Deep Adversarial Image Synthesis for Nuclei Segmentation of Histopathology Image

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***Abstract*—Nuclei segmentation is a fundamental upstream task of digital pathology image analysis. Existing nuclei segmentation methods usually require pixel-level labeled images from experienced pathologists. In this paper, we proposed an innovative data augmentation workflow for histopathology images: a) generates a set of initial central points randomly with existing human-annotated histopathology image datasets; b) generates nuclei segmentation masks based on the generated centroid points of step a); c) generates Haematoxylin and Eosin (H&E)-stained histopathology images corresponding to the generated nuclei masks. In addition, we proposed a deep attention feature fusion generative adversarial network (DAFF-GAN) to improve the image quality and the photorealism of the generated image. We conducted extensive experiments on several existing nuclei segmentation methods, comparing using raw data with the augmented data by our strategy. Extensive experiments proved the effectiveness of our proposed strategy.**

Keywords—histopathology image, nuclei segmentation, data augmentation, GAN

I. INTRODUCTION

Cancer is divided into different types depending on the growth and uncontrolled proliferation of abnormal cells [1]. Traditionally, pathologists examine patients' pathologic slices under a light microscope, which is labor-intensive and time-consuming. The application of digital histopathology images and computational algorithms has brought significant changes to the routine work of pathologists.

In digital pathology analysis, nuclei segmentation is the critical precondition and base for qualitative and quantitative analysis of histopathology images. In recent years, researchers have proposed some strategies based on convolutional neural networks (CNNs) for nuclei segmentation [2] [3]. Existing nuclei segmentation methods usually demand huge pixel-level labeled images from experienced pathologists. However, acquiring pixel-level annotations is extremely tedious and complex. Furthermore, there are only a limited number of public datasets for nuclei segmentation. Therefore, it is difficult to improve the segmentation performance due to the lack of datasets. Compared with proposing a nuclei segmentation method, maybe it is more valuable and meaningful to propose a data augmentation method for existing data, which is universal for existing nuclei segmentation methods to improve the performance.

In this paper, we present an innovative workflow for histopathology images synthesis. We synthesize histopathology images and corresponding masks for nuclei segmentation task. In theory, we can synthesize an infinite amount of data because the original data used to synthesize the images and masks is randomly generated. In our proposed workflow, the centroid points of histopathology images and corresponding masks are stochastically generated firstly. In the second stage, segmentation masks in different types are generated by the centroid points. Finally, verisimilar H&E images corresponding to the generated masks are generated. To improve the image quality and the photorealism of the generated images, we proposed a deep attention feature fusion generative adversarial network. It works in the second and the third stage.

The main contributions of this work are as follows:

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- We proposed an innovative data augmentation workflow and a novel deep attention feature fusion generative adversarial network for pathology image synthesis.
- The proposed DAFF-GAN performs better than the existing image synthesis method. Extensive experiments on several existing nuclei segmentation methods proved the effectiveness of the proposed data augmentation strategy.

II. Related Works

A. Nuclei Segmentation

Nuclei segmentation is a critical step in automating histopathology image analysis. The traditional method is to segment the nuclei first, and then classify the segmented nuclei. Segmentation approaches include traditional and deep learning methods. For traditional methods, there are OTUS[4] threshold and market controlled watershed[5] methods, which were used in some strategies [6] [7] [8] to segment nuclei in histopathology images. On the other hand, methods based on deep learning, Kumar et al. [9] proposed an approach based on deep learning to mark the nuclei and nuclear contours and then conducted the segmentation with a region-growing approach. Nguyen et al.[10] proposed an approach to classify nuclei as lymphocyte, stromal and other tumour using morphological features. Yuan et al.[11] segmented nuclei firstly and then classified each nuclei with AdaBoost classifier. Zhao et al. [12] proposed a method based on Hematoxylin-aware CNN to segment histology images. Recently, Hover-Net[2] was proposed to segment and classify nuclei in histology images simultaneously.

However, most of the existing nuclei segmentation methods demand histopathology images with human-annotated masks. Although some researchers have proposed nuclei segmentation methods [13] [14] based on weakly supervised learning, the performance of these methods is not as good as that based on fully supervised learning. Therefore, the methods based on fully supervised learning are still the most ideal methods to achieve high precision nuclei segmentation up to now. It means that using datasets with human-annotated pixel-level label is still inevitable. However, there are only a few publicly available datasets for nuclei segmentation task. Existing nuclei segmentation methods usually need to train a unique model for each dataset because of the enormous differences in the characteristic distribution of data between various datasets. To solve the problem of limited data, we proposed a universal data augmentation strategy for histopathology images. It helps to improve the existing nuclei segmentation method.

B. GANs for Histopathology Image Synthesis

Generative Adversarial Networks (GANs) were firstly proposed by Goodfellow et al. [15]. With the great ability to synthesize images and to simulate data distributions, GANs have since been adopted into a series of computer vision and medical image analysis tasks including image-to-image translation, image reconstruction, image segmentation, and domain adaptation. The framework can be seen as a min-max game between two networks. One of the player (the generator) is aimed to mimic a special data distribution from a random input. The other player (the discriminator) is tasked with distinguishing whether the distribution is synthesized or not.

GANs have been used for medical image synthesis in recent years. Wolterink et al. [16] proposed an approach to synthesize brain CT images from MR images. Frid-Adar et al. [17] proposed an approach to generate three different classes of liver lesions by three DC-GANs. The synthesis data were found to improve the performance of the lesion classification task. Mok and Chung [18] proposed a method based on conditional generative adversarial networks (cGANs) to synthesize training data for tumour segmentation. In addition, Le et al. [19] synthesized the background patched and the foreground(nuclei) patches, respectively, then combined the background patches and foreground patches. Faisal et al.[20] used a cycleGAN framework to learn a mapping from randomly generated polygon masks and unpaired histopathology images. Though these approaches can be used to synthesize training data, they can not distinguish between different cell types in synthesizing histopathology images. In this paper, we proposed a novel data augmentation strategy to synthesize histopathology images containing multi-type of cells.

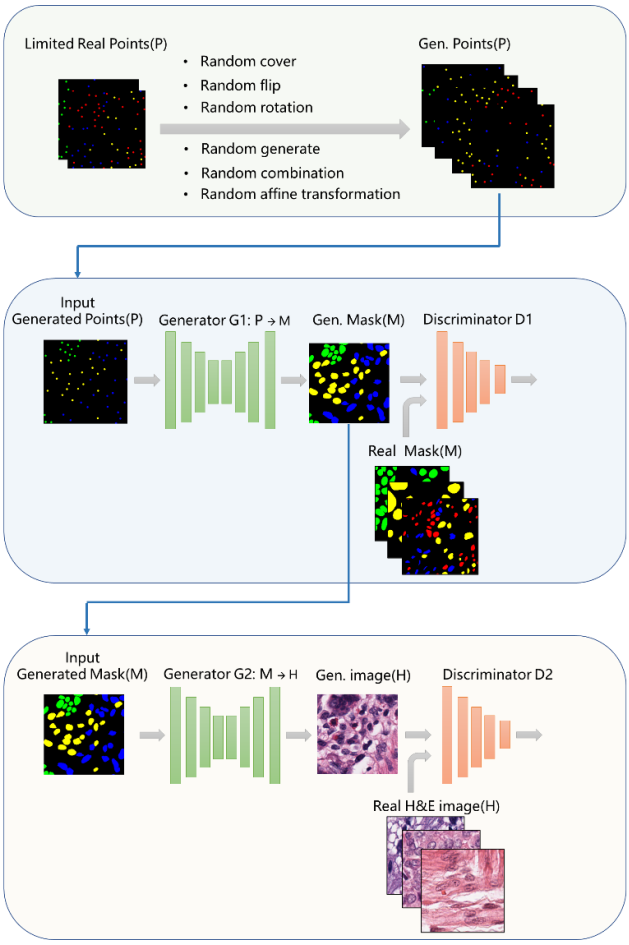

Fig. 1. (a) Synthesize random points by various image transformation operations. (b) Synthesize nuclei segmentation masks from generated random points. Red, yellow, green, blue represent miscellaneous, inflammatory, epithelial, spindle-shaped classes of cell, respectively. (c) Synthesize H&E-stained histopathology images from generated masks.

III. METHODS

To augment existing limited datasets and improve the performance of existing nuclei segmentation methods, we propose an innovative data augmentation workflow for histopathology images (in Section III.A). In addition, we propose a novel deep adversarial training method named DAFF-GAN to improve the image quality and the photorealism of the generated image (in Section III.B).

A. Workflow for Histopathology Images Synthesis

The proposed innovative data augmentation workflow for histopathology images includes three stages:

1) Synthesize random points from limited original data

We first calculate the center point of each cell instance based on the segmentation mask labels in the original training dataset. All the original point images will be collected and stored in a library. There are only a few point images because the raw training data is limited. We extract images from the original point image library and randomize them using various image transform operations including random cover, flip, rotation, random generate, random combination, and random affine transformation. In this way, we have a large number of nucleus centroids that can be used in the downstream work.

2) Synthesize nuclei masks from generated centroid points

In the second stage for histopathology images synthesis, we use DAFF-GAN (details in Section III.B) to synthesize verisimilar nuclei masks. For this stage, the generator G1 aims to translate centroid point images to different types of nuclei masks, while the main task of the discriminator D1 is to distinguish whether the input images are synthesized or not.

3) Synthesize histopathology image from nuclei mask

In the last stage of the data augmentation workflow, we also use DAFF-GAN to synthesize histopathology images. Different from the second step, the generator G2 in this stage aims to translate nuclei masks to corresponding histopathology images. The synthesis of nuclei masks and histopathology images are performed in a supervised environment. Taking histopathology image synthesis as an example, nuclei mask and histopathology image are bound together as a pair of training data $\{(M_i, H_i)\}$, while M_i is a nuclei mask image from original data and H_i is the corresponding histopathology image. The optimization objectives of the entire framework can be expressed as follows:

$$\max_{G} \min_{D} \mathcal{L}_{GAN}(G, D) \tag{1}$$

where the objective function $\mathcal{L}_{GAN}(G, D)$ can be expressed as:

$$\begin{aligned} \mathcal{L}_{GAN}(G, D) = & \mathbb{E}_{(M)\sim p_{data}(M)}[\log(1 - D(M, G(M)))] \\ & + \mathbb{E}_{(M,H)\sim p_{data}(M,H)}[\log D(M, H)] \end{aligned} \tag{2}$$

B. DAFF-GAN for Images Synthesis

1) The pix2pixHD baseline

The pix2pixHD [21] is an image-to-image translation method based on cGANs. It works for generating images with high-resolution and photo-realistic using semantic label maps. Compared with its predecessor work, pix2pixHD performs better. It is helped by a group of generators (global generator and local generator) and a multi-scale discriminator. The method achieves both the high quality and the high resolution of image synthesis.

Considering its excellent performance for image translation, we set pix2pixHD as our baseline in this work.

2) Deep Attention Feature Fusion Generative Adversarial Network

Following with pix2pixHD, we use two sub-networks to complete the data synthesizing task together. As shown in Fig.3, the global generator network operates at the original resolution of the input image, while the local generator network operates at the 4× size of it (2× along image height and 2× along image weight). The input to the local generator's latter part is the sum of the global generator's output and the output of the local generator's front part. In this way, the global information can be integrated for the local generator.

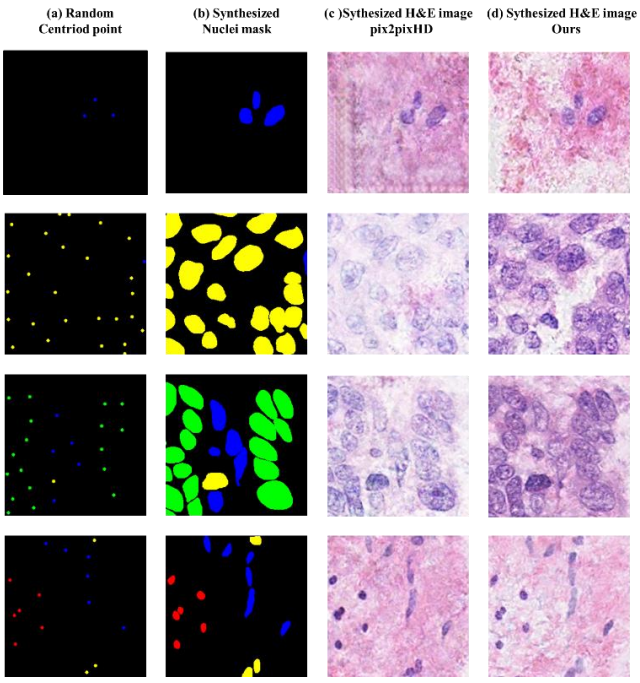

Fig. 2. Comparison of synthesized H&E images. Red, yellow, green, blue represent miscellaneous, inflammatory, epithelial, spindle-shaped classes of cell, respectively.

However, we found that only these architecture and technique cannot achieve satisfactory performance in nuclei mask to histopathology image translation. As Fig.2 (c) shows, pix2pixHD synthesized image with ghosting when the nuclei masks are uneven in the input image, so the networks could not learn and utilize the holistic feature in the training data effectively. We propose a novel deep adversarial network (as shown in Fig.3) to improve the performance of data synthesis.

Inspired by Huang et al.[22], we added criss-cross attention module before the residual blocks in the global generator and the local generator network. In the criss-cross attention module, every pixel can obtain the contextual information of all the

pixels on its criss-cross path. In the way, each pixel will harvest the dependencies of the whole picture. It is of great help for mining and fitting image features.

In addition, we added a remote skip connection for both the global generator and the local generator. The skip connection can effectively reduce the problem of gradient disappearance and network degradation. It helps make training easier.

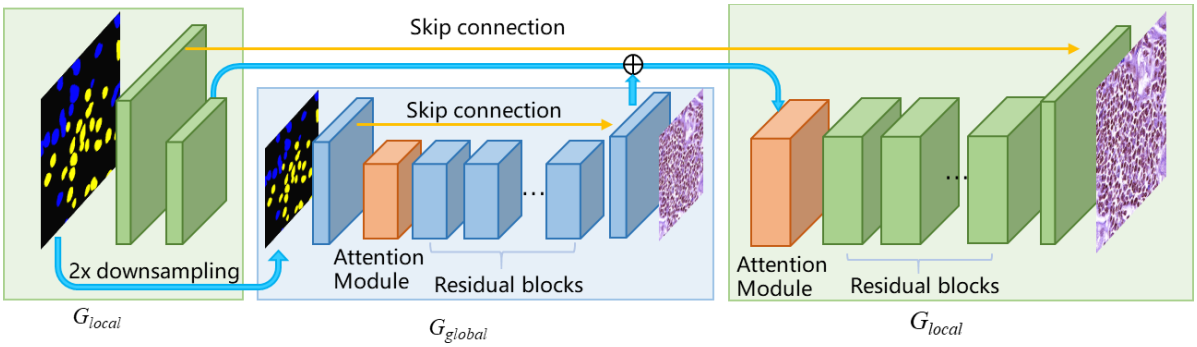

Fig. 3. Network architecture of DAFF-GAN. Attention module represents the criss-cross attention module.

IV. Experiments and Results

A. Dataset and Evaluation Metrics

We evaluate the proposed strategy on a dataset named colorectal nuclei segmentation and phenotypes (CoNSeP)[2]. CoNSeP contains 41 H&E stained histopathology images with 1000×1000 size. The organizer annotated nuclei as different types, including muscle, fibroblast, normal epithelial, tumour epithelial, inflammatory and necrotic. For our experiments, we conduct the same settings for 7 different types, i.e., grouping the fibroblast and endothelial nuclei into spindle-shaped, grouping the normal and malignant/dysplastic epithelial nuclei into a single class (epithelial). Finally, 4 types of nuclei are chosen for nuclei segmentation, i.e., epithelial, inflammatory, spindle-shaped and muscle. We split 27 images for the training set and 14 images for the test set.

In the experiments, we use five different common nuclei segmentation metrics including Dice, AJI[9], detection quality (DQ), segmentation quality (SQ) and panoptic quality (PQ) [23].

B. Implementation and Training Details

Aiming to prove the effectiveness of our proposed strategy, our experiments revolve around whether the proposed data augmentation strategy can improve the performance of existing nuclei segmentation methods.

1) Data augmentation based on GANs

We first synthesized augmentation data using pix2pixHD and our method (DAFF-GAN). To train the generator of GAN for synthesizing histopathology images, we crop 108 patches (512×512) from 27 images by using a sliding window. 659 centroid point patches (256×256) and synthesized nuclei masks using these patches are generated. Finally, 659 histopathology images with the size of 256×256 are synthesized.

2) Nuclei segmentation

We use two existing nuclei segmentation methods to verify the effectiveness of the proposed data augmentation strategy. 1057 patches (256×256) from 27 images are cropped as original CoNSeP training data. The synthesized data generated by pix2pixHD and DAFF-GAN were added separately to the original CoNSeP training dataset.

All experiments were completed in the following environment:

Ubuntu18.04 Server, NVIDIA RTX3090, Pytorch1.7.1.

C. Evaluation and Results

Here we show several nuclei segmentation results in Fig.4. These cases are the segmentation results using Hover-Net& ResNet34. It can be seen that the segmentation performance is improved when applying the data augmentation strategy to the existing segmentation method. It means that the data augmentation method is helpful to the existing segmentation methods.

In TABLE I, the segmentation performance using CoNSeP and augmentation data synthesized by pix2pixHD is better than using CoNSeP. Further, the segmentation result using CoNSeP and augmentation data synthesized by ours DAFF-GAN performs better than that by employing pix2pixHD.

We can see from the yellow boxes in Fig.4 that our method has the best performance in nuclei segmentation.

TABLE I. Quantitative Comparison with Existing Methods. Hover-Net&ResNet34 represents That the Backbone in Hover-Net is Replaced with ResNet34 in [3]

Training Dataset	Hover-Net[2]					Hover-Net & ResNet34[3]				
	Dice	AJI	DQ	SQ	PQ	Dice	AJI	DQ	SQ	PQ
CoNSeP	0.8381	0.5245	0.6440	0.7614	0.4917	0.8359	0.5464	0.6767	0.7705	0.5225

CoNSeP + Gen. pix2pixHD	0.8388	0.5286	0.6454	0.7640	0.4944	0.8365	0.5494	0.6800	0.7727	0.5267
CoNSeP + Gen. DAFF-GAN	**0.8411**	**0.5325**	**0.6577**	**0.7683**	**0.5067**	**0.8381**	**0.5577**	**0.6946**	**0.7742**	**0.5388**

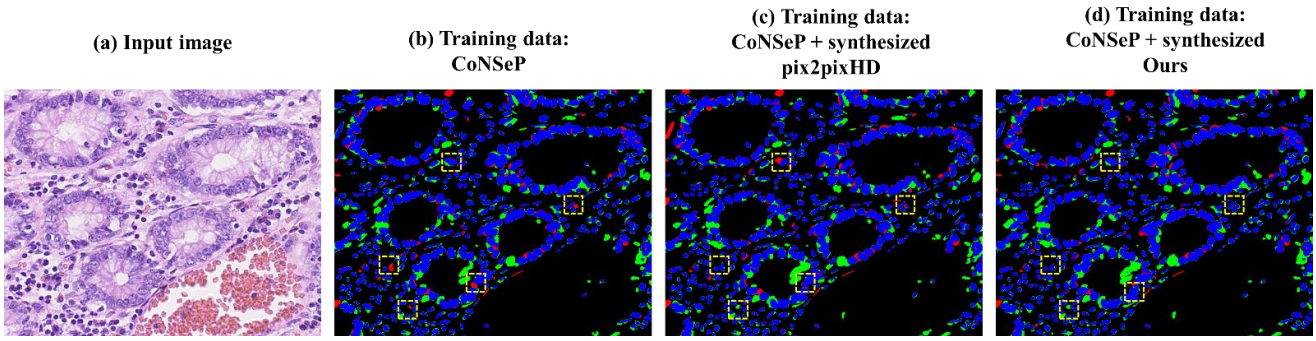

Fig. 4. Qualitative results of using different training data. We show the difference maps between the predicted result and the ground truth image [12]. Blue areas represent the intersection of the predicted result and the ground truth. Green areas represent the false positive segmentation. Red areas represent the false negative segmentation. Yellow boxes underline the obvious differences between the different schemes.

V. Conclusion

This paper proposed a novel data augmentation strategy for histopathology images. Firstly, we generated a set of initial central points randomly with existing human-annotated histopathology image datasets. Then, the nuclei segmentation masks were synthesized using the generated centroid points. At last, the H&E-stained histopathology images corresponding to the generated nuclei masks were synthesized. In addition, a method named DAFF-GAN was proposed to improve the image quality and the photorealism of the generated image. We employed the proposed strategy on existing nuclei segmentation methods. Extensive experiments proved that our data augmentation strategy was valuable and helpful to the existing nuclei segmentation methods.

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