

AugHover-Net: Augmenting Hover-net for Nucleus Segmentation and Classification.

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Abstract—Nuclei segmentation and classification have been a challenge in digital pathology due to the specific domain characteristics. First, annotating a large-scale dataset is quite consuming. It requires specific domain knowledge and large efforts. Second, some nuclei are clustered together and hard to segment from each other. Third, the classes are often extremely unbalanced. As in Lizard, the number of epithelial nuclei is around 67 times larger than the number of eosinophil nuclei. Fourth, the nuclei often exhibit high inter-class similarity and intra-class variability. Connective nuclei may look very different from each other while some of them share a similar shape with the epithelial ones. Last but not least, pathological patches may have very different color distributions among different datasets. Thus, a large-scale generally annotated dataset and a specially-designed algorithm are needed to solve this problem. The CoNIC challenge aims to promote the automatic segmentation and classification task and requires researchers to develop algorithms that perform segmentation, classification, and counting of 6 different types of nuclei with the large-scale annotated dataset: Lizard. Due to the 60-minute time limit, the algorithm has to be simple and quick. In this paper, we briefly describe the final method we used in the CoNIC challenge. Our algorithm is based on Hover-Net and we added several modifications to it to improve its performance.

I. INTRODUCTION

Nuclei segmentation and classification in Haematoxylin & Eosin stained histology images is of vital importance in computational pathology. It enables further cell-based analysis such as tumor grading [1]. The CoNIC challenge [2] is a challenge aims to promote the automatic segmentation, classification and counting of nuclei. These tasks have been difficult problems in digital pathology due to several factors.

First, annotating nuclei datasets is a high-cost and time-consuming task, as it requires specific domain knowledge and large efforts. A pathologist may need several years of training to correctly distinguish between different nuclei. Also, a single image patch may contain hundreds of nuclei which are crowded and clustered, increasing the trouble of nucleus annotation. The CoNIC challenge [2] addresses this by providing the researchers with a large-scale annotated dataset, Lizard [3], which contains more than half a million nuclei. Lizard [3] uses a semi-automatic pipeline which includes both automatic annotation and expert refinement. The nuclei are segmented and classified into 6 classes: neutrophil, epithelial, lymphocyte, plasma, eosinophil, and connective.

Second, the nuclei classes are often extremely unevenly distributed. For example, there are 244,563 epithelial nuclei and only 3,604 connective nuclei in Lizard [3]. The number of epithelial nuclei are around 67 times larger than the number of connective nuclei. Though HoVer-Net does not have any specific design to solve this, we tried several methods to address it and improve the model’s performance. We first tried to use a two-stage pipeline which segments the nuclei first and then classifies them. In the classification, we adopted data-resampling to refine the classification result and help the model focus more on the tail classes. However, due to the time limit of the challenge [2](60 minutes), we have to adopt a method that can work quickly and robustly. Finally, we simply added some weighting parameters on the losses to emphasizing on the tail classes. Specifically, we used weighted cross-entropy loss on the classification branch and did a simple search on the best weighting parameters with the validation dataset.

Third, the nuclei often exhibit high inter-class similarity and intra-class variability. Thus, the model has to see enormous amount of data before it could accurately distinguish between different classes of nuclei. As extra dataset is not allowed in this challenge [2], we tried a large amount of data augmentation methods to improve the data variety and thus improve the model performance.

Last but not least, pathological patches may have different color distribution among different hospitals. To avoid overfitting to a specific domain, we added several drop-out layers in the model, which significantly improved the performance of our model on the preliminary test leaderboard.

In summary, we tried a bunch of different techniques and finally picked the ones that actually improve model performance to the baseline Hover-Net in the CoNIC challenge [2]. Thus, we call the augmented HoVer-Net as AugHover-Net. It includes the following key components:

- Fine-tuned weighted cross entropy loss to emphasize more on the tail classes.
- Carefully selected data-augmentation methods to increase data variety.
- Increased the weight of the loss of horizontal and vertical maps and added one more group of diagonal distance maps to avoid unnatural predictions of the horizontal and vertical distance maps.

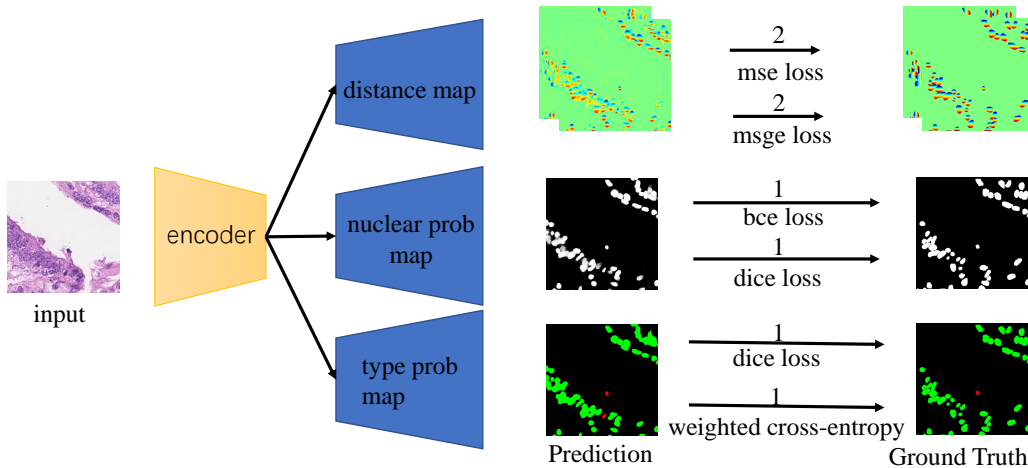


Fig. 1: Pipeline of our final framework. We follow HoVer-Net in three decoders predicting the foreground/background, horizontal/vertical/diagonal distances, and the types for each pixel. We then use a similar post-processing function as HoVer-Net to get the instance segmentation. The only difference is that we used two groups of distance maps and take the minimum one for each pixel in the final distance map for the watershed algorithm.

- Drop out layers to avoid over-fitting to the training data domain.

II. METHOD

To solve the nuclear segmentation, classification and quantification within Haematoxylin & Eosin stained histology images in the CoNIC challenge [2], we added multiple augmentations to the baseline HoVer-Net to improve its performance. The pipeline of our framework is shown in Figure 1. We split the training dataset into five folds by their domains. In this way, we can find out whether one augmentation component actually helps in cross-domain validation. In this section, we describe each of the working components in detail.

A. Weighted cross-entropy loss

The nuclei classes are extremely uneven in all the domains of the training data as shown in the description paper. The number of the epithelial nuclei is often more than 30 times larger than the number of eosinophil nuclei. Specifically, both neutrophil and eosinophil nuclei are of small amount and can be considered as tail classes. These two kinds of nuclei are also small in shape. Thus, during the model training, the losses on these two kinds of nuclei should be emphasized as the final metrics are calculated by averaging all the nuclei types. Those difficult types are much more essential than the easy types. We tried to use a second stage classification head for the classification refinement but it is very time consuming. At last, we simply train the model with the weighted cross-entropy loss which emphasizing on the tail classes. As the background is also included in the classification branch and it occupied the most of the pixels, we give it the least weighting of 0.1. For the head classes such as epithelial, lymphocyte, plasma, and connective, we give each of them a weighting parameter of 0.2. For the tail classes of neutrophil and eosinophil, we give each of them an emphasizing parameter of 0.8.

B. Data augmentations

Though Lizard has around half a million nuclei annotated, we only have several thousands of patches of 256×256 . Due to the high inter-class similarity and intra-class variability, the problem is hungry for a large amount of data. In order to improve the data variety, we tried a lot of data augmentation methods with the Albu lib [4]. In our final training, we used a combination of horizontal flip, vertical flip, random 90 degree rotation, transpose, color jitter, Gaussian blur, Median blur, and motion blur. Detailed parameters of the augmentations are included in the Section III.

C. Drop out layers

In the preliminary test phase, we found that the model performs much worse online than the offline validation. We take it as the problem of over-fitting. We thus included a technique to avoid over-fitting: heavy drop out layers. We adopt heavy drop out layers in our AugHoVer-Net. Basically, after each up-sampling convolution in the decoder, we added a drop out layer with the drop out rate of 0.5. The validation performance offline does not show much difference, but it greatly improves the validation performance online in the preliminary phase, showing that the drop out layers help avoid over-fitting of the original model.

D. Hyper-parameter for the losses

The original HoVer-Net treats every loss equally by setting the weighting parameter for each loss as 1. However, we find out that the horizontal and vertical maps are not precise enough and often leads to wrong segmentation. Specifically, it often segments one nuclei into two if the nuclei is large or long. As neutrophil nuclei tends to have multi lobes, it is also difficult for the models to learn correct horizontal and vertical maps. Thus, we decide that we should emphasize more on the horizontal and distance maps. We set the weighting parameter

of mean square error of the distance maps and the mean square error of the gradient of the distance maps as 2 in our final training.

E. Model ensemble

As a common strategy in challenges, we train the model on several splits and merge the predictions together to improve the model performance. To be specific, unlike other methods that merge different segmentation and classification results, in our model ensemble, we simply merges the predicted output of the three branches by averaging them one by one. We then perform the post-processing steps on the averaged maps and this can also give a significant improvement on the model performance. As model ensemble requires to run the models for several times, each basic model should be simple and quick. Thus, we did not use any heavy two-stage pipelines in our final algorithm.

III. TRAINING DETAILS

We tried the de-facto detection methods like Mask RCNN, but they do not perform as good as the U-Net like method(HoVer-Net). After carefully checking the labeled ground-truth data, we found that the ground-truth segmentation labels are more similar to those ones predicted by HoVer-Net than Mask-RCNN. We take this as a feature of the dataset as it is semi-automatically annotated with the aid of HoVer-Net. Thus, we simply follow HoVer-Net with one encoder and three decoder branches. We tried different encoder backbones and found that larger backbones tend to perform better. Therefore, we changed the backbone into se-resnext101 [5].

After careful experiments, we found that there is no much difference between training 2 phases(freeze the encoder in the first phase and unfreeze it in the second phase) and training one phase alone. Thus, we simply train the model with only one phase for 50 epochs. The learning rate is set as $3e-4$ at first and decays by γ of 0.1 at step 30.

Data augmentation is critic in training a general model. In training the final model, we used several reasonable augmentations to improve the model performance. They are random horizontal flips of probability 0.5, random vertical flips of probability 0.5, random 90 degrees rotation, random transpose, random color jitter (brightness of 0.2, contrast of 0.25, saturation of 0.2, and hue of 0.05), Gaussian blur (kernel of 3 and sigma of 0.3), median blur (kernel of 3), and motion blur (kernel of 3).

To valid the performance of each augmentation technique offline, we split the training dataset into five folders by their original domains, which are DigestPath, CRAG [6], GlaS [7], CoNSEP [8] and PanNuke [9]. Each time, we train with four folders and valid the model on the other. We tried many different techniques and only kept the ones that improve the performance consistently.

IV. EVALUATION METRICS

The two metrics of the CoNIC challenge evaluate the segmentation, classification and quantification within histology

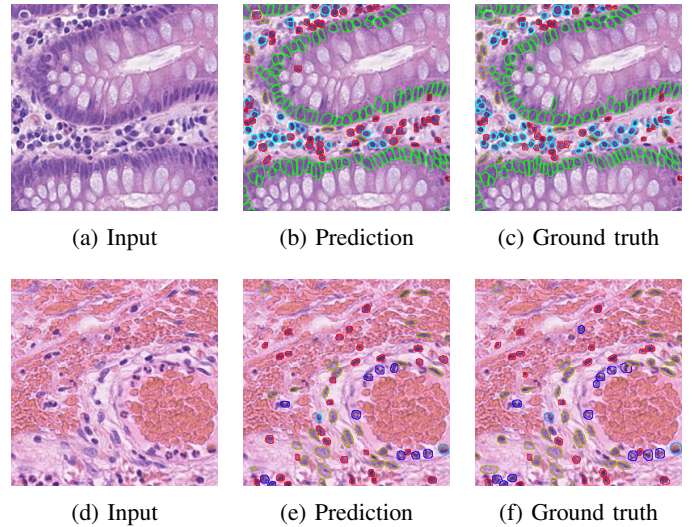


Fig. 2: Two example groups of visual results. The first column is the raw input of the algorithm, the second column shows the overlay of the predictions, and the third column shows the overlay of the ground-truth.

images. $mPQ+$ is the metric evaluating segmentation and classification while R^2 is the metric for quantification.

A. $mPQ+$

$mPQ+$ calculates the statistics over all images and takes averages of the PQ over all classes. This ensures that there are no issues when a particular class is not present in a patch. Since the metric is averaged over all classes, it is vital to make sure the models can perform well on the difficult classes.

B. R^2

R^2 counts the number of the nuclei and evaluates how close the number is to the ground-truth counts. This is also averaged over all classes and is very sensitive. Even nearby checkpoints may vary a lot in R^2 . We tried several methods to achieve a steady performance on this metric but they all failed. We then did not take this into consideration and only focused on $mPQ+$. We only used those techniques that could improve the performance on $mPQ+$ and simply used the same checkpoint for R^2 .

V. RESULTS

We achieve good validation results on all the folds and show the validation results on Glas and PanNuke in Table I. Note that in this table, we did not use any test-time augmentation or model ensembling (PanNuke and Glas).

VI. CONCLUSION

In this paper, we proposed AugHover-Net, which contains several techniques that can improve Hover-Net on nucleus segmentation and classification. It includes fine-tuned weighted cross-entropy loss which emphasizes tail classes, large data-augmentation transformations which increase data variety, increased weight of horizontal and vertical maps, increased

TABLE I: Table for comparison with the baseline. Results show that our framework consistently out-performs the baseline method, showing the superiority of the augmenting techniques we used.

	PanNuke		GlaS	
	$mPQ+$	R^2	$mPQ+$	R^2
HoVer-Net	0.4582	0.6953	0.3755	0.1307
AugHoVer-Net	0.4997	0.7384	0.4411	0.1506

group of distance maps, and heavy drop out layers to avoid over-fitting. Results show that our algorithm performs much better than the baselines, indicating the superiority of techniques we adopted.

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