes [32]. This software uses a simple threshold approach to identify patients with a treatable penumbral pattern. Significantly hypo-perfused tissue volume is defined when Tmax $>$6 seconds or Delay Time $>$3 seconds. Infarct core is defined by using a double threshold of Tmax $>$6 seconds (or Delay Time $>$3 seconds) with a relative (to the contralateral hemisphere) CBF of $<$30%) [33]. These definitions of core and penumbra have been validated in stroke trials to identify patients that benefit from therapy. However, there remains significant variation in the predicted core on baseline CT perfusion and final infarct size estimated using DW-MRI imaging [34].

Such approaches have the drawback of only modeling a single univariate threshold (hard decision border) between affected and non-affected tissue. Since ischemic stroke lesions are varying widely over time, these simple algorithms are not suitable for accurately predicting the regions at risk. Some previous works have attempted to overcome these limitations by considering flexible thresholds [35], [36]. However, this problem cannot accurately be solved because they cannot make a precise prediction of the stroke lesion that is varying quickly after stroke onset.

Until the introduction of deep learning networks, almost all medical imaging tasks, e.g., classification, regression, and segmentation have been performed using hand-crafted features. In addition, some previous studies have used transformation techniques, such as nonlinear kernel methods to transform the input data representation to another representation or feature space that is hopefully more linearly separable. These algorithms simplify high-level tasks such as classification and regression. Due to the large variety of shapes and boundary of stroke lesions, such approaches cannot effectively cope with the ischemic stroke segmentation problems.

As opposed to hand crafted-features, one can exploit deep neural networks to learn high-level features and do the high-level task (classification or regression) both at once. Such deep neural networks are capable to learn sufficiently complex models without having to tune the right parameterization by hand.

The most popular deep neural network for medical imaging task is a convolutional neural network (CNN). Of many deep neural network architectures proposed in the literature, the U-Net architecture has successfully been used to segment and classify medical images [26].

A. Deep Neural Networks for Stroke Lesion Prediction

Recently deep neural networks have (DNN) become one of the most popular methods in the fields of computer vision and image processing, specifically medical image processing [37]. The recent availability of graphics processing unit (GPU), which allows fast training processes, as well as large annotated training sets have enabled the development of computer vision applications based on deep learning algorithms that are considerably more precise than traditional machine learning methods.

For ischemic stroke lesions prediction problem, there are some critical challenges that must be addressed. These main challenges here are:

1) The large variety of shapes of the outer boundaries of the stroke lesions;
2) Widely varying size and shape over time, which make it difficult to predict the appearance of the lesion;
3) The limited amount of data to properly train a prediction model.

DNN is a promising technique as it possesses several advantages over traditional machine learning methods that ischemic stroke lesion segmentation challenges require. These advantages are [38]:

1) By using high-level classification objective functions, features of different abstraction levels are automatically learned;
2) One can design methodologies end-to-end, where the system can learn how to extract image features, detect them, and then segment visual objects that can be classified using a unified classification model;
3) DNN largely saves researchers' time by automating this process. Also, it is capable to use the complex feature patterns to perform prediction;

4) DNN can learn the feature hierarchy in a layer-by-layer manner, by first learning the low-level features and then recursively building more comprehensive high-level features based on the previously learned low-level features.

Since DNNs require to estimate an extremely high number of parameters during the training process, the most challenging problem is to find a large set of annotated training images. This challenge particularly occurs in the medical image analysis (MIA) applications because of the limited availability of large annotated training set. To address this issue, U-Net was specifically designed to be trained using a small number of training data.

B. U-Net Architecture

U-Net architecture has been proposed by Ronneberger *et al.* [26] and became very popular in medical image processing community because of its versatility and its ease of training [15], [27]. It is capable of producing semantic segmentation via a fully-convolutional CNN that additionally incorporates skip connections between the context encoding and the refining decoding path for each scale level [39].

One can see in Figure 1 a diagram of the U-Net architecture. The network is composed of two main sections: an encoding section (left side) and a decoding section (right side). The encoding section acts like a typical CNN architecture. It consists of a repeated application of 3×3 convolutions (unpadded convolutions) filters followed by a ReLU function unit and a 2×2 max pooling operation which performs a factor 2 for down sampling. Feature channels are doubled at each down sampling step. In the decoding section, every step consists of up sampling the feature map which is followed by a 2×2 convolution (up-convolution) which halves the number of feature channels, a concatenation with the correspondingly cropped feature map from the contracting section, and two 3×3 convolutions, each followed by a ReLU. Due to the loss of pixel border at every convolution, cropping is necessary. At the last layer, a 1×1 convolution is used to map each 64-component feature vector to the desired number of classes. In total the network has 23 convolutional layers in our implementation [26].

III. Proposed Algorithm

In this implementation, a prediction section, which is composed of two sub-sections, is proposed to segment the ischemic stroke lesion. As shown in Figure 2, the first part of the model consists of four U-Nets, processing data in a parallel manner, and the second one is a pixel-level classifier.

For the first part, we have tried both a 3D U-Net and multiple 2D U-Nets and found that the performance of the 2D U-Nets was better. In 3D U-Net model, we have trained the model by 3D inputs that are constructed by four CTP maps. For the 2D U-Nets, they are separately trained using different CTP maps (CBV, CBF, Tmax, and MTT). In both networks, brain tissue density extracted from CT scans is used as an additional feature to train the model. The input size of the

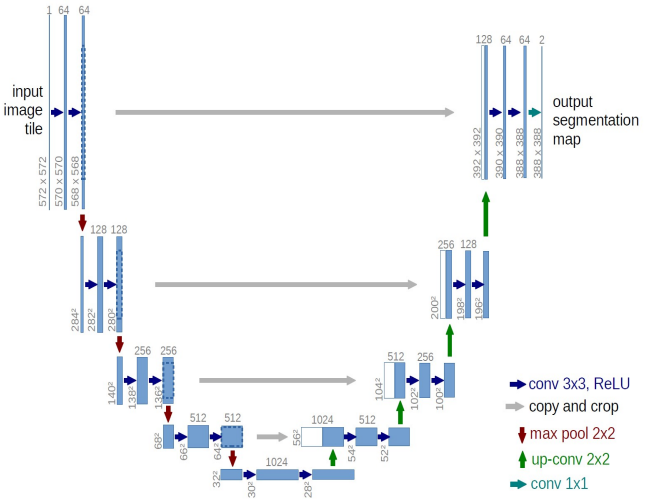

Fig. 1. U-Net architecture [26].

3D model is (5×256×256) which include four CTP map and brain tissue density. In the 2D model, each U-Net input is a two-channel 2D image that is produced by stacking brain tissue density of that slice with its corresponding CTP map.

It is true that all the CTP maps contain information as for the ischemic stroke lesion volume and appearance, but the value of their information is not equal. Hence, we have trained a prediction model that separately uses CTP maps to extract information from each pixel using a U-Nets. Then a classifier combines the extracted information from the CTP maps, according to their contributions, to determine the pixels labels (Lesion or Healthy). The contributions of the CTP maps have been determined by the value of the information they carry on the appearance of the stroke lesion. We have trained various types of classifiers for the classification task: voting, simple weighted averaging, and logistic regression.

The whole segmentation algorithm is divided into three main steps are: preprocessing and image augmentation, parallel U-Nets, and pixel-level classifier.

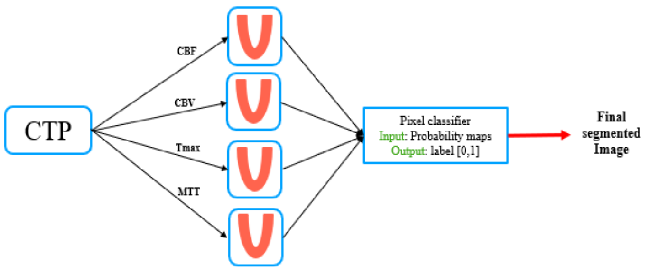

Fig. 2. Stroke lesion prediction model pipeline.

A. Preprocessing and Data Augmentation

Before training the model, images are preprocessed by removing some outliers and normalizing the remaining images

to make them comparable. Since the number of patients in the dataset is limited to train the model in an appropriate way and to avoid overfitting, we have augmented the dataset using some well-known techniques.

When a model tries to learn frequent features (patterns that occur frequently) which may not be useful, over-fitting usually happens. To tackle this problem, one can add zero-mean Gaussian noise to images. By adding Gaussian noise, one can effectively distort high-frequency features and improve the learning capability of the neural net. Image translation consists of moving the image along both X and Y directions or just one of them. By doing so, the model is forced to look everywhere. In order to increase the dataset, we have created new images by randomly rotating them by [-20∠, 20∠], translating them by [-15%, 15%] of the size, scaling them by [0.8, 1.2], and adding Gaussian noise with zero mean.

B. Parallel U-Nets Model

Figure 2 shows how we are using U-Nets in a parallel way. Instead of using 3D U-Net that has been used in most of the previous segmentation works, we have used four 2D U-Nets. Each U-Net input is a two-channel image comprising a CTP map over the same size image which is the brain tissue density corresponding with that slice. The size of the input images is (2××256×256).

The softDice loss function has been used for training the U-Nets score and is defined by:

$$SoftDice(A, B) = \frac{2 \times \sum_i (A_i, B_i) + 1}{\sum_i (A_i A_i + B_i B_i) + 1} \qquad (1)$$

where for all voxel positions i in a segmentation A with ground truth B and a smoothing constant which is 1.

C. Pixel-level Classification

The main goal of this step is to investigate the influence of combining the information generated from the U-Nets from different CTP maps. In addition, the idea behind this step is that by considering the different values of the information that is carried out by different CTP maps and combining them based on their contributions, one can achieve better results in stroke lesion prediction. We have investigated various approaches to tackle the classification task. The tested approaches were in a wide range in terms of complexity, from simple voting to high-level classifiers.

The outputs of the U-Nets are four probability maps in which the value of each pixel indicates the probability of being a stroke lesion. Hence, to classify each pixel according to the two lesion and non-lesion classes, we use these maps as the attributes. The following paragraphs detail the pixel-level classification problem.

- First, the probability maps extracted by U-Nets, have converted to the binary masks by using thresholding (the threshold have been determined by experiment and error and it was 0.65). Then a simple voting method has been used to classify each pixel. In this classification method, we classify a pixel as a lesion if two or more masks say that the pixel is a lesion;
- In the second, the segmentation accuracy of each U-Net has been used as a criterion to determine the contribution of the output of that U-Net in the pixel-level classification task. In other words, first, all U-Nets have been trained by the same training set and then tested by a same test set. For each U-Net, the accuracy of the segmentation task has been computed using the Dice score. We have computed the value of each U-Net output contribution by:

$$W_i = \frac{A_i}{\sum_i A_i} \qquad (2)$$

where A_i is the accuracy of i^{th} U-Net, and W_i is the contribution weight of the output of i^{th} U-Net in the pixel-level classification.
Finally, a weighted average of four probabilities, corresponding to four U-Nets, is calculated in which the weights are determined based on equation (2). Using the following equation:

$$P = \sum_{i=1}^{4} W_i \times p_i \qquad (3)$$

one can compute the weighted average, where i is the index of the U-Nets, w_i is the contribution weight of the output of the i^{th} U-Net, and pi is the probability of being a lesion based on the output of the i^{th} U-Net. In the end, the average value P is converted to a binary value by comparing its value to a 0.55 threshold. This threshold was chosen experimentally.
- We believe that there is valuable information about the link between the central pixel label and each pixel in its neighborhood. Therefore, in this model, to predict the label of each pixel, four corresponding N by N neighborhoods, centered by that pixel in four outputs of four U-Nets, are considered as features. As shown in Figure 3, one can concatenate these neighborhoods to create a vector with length (4×N×N). Then this feature vector is used as the input of a logistic regression model that is used as a pixel-level classifier. The idea behind this method is that by using the valuable information that is hidden in the neighborhood of each pixel, one can achieve a smoother and homogeneous predicted lesion, thereby increasing the final segmentation performance. We have tried different neighborhood size (N=3, 5, 7, 9, 11, 13) but the best results have been achieved with N=9.

D. Implementation Details

To implement the U-Nets, we have used Keras deep learning library, on a PC which had GeForce GTX 780 GPU and 16 GB RAM. To improve the training process, the dice score has been monitored on the validation set, after every training epoch (see Figure 4 shows the variation of the dice score of MTT U-Net for every epoch). If we had not seen any improvement after 15 epochs, the learning rate was reduced to achieve better

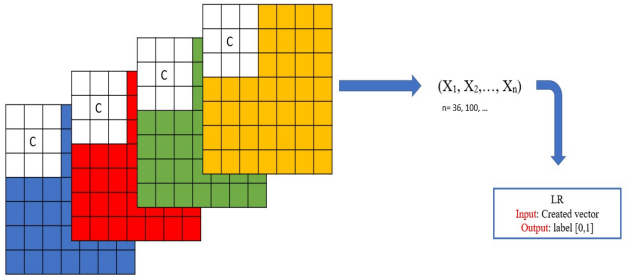

Fig. 3. Input/output of logistic regression model.

validation accuracy. The batch size of the U-Nets is 32, and the kernel size is 3 by 3. In addition, Adam has been utilized as an optimizer in this work (which is introduced by Diederik Kingman and Jimmy Ba [40]).

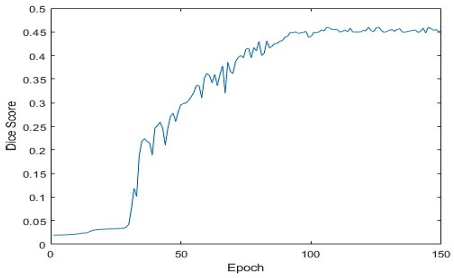

Fig. 4. Variation of the Dice score for every epoch (MTT U-Net).

IV. Experiments and Results

A. Dataset

To evaluate the proposed model, the ISLES challenge 2018 dataset has been used. The dataset consists of CT images, CTP maps, and DWI scans, from acute stroke patients, which are collected from two imaging centers. All the patients have been admitted and scanned (CT and CTP) within 8 hours of stroke onset and underwent an DW-MRI within 3 hours after CTP scan. CTP maps are derived from the raw CT data for clinical interpretation. Infarcted brain tissue can be identified as hyperintense regions of the DWI trace images (DWI maps). The ground-truth segmentation maps are manually drawn on those scans by medical experts.

The scans had varying depth in the axial dimension, ranging from 2 to 22 slices. Because CTP scans were acquired as slabs covering sparse areas (5mm axial spacing) with stroke lesion in the brain. The size of each slice is (256×256) pixels. The training set consists of 63 patients and 94 scans, and the test set is composed of 40 patients with 62 scans. Some of the patients have two slabs to cover the whole stroke lesion.

B. Evaluation and Metrics

In order to validate the proposed model by using 10-fold cross-validation, we made sure that there was no overlap between patients folds. In addition, the scans of the patients who have multiple slobs existed only in the same fold. Overfitting of the model has been prevented by training until the validation loss converges and choosing the model with the lowest validation loss. We have used the SoftDice loss function in our experiments (Equation (1)).

The model tested by using patients which have not been used for the training and validation. Therefore, evaluation results could not be tuned on the validation loss optimum, making the results more reliable.

In order to accurately evaluate the proposed model, we used a common similarity metrics that test different capabilities of the model. These metrics are:

- Dice similarity coefficient (DSC)

$$DSC = \frac{2TP}{2TP + FP + FN} \tag{4}$$

- Volume similarity (VS)

$$VS = 1 - \frac{|FN - FP|}{2TP + FP + FN} \tag{5}$$

- Sensitivity (Recall)

$$P = \frac{TP}{TP + FN} \tag{6}$$

Since, in some applications, it is crucial that we predict the volume of the stroke lesion in an accurate way, we have evaluated the proposed model performance using VS.

C. Prediction Results

Table I shows the ability of the U-Nets to segment ischemic stroke lesion. The results show the amount of information can be extracted from different CTP maps. As one can see, the accuracy (DSC) of the network which has been trained by using Tmax maps is better than other networks. Therefore, the Tmax map has the greatest contribution to the classification problem. However, if we consider VS as the main criterion for evaluation, Tmax is not the best. In that case, CBV map is the most valuable information about the volume of the stroke lesion.

TABLE I
Ischemic stroke lesion prediction performance of the U-Nets

U-Net Input	Metric		
	DSC	***VS***	***Recall***
CBF	0.30	0.33	0.35
CBV	0.32	0.47	0.38
MTT	0.35	0.46	0.4
Tmax	0.40	0.41	0.41

Table II shows the accuracy of the final prediction of ischemic stroke lesion by using different classifiers. One can see that the accuracy of the logistic regression model is by far the best among the three classifiers. DSC and Recall of the LR model that reported in Table II are related to the (9×9) neighborhood size and VS is related to (11×11) neighborhood size.

Figure 5 shows the effect of changing the size of the neighborhood of each pixel on the final prediction performance. The

TABLE II
THE ACCURACY OF FINAL PREDICTION BASED ON DIFFERENT CLASSIFIERS

Classification Model	Metric		
	DSC	***VS***	***Recall***
Voting	0.41	0.50	0.44
Weighted Average	0.57	0.66	0.56
Logistic Regression	0.71	0.82	0.73

results show that the best DSC and Recall is related to kernel size (9×9). In addition, the best VS has been obtained using an (11×11) neighborhood.

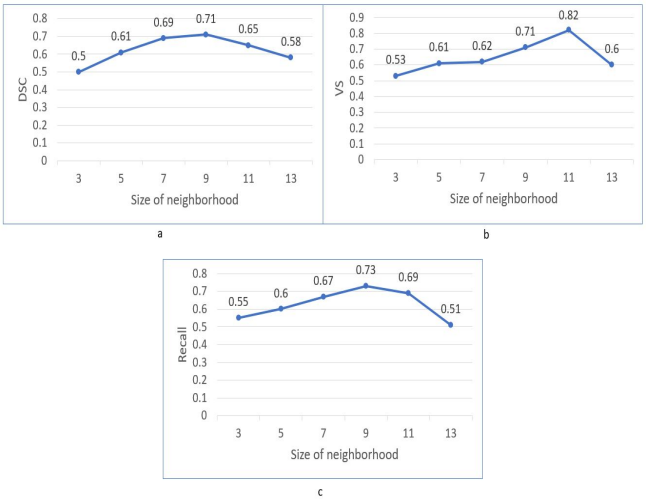

Fig. 5. a) DSC b) VS, and c) Recall of the LR model based on different size of neighborhood.

One can see in Figure 6 the ischemic stroke lesion segmentation, for one patient. In this figure, the first column shows CTP maps by using different color maps (just for clarity). The middle column is the segmentation results of each U-Net, separately. The third column shows the final segmentation results based on three pixel-level classifiers. In these images, the red lines are prediction area and white area is the ground truth. As one can see in this Figure 5, the best prediction is obtained by the LR model (with neighborhood size 9×9).

D. Compassion with Other Algorithms

Table III shows the results of our proposed algorithm in compared to the best results that have been achieved during the ISLES challenge 2018 competition [29], [30], [41]. As one can see in most cases our results are significantly better.

V. CONCLUSION

In this paper, we proposed a prediction model for ischemic stroke lesion identification using CTP scans. The whole prediction algorithm consists of three main steps: preprocessing and image augmentation, parallel U-Nets, and pixel-level classifier. For preprocessing, outliers were removed, and the remaining scans were normalized. Then, the preprocessed dataset

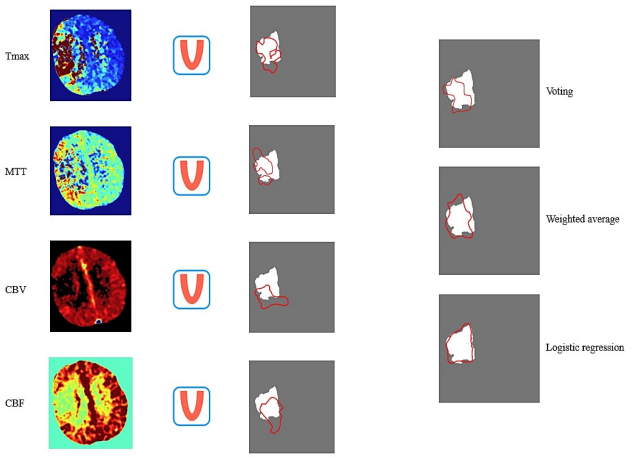

Fig. 6. The first column is color maps of CTP parameters. The second column is the segmentation result of each U-Net. The third column is the final segmentation results based on three classifiers. Red lines are predicted region boundary and white area is the ground truth.

TABLE III
COMPARISON OF THE RESULTS

Segmentation Model	Metric		
	DSC	***VS***	***Recall***
The Best Previous Model	0.56	-	0.58
Voting Based Model	0.41	0.50	0.44
Weighted Average Based Model	0.57	0.66	0.56
Logistic Regression Based Model	0.71	0.82	0.73

was augmented by translating, rotating, scaling and adding Gaussian noise. The second part of the algorithm is multiple parallel U-Nets learned by different CTP maps. This section was designed for extracting information as for the appearance of stroke lesion from four CTP maps separately. To do so, we used four 2D U-Nets in a parallel manner that learned by using different CTP maps. The output of each U-Net is a probability map that shows the probability of being a lesion for each pixel. The third section is a pixel-level classifier that combined the outputs of the U-Nets to label each pixel as lesion or healthy.

Experiment results of our proposed approach on the publicly available ISLES challenge 2018 dataset demonstrate better prediction performance in comparison to the previous ischemic stroke lesion segmentation works. The effectiveness of the proposed algorithm is evident by the remarkable improvement in the value of DSC, recall, and VS compared to the best previous studies on this problem. Our algorithm achieved DSC 71.3%, Recall 73.6%, and VS 82.1% by using logistic regression as a pixel-level classifier.

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