Fully Convolutional Networks in Localization and Classification of Cell Nuclei

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Abstract

In this study, an automated method was developed to localize, and subsequently classify nuclei figures into three categories of lymphocyte, benign epithelial, and malignant epithelial figures from post-neoadjuvant therapy tissue slides of breast cancer. A fully convolutional network (FCN) was developed to perform both tasks in an efficient way. The algorithm consisted of applying a pre-trained FCN to an image patch to generate four heatmaps, followed by a non-maximum suppression algorithm to estimate the nuclei locations. The final classification accuracy on detected nuclei was 95.2%, surpassing previous machine learning methods based on hand-crafted features on the dataset.

1 Context

Neoadjuvant therapy (NAT) is an option for locally advanced breast cancer patients to downsize tumours. The quality of NAT is assessed by examining the amount of residual cancer within the tissue sections [Rajan et al., 2004]. Currently, the process of assessing residual tumour burden is qualitative, which may be time-consuming and impaired by inter-observer variability [Peikari et al., 2017]. In this study, we develop an automated method to localize, and subsequently classify nuclei figures into three categories of lymphocyte (L), benign epithelial (BE), and malignant epithelial (ME) figures from post-NAT tissue slides of breast cancer.

The data used consisted of 148 rectangular subsections of 20$\times$ magnification H&E stained pathology slides. The centers of the nuclei in this data were annotated by a pathologist as one of the three classes, so that in total, there were over 27000 annotated nuclei.

Nuclei localization can be approached using a variety of methods, including semantic segmentation [Shelhamer et al., 2017, Ronneberger et al., 2015, Chen et al., 2016, Ning et al., 2005, Ciresan et al., 2012, Farabet et al., 2013], object detection [Ren et al., 2015, Redmon et al., 2016], or regression

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[Cohen et al., 2017, Xie et al., 2016] methods in conjunction with either deep learning or hand-crafted features [Peikari et al., 2017]. However, since pixel level labels were not provided for the data used in this study, semantic segmentation and object detection methods were difficult to apply directly. Regression-based models, on the other hand, were not considered as they were not able to provide the precise location of each nucleus. A fully convolutional network (FCN) [Shelhamer et al., 2017] was alternatively trained in order to recognize diffeent categories of nuclei figures, and subsequently applied across an image, with non-maximum suppression (NMS) algorithm for localization of nuclei centres. Classification was ultimately performed by considering the maximum nuclei probability at the predicted nuclei locations. In case of high uncertainty in nuclei classes based on NMS algorithm, an FCN with a larger input region was employed. The proposed approach is in contrast to previous two-stage approaches [Janowczyk et al., 2016, Chen et al., 2016], where higher resolution was used instead of larger input dimension.

2 Methodology

The methodolgy consisted of three steps described as follows:

1. **Training an FCN to recognize nuclei subtypes:** - An FCN using inception modules [Szegedy et al., 2015] was trained to recognize different nuclei classes in addition to no-nuclei class. To this end, a training dataset was created consisting of tiles that each included nuclei from each of the three classes, as well as non-nuclei samples. The tiles were created by taking a box of fixed size around each nucleus, centered at the pathologist's annotation. Tiles of non-nuclei tissue were created by randomly selecting points that were at least $5\,\mu\mathrm{m}$ (10 pixels) from any other nuclei. Since there could be more than one nucleus in each tile, the FCN was trained to identify the nucleus at the center of a tile.
2. **Localization** - The trained FCN could be applied to an image of arbitrary size because of the fully convolutional architecture, generating four heatmaps corresponding to each of the nuclei probabilities, as well as the probability of no nuclei. In order to convert the four heatmaps into a set of nuclei locations, a non-maximum suppression algorithm was employed. This relied on the fact that the points on the nuclei probability heatmaps corresponding to the highest probability were most likely to be the center of the nuclei. In this procedure, the pixels with the highest nuclei probability were iteratively found, and then all points within a radius *r* of these pixels were set to 0.
3. **Classification** - In order to classify the predicted locations in the previous step as L, BE, or ME, the class of corresponding highest probability heatmap was assigned to the locations. For the most uncertain cases, we applied a more computationally expensive classifier taking a larger input region, which resulted in a more accurate prediction of the nuclei class.

3 Results

A fully convolutional network equipped with inception modules was designed to localize and classify cell nuclei in post-neoadjuvant therapy tissue slides of breast cancer, with final classification accuracy on detected nuclei of 95.2%. The perfromance of the proposed netwrok surpassed the previous machine learning methods based on hand-crafted features on this dataset (Table 1).

The proposed method, where a classifier taking a larger input region was used for the most uncertain classes increased the speed of classification by a factor of three, without compromising the accuracy.

Table 1: Performance of proposed network compared to hand-crafted features on test set

Class	Accuracy (%)		Sensitivity (%)		Specificity (%)	
	FCN	SVM*	FCN	SVM*	FCN	SVM*
L	99	92	96	80	99	94
BE	96	75	96	50	96	92
ME	96	77	95	91	98	69

*SVM: Rival method based on handcrafted features and SVM classifier

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