Semantic Segmentation of highly class imbalanced fully labelled 3D volumetric biomedical images and unsupervised Domain Adaptation of the pre-trained Segmentation Network to segment another fully unlabelled Biomedical 3D Image stack

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Abstract

The goal of our work is to perform pixel label semantic segmentation on 3D biomedical volumetric data. Manual annotation is always difficult for a large biomedical dataset. So, we consider two cases where one dataset is fully labeled and the other dataset is assumed to be fully unlabelled. We first perform Semantic Segmentation on the fully labeled isotropic biomedical source data (FIBSEM) and try to incorporate the trained model for segmenting the target unlabelled dataset (SNEMI3D) which shares some similarities with the source dataset in the context of different types of cellular bodies and other cellular components. Although, the cellular components vary in size and shape. So in this paper, we have proposed a novel approach in the context of unsupervised domain adaptation while classifying each pixel of the target volumetric data into cell boundary and cell body. Also, we have proposed a novel approach to giving non-uniform weights to different pixels in the training images while performing the pixel-level semantic segmentation in the presence of the corresponding pixel-wise label map along with the training originaal images in the source domain. We have used the Entropy Map or a Distance Transform matrix retrieved from the given ground truth label map which has helped to overcome the class imbalance problem in the medical image data where the cell boundaries are extremely thin and hence, extremely prone to be misclassified as non-boundary.

1 Introduction

In the bio-medical domain, the fully annotated images are not always available. The UNet developed by Olaf Ronneberger et al. [5] for Biomedical Image Segmentation became very popular as it relies on the strong use of data augmentation to use the available annotated samples more efficiently. It consists of two paths - contraction path (also called as the encoder) which captures the context in the image and the second path the symmetric expanding path (also called as the decoder) which localizes the context in the image. UNet can accept the image of any size as it has no dense layer.

In the UNet, we have skip connection between layers of Encoder and Decoder of the same level so that the small object information which might get vanished during downsampling can be added as a residual during the Upsample phase.

Also, Bio-Medical Image segmentation involves the volume of 3D cross-sectional slices where each pixel on every slice is to be labeled as a class object. There are problems of anisotropy involved with the 3D image stack as the resolution of the ion beam varies with depth thus producing cross-section images with varying intensity and resolution. Hence, accurate segmentation of 3D EM images requires not only accurate segmentation of 2D slices but also making consistent predictions across slices to deal with misalignment problems. To perform semantic segmentation on 3D volumetric biomedical image data, a 3D architecture was proposed in 2016 in the paper 3D U-Net: Learning Dense Volumetric Segmentation from Sparse Annotation[3]. But, the major drawback with 3D architecture for semantic segmentation is computational expensiveness. In the paper DeepEM3D: approaching human-level performance on 3D anisotropic
EM image segmentation\textsuperscript{6} the authors proposed to employ a combination of novel boundary map generation methods with optimized model ensembles (2D-3D Ensembling) to address the challenges of segmenting anisotropic images. They trained multiple deep models variants that accepted different numbers of input slices and predicted boundaries of different thickness suppressing noise in Z-direction alignment. Due to the limitations of both GPU memory and computing power, when designing 2D/3D CNNs for 3D biomedical image segmentation, the trade-off between the field of view (achieved by 2D CNN) and utilization of interslice information in 3D images (achieved by 3D CNN) remains a major concern. Also, their method requires a little human labor to identify the misaligned slices. This limitation was addressed in the paper ‘Combining Fully Convolutional and Recurrent Neural Networks for 3D Biomedical Image Segmentation’\textsuperscript{2} where the authors proposed BiDirectional LSTM on the top of the FCN to capture the inter slice information. They used a different variety of UNet called as k-UNet to extract the intra-slice information at different scales sequentially (from the coarsest scale to the finest scale). The information extracted by the submodule FCN responsible for a coarser scale will be propagated to the subsequent submodule FCN to assist the feature extraction in a finer scale. In our experiment, we have used the simple 2D UNet architecture to perform semantic segmentation on each slice independently at the expense of interslice context information as our main objective is to make the UNet adapt to another domain in an unsupervised fashion. We wanted to avoid further complexity of training the complex UNet model in the unsupervised fashion after the pretraining phase.\textsuperscript{1}

Also, Bio-Medical Images are highly class imbalanced. In our case, the main objective is to segment the image into the cell boundary and cell body. Cell boundary is so thin that during classification the UNet is very likely to label them as cell bodies. This challenge we have overcome in a novel manner (details are in the Methodology section). Also, we have performed unsupervised domain adaptation on our segmentation network where we considered the target domain data to be fully unlabeled.

In a brief, we trained a 2D UNet on the slices of FIB-SEM data, and then, we try to perform unsupervised domain transform on the target data SNEMI3D.\textsuperscript{11}

2 Related Work

In recent days, there have been a lot of studies of domain adaptation for biomedical images. In the paper \textsuperscript{1}A domain-adaptive two-stream U-Net for electron microscopy image segmentation the authors proposed a two stream UNet, one for the source domain and one for the target, and allowing some of their weights to differ, while the others are shared. The main idea was a compromise between preserving what can be learned from the source domain using enough training data and adapting the weights to the potentially different statistics of the target domain. A slight modification of this approach was proposed in Domain Adaptive Segmentation In Volume Electron Microscopy Imaging where a second decoder is attached to the encoder-decoder segmentation network which reconstructs both the source and target data. Although, our approach to handle the domain adaptation is different from the ones mentioned above. We try to learn the label distribution of the
source dataset in an adversarial manner as the final segmentation result is boundary and non-boundary for both the domain and hence, we try to minimize the gap between the label distribution between source and target domain.

3 Dataset Description

In the FIBSEM dataset, the images are generated from a 5 micrometer cube volume of D. Melanogaster larval neuropil imaged at 10x10x10nm resolution using focused ion beam scanning electron microscopy. The dataset contains 500 cross-section slices of the 3D volume, where each slice contains 500X500 pixels. Pixel Label annotation map was provided for this dataset where each pixel in the volume is identified as cell boundary (1), cytoplasm (2), mitochondria (3), or glial cell (4). The resolution and intensities do not vary among slices. Then we try to perform unsupervised domain transform on the target data SNEMI3D, a 6X6X30 nm per voxel resolution serial section scanning EM (ssSEM) volume which covers a micro-cube of approximately 6 X 6 X 3 microns.

4 Methodology

4.1 Formulation of Entropy Map for each pixel from given training labelmaps(Experiment1)-

First, we had to deal with the class imbalance problem while performing segmentation on the FIBSEM data as the cell boundary contains almost 10 percent of total pixels in a 2D slice. Here, we introduce a novel approach of using entropy information of a pixel as weights in the classification layer of the UNet. The entropy of a pixel is calculated computing the entropy of a 5X5 kernel matrix centered on the target pixel, the elements of which are the class labels of the neighboring pixels. The idea is to give more weights to the pixels which have more entropy (i.e., different labels are assigned in its neighboring pixels) while classifying a pixel as one of the 4 classes in the ground truth label map.

4.2 Formulation of Distance Transform matrix from training label maps(Experiment2)-

As the main task is to find cell boundary and non-boundary in the target dataset which is a binary classification problem, we first performed a similar binary classification on FIBSEM data (cell boundary and the rest 3 classes as non-boundary). For this binary classification task, we had a similar problem of class imbalance which was taken care of by using the Distance Transform of the original boundary map. Also, we had to smooth the distance transform matrix with a Gaussian kernel of sigma=10 in order to avoid giving 0 weights to most of the nonboundary pixels.
4.3 Training the pretrained UNet(On labeled source domain) in adversarial fashion(Experiment3)-

Here, we use the trained model from Experiment 2 as the initial segmentation model and then try to learn the label distribution of boundary and non-boundary in the source domain in an adversarial fashion as we assume that the images in the target domain follow almost a similar boundary non-boundary distribution. To achieve the goal we need a discriminator that will identify the true source label map as true and generated label map from the segmentation UNet as false for the target domain.

So, we have 3 loss components: Supervised loss on Source domain (say L1) which was used to train the segmentation network UNet in Experiment 2 for boundary non-boundary prediction, and the losses incurred by the Discriminator while being trained on the source ground truth as true (say L2) and UNet generated label map of the images in target domain as false (say L3) respectively. Now, we will train the UNet to maximize the Discriminator’s loss L3. We will no longer use the Supervised Loss L1 to update the parameters of the UNet as it is trying to find the embedding for the target distribution only.

Basically, we are using the weights of trained UNet (trained on L1) to initialize the weights for our segmentation network for the target domain and learn the weights of the network for the target domain in an adversarial manner. As the adversarial training progresses, the network will capture the Target domains embedding.

5 Result-

5.1 Experiment 1-

After 120 iterations with initial learning rate of .0001 in the first experiment (Experiment 1) on FIBSEM, we receive the model M1 which achieves the validation Jaccard Score 72 % which is quite satisfactory considering multi-class classification of every pixel in the medical images where cell boundary class is extremely thin and dominated by the other 3 classes. As our primary goal was to find cell boundary and non-boundary in the target domain (SNEMI3D), we did not continue this supervised segmentation task with 4 classes further.

5.2 Experiment 2-

To obtain the model for determining the only boundary and non-boundary (Say M2) on FIBSEM we initialize the weights of all layers (excepting the classification layer) of the 2D UNet with the trained model obtained from experiment 1, i.e., M1 and after 20 iterations the model M2 is achieved with similar Jaccard Score of 80 % which is quite good considering we used only 2D UNet for 3D volume segmentation which can not capture the interslice information. We did not go for 3D UNet as it will be computationally expensive and our primary goal is not to perform semantically segmentation on Source Domain Images. In this setup, we used the Distance transform matrix as the pixel weight map to find the weighted cross-entropy.

Even, if we only train to predict boundary and non-boundary on FIBSEM without using the model M1, after 90 iterations we obtain a similar accuracy.

Another observation is that to tackle the problem of class imbalance if we had used weights for boundary
and nonboundary with specific ratios (say 2:1, 5:1 or 10:1), after the same number of iterations none of them achieve as good as the Jaccard Score achieved with the distance transform the matrix used as a weight map. As target domain has varying intensity and resolution across the depth of the slices, we train the model M2 for another 10 iterations after applying some random Jitter transform on the input image slices and the obtained model M3 works as an initial segmentation model for target data.

5.3 Experiment 3-

Results after each iteration are shown in the table for an image sampled from the target domain. Here, we did not use the label information of target domain images to train the network as our main purpose is to make the network M3 obtained from Experiment 2 adapt to the target domain in an unsupervised manner assuming no label information was provided for the images in the target domain.

6 Future Work

We are planning to impose condition on the Discriminator where we can give a pair of inputs: Input Image and corresponding true Label Map for the source domain as true (say loss contributed by these set of examples as L1), Input Image and Label Map of another slice (negative example) for the source domain as False (say loss contributed by these set of examples as L2), and Input Image and corresponding generated Label Map for the target domain as false (say loss contributed by these
set of examples as L3) and the segmentation network will only be trained on negative of L3 i.e., the Input Image and corresponding generated Label map as True. In this way, we can learn the joint embedding of both the Input Image and corresponding label map.

Also, we plan to learn the joint embedding of both the source and target domain as our present experiment is moving the network away from the source domains embedding, its not finding out the common embedding between source and target data.

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