

Point annotations for nucleus segmentation in histopathology images via envelope enhancement network

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Abstract. Nucleus segmentation in histopathology images holds great clinical value for disease analysis. With the advancements in deep learning and continuous iteration of devices, existing nucleus segmentation algorithms can achieve satisfactory performance. However, these fully supervised nucleus segmentation methods require pixel-level annotation information, which requires a significant amount of time and effort. To ease this burden of annotations, we propose an envelope enhancement segmentation Network (EESNet) for weak supervision nucleus segmentation. Specifically, we first employ a Voronoi diagram and adaptive k-means clustering algorithm to derive two kinds of informative pixel-level pseudo labels, which are used for pixel-wise segmentation. Furthermore, we introduce an envelope enhancement network to provide rich envelope structure information to the segmentation network, which helps mitigate the problem of inaccurate boundary segmentation caused by point annotations. Finally, our network is verified on a mainstream nucleus segmentation datasets (consep) and achieves satisfactory performance.

Keywords: nucleus segmentation; point annotations; weak supervision.

1. Introduction

Segmentation of nucleus stands as a crucial stage in automating histopathology image analysis. By analyzing segmentation results, pathologists are able to diagnose and grade cancer, as well as undertake further interventions and treatments. Though existing fully-supervised methods [1] display potential, they demand numerous pixel-level masks. Yet, meticulously annotating these masks for densely packed nuclei proves laborious and demands expert insight, thus greatly constraining practical utility. This challenge has prompted the development of weak supervision segmentation methods, including point-based approaches [2, 3], box-based approaches [4], and image-level weak supervision approaches [5]. Among these methods, point-level annotations stand out for their efficiency and ability to provide location information. Therefore, leveraging point annotations for nucleus segmentation represents the mainstream direction in weakly supervised nucleus segmentation.

Recently, many point-annotated methods have been proposed. Qu et al. [2] first used central points to yield pseudo labels for training segmentation networks. Their model is simple but proficient for the reason that cluster labels can provide useful boundary. But the approach is entirely rely on the accuracy of cluster label generated from point. [3] further reduces the annotation burden by utilizing partial point annotations for nucleus segmentation. They use semi-supervised detection step to search center point and then employ all the points to generate label and guide model segmentation. But the semi-supervised methods may fail to detect all nucleus center points, which could limit segmentation performance. Additionally, determining the appropriate ratio of center points to use is a challenging issue. [6,7] utilized the Sobel filter to receive edge maps. Although they don't yield pseudo labels during the training process, the Sobel filter is more prone to generating noise than convolutional networks. [8] employed objectness to generate pseudo masks for supervision.

In this manuscript, we propose a new point annotation nucleus segmentation method aiming at reducing the gap between point-annotated methods and pixel-level mask-annotated methods. Departing from generating two pseudo labels to supervise the segmentation network, we attempt to offer more nucleus envelope information to our segmentation network using an envelope

enhancement network, which is vital to point-annotated approaches. We carry out sufficient experiments to assess the performance of our model using the consep datasets. The results consistently demonstrate that our model outperforms previous methods. In summary, our manuscript includes two main contributions:

- We present a new weak supervision network (EESNet) for nucleus segmentation, which employs the adaptive k-means cluster algorithm to generate adaptive clustering labels for pixel-level mask supervision.

- The envelope enhancement network is introduced to offer additional envelope structure information to segmentation network.

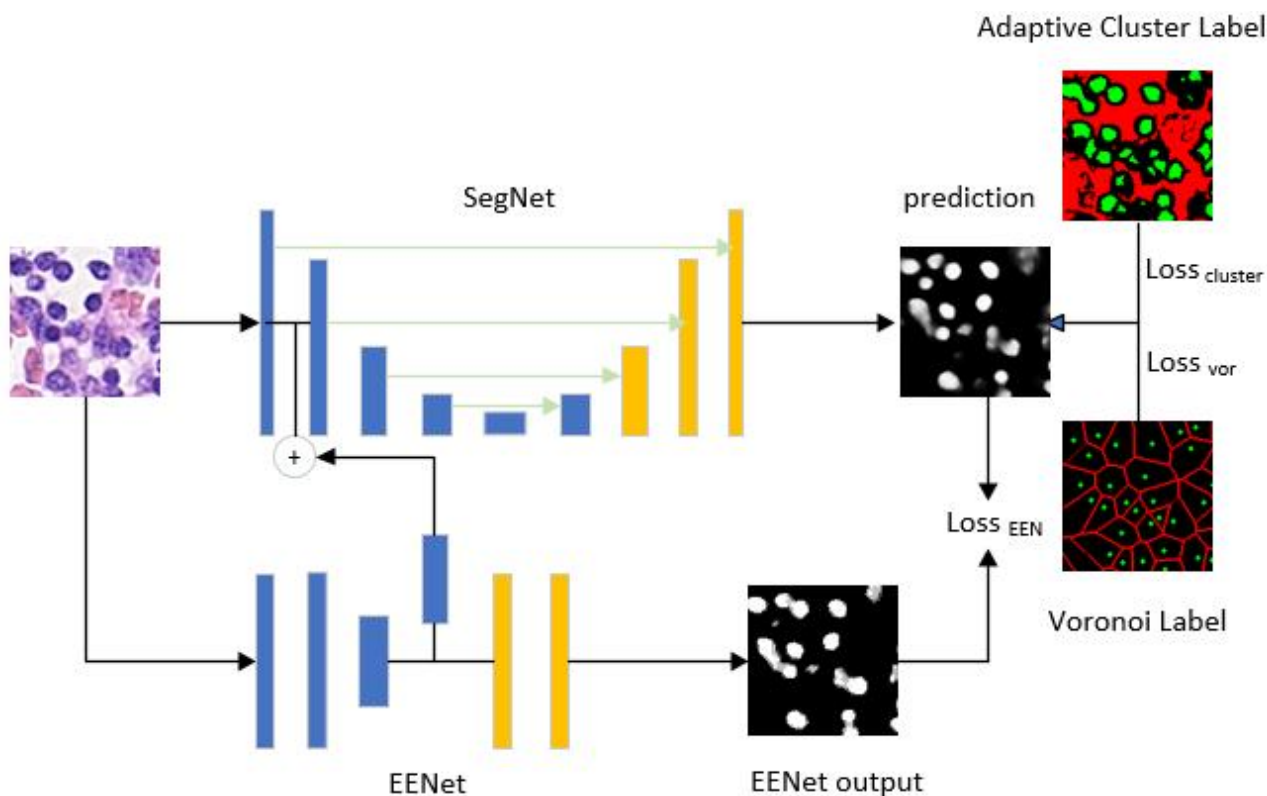


Fig. 1 Flowchart of our EESNet.

2. Methods

The flowchart depicting EESNet is presented in Figure 1. EESNet comprises two main components: the segmentation network (SegNet) and the envelope enhancement network (EENet). The SegNet is based on ResUNet34, which is a UNet-like encoder-decoder structure. The structure is simple yet possesses strong feature representation capabilities by combining ResNet34 with U-Net. The SegNet is supervised by two pseudo labels, voronoi label and adaptive cluster label. The former is same to the original paper[2] without any changes, the latter is a new clustering label obtained by introducing adaptive k-means cluster algorithm.

The EENet is introduced here to enhance the envelope information. Point-annotated algorithms are lacking for envelope information and usually result in inaccurate boundary segmentation problem. Although cluster label can offer coarse boundary information, the supervision is still insufficient. Inspired by [9], we introduce EENet to provide additional edge structure information and integrate it to shallow layer of the SegNet by element-wise addition operation. Furthermore, the output of the EENet is supervised by the output of the SegNet, which further improves segmentation performance.

Moreover,our EESNet is refined by Dense CRF,which can optimize the nucleus boundary .For convenience, we do not include it in the Fig.1, as it is identical to the original setting without any alterations.

2.1 Adaptive k-means cluster

Based on[2],although we can receive voronoi labels and vanilla k-means cluster labels to accomplish pixel-level segmentation,the performance are limited by the quality of two kinds of pseudo labels.Especially for clustering labels, among the two generated pseudo labels, the clustering labels will encompass three categories: nucleus, background, and disregarded regions. This clustering strategy indirectly provides partial boundary information to the segmentation network. However, traditional clustering algorithms primarily control the generation results of clustering based on color and distance. In the complex background of pathology images, imaging conditions often vary greatly, making it difficult for the generated clustering labels to meet the requirements, further impacting the final segmentation results.In this manuscript,to improve accuracy of cluster labels,we introduce adaptive k-means cluster algorithm to optimize the cluster labels.

The adaptive k-means cluster algorithm is crafted to address the challenges posed by complex imaging environments, thereby improving feature representation in histopathology images and generating more effective cluster pseudo labels. Specifically,For an input image I , let i denote any pixel in the image. To obtain clustering results, we need to retrieve the corresponding RGB values $color_i$ and the distance value d_i from the nearest point annotation for pixel i .The adaptive k-means cluster algorithm use same d_i as vanilla cluster algorithm ,but redesign the $color_i$,the $color_i$ can be written as follow:

$$color_i = \alpha(r_i, g_i, b_i) / \beta. \quad (1)$$

Where α denotes the global scale parameter to balance color and distance, β is region term to scale RGB value .The color distribution of each image can be adapted by parameter β . β is not a manually set fixed parameter value, it is calculated for each input image. We normalize the RGB values of the central pixel using the 8-neighborhood image processing methods.In other words,we compute the color distance between each pixel and its eight surrounding points, and finally calculate an annotation difference based on these color distances. β corresponds to the value of this annotation difference.

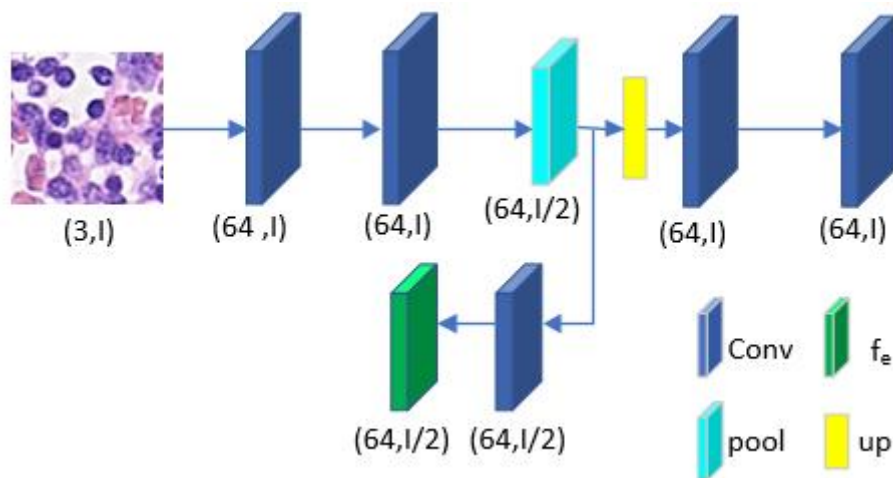


Fig. 2 The flowchart of EENet.The blue blocks denote conv1 to conv5 as the sequence from left to right and top to down.

2.2 Envelope enhancement network

Using the pseudo labels from adaptive k-means cluster and voronoi algorithm to supervise nucleus segmentation, we can obtain satisfactory segmentation results, but the supervision around the boundary of nucleus is still weak. To cope this problem, we need to obtain more information related to the boundary of the nucleus. Inspired by [9], we introduce EENet to offer envelope information to our segmentation network.

We enhance SegNet by incorporating a parallel EENet, which provides additional structural insights. As depicted in Fig.2, the input image undergoes two convolutional layers (conv1 and conv2) within SegNet, each employing a 3×3 filter and a 64-dimensional output. Subsequently, a max-pooling layer processes the conv2 feature map, retaining essential clues while reducing spatial dimensions. Moreover, we introduce two branches after the max-pooling layer: the main branch, with an upsampling layer followed by conv3 and conv4, and another branch handling features with conv5, yielding a low-level feature map, fe , rich in envelope details. Leveraging this additional envelope information provides enhanced supervision for nucleus shape and boundary. Finally, we integrate fe into SegNet via element-wise addition, maintaining scale invariance. The main branch's output serves as prediction values, while the SegNet's result acts as ground truth for EENet supervision.

2.3 Loss functions

The loss functions of our model can be written as follow:

$$\text{Loss}_{\text{total}} = \text{Loss}_{\text{vor}} + \text{Loss}_{\text{cluster}} + \text{Loss}_{\text{EEN}} + \text{Loss}_{\text{CRF}}. \quad (2)$$

where Loss_{vor} and $\text{Loss}_{\text{cluster}}$ are pixel-level pseudo labels, we use cross-entropy loss to compute the result. The Loss_{EEN} denotes the loss of envelope enhancement network, and we utilize L_1 loss to train the network for stable. The Loss_{CRF} is the Dense CRF loss, which is used to refine the whole model instead of post-processing.

3. Experiments

3.1 Training strategy

We validate our model's efficacy in histopathology images using the consep datasets. These datasets include 41 H&E images, each with dimensions of 1000×1000 pixels. We divided the dataset into two parts: a training set with 27 images and a test set with 14 images. We utilized the pixel-level instance labels provided in the original dataset, but for our point-supervised methods, we only required point labels for nucleus segmentation. Hence, we derived point labels from the instance labels. During testing, we used the instance labels solely for performance evaluation.

For our experiments, we employed our code on an RTX A5000. The optimization problem was addressed using the Adam optimizer. Additionally, we choose the learning rate to 0.0001 and conducted training for 70 epochs.

3.2 Evaluation metrics

To assess the nucleus segmentation performance, we employ five evaluation indicators, including ACC, F1, DICE, AJI and Precision. The initial pair pertains to pixel-level metrics, whereas the subsequent pair relates to object-level metrics.

Table 1. Ablation study of ADK and EEN

Methods	ACC	F1	DICE	AJI	Precision
Baseline	0.8545	0.5825	0.5619	0.3397	0.7446
Baseline+ADK	0.8789	0.6424	0.5613	0.2908	0.7914
Baseline+EEN	0.8733	0.6101	0.5683	0.3416	0.7735
Baseline+EEN+ADK	0.8880	0.6615	0.6014	0.3533	0.8118

3.3 Ablation study

To demonstrate the validity of our EESNet, we perform an perturbation experiment using the consep histopathology datasets. Specifically, we use the classical weak supervision algorithms [2] as the baseline and all parameter settings are consistent with the original paper. The EEN is the envelope enhancement network and ADK is the adaptive k-means clustering. In this study, our EESNet achieves a higher performance on all metrics, as reported in Table 1.

Table 2. Comparison to other point-annotated methods

Methods	ACC	F1	DICE	AJI	Precision
PA	0.8545	0.5825	0.5619	0.3397	0.7446
PPA	0.8635	0.5489	0.5454	0.2943	-
Ours	0.8880	0.6615	0.6014	0.3533	0.8118

3.4 Comparison study

The comparison of segmentation performance with previous point-annotated methods on the consep datasets is depicted in Table 2. It is evident that our model outperforms PA[2] and PPA[3] across most metrics. Figure 3 presents visual comparisons of results on the consep datasets. Compared to PA, the segmentation results of our model is more accurate because our model fuses rich envelope information from EENet and supervised by better cluster labels. Compared to PPA, although PPA further decrease the burden of annotation, limited point annotations result in limited supervision information. Further reducing the number of points also leads to a further reduction in supervision information.

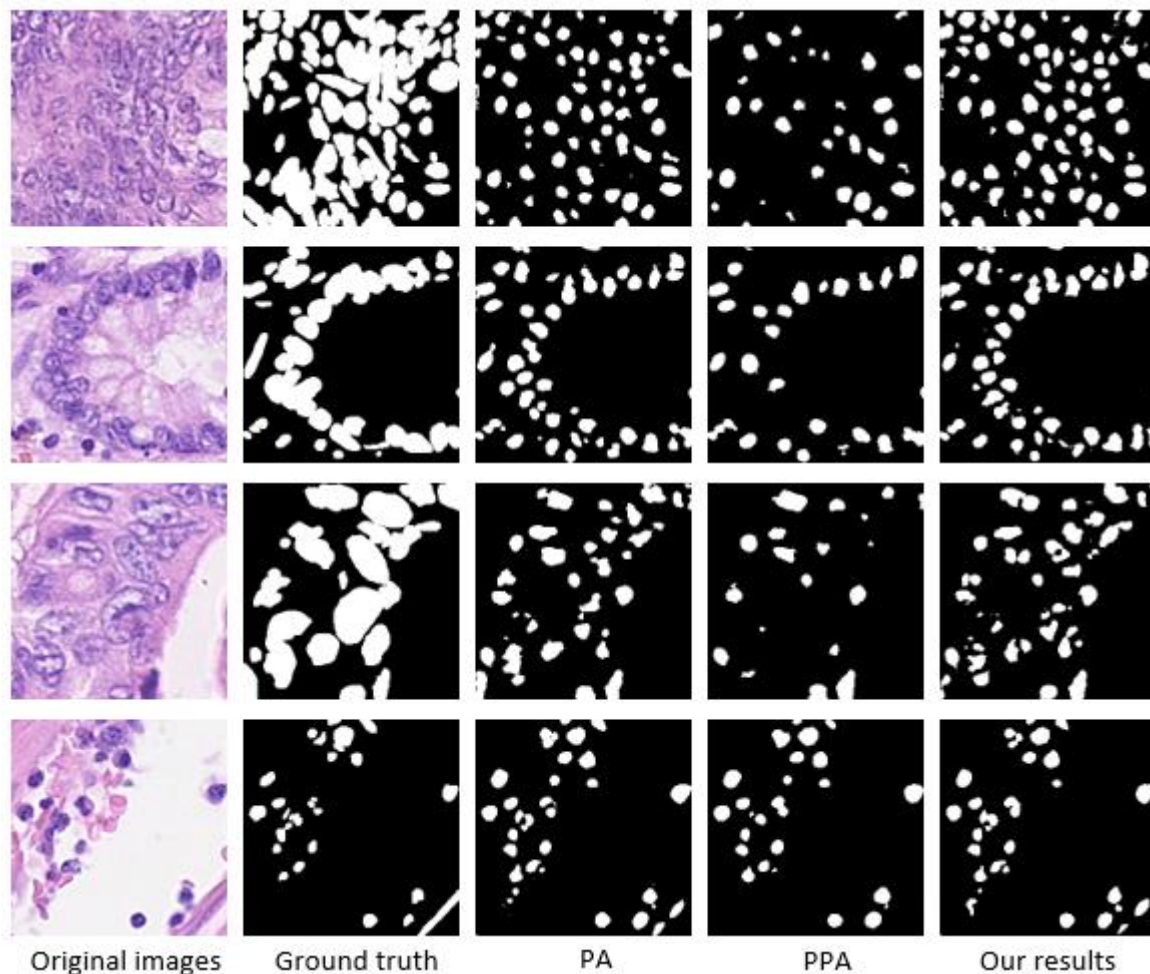


Fig. 3 Visual results of comparison study.

4. conclusion

In this paper, we propose a weak supervision nucleus segmentation model in histopathology images. Our EESNet can usefully acquire nucleus envelope information and achieve satisfactory segmentation results in the case of only use point labels.

Specifically, we introduce the adaptive k-means clustering algorithm to yield new cluster labels, which redesigns the feature vector to adapt complex images environment. The new cluster labels can offer more effective pixel-wise supervision during the segmentation. In addition, the envelope enhancement network has been employed to provide extra envelope structure information to segmentation network, which alleviates the issue of inaccurate boundary. Experiments demonstrates that our EESNet has good result in the weak supervision nucleus segmentation task.

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