Deep Detection and Classification of mitotic figures

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ABSTRACT

Breast cancer is the second largest cause of cancer death among women after skin cancer. Mitotic count is an important biomarker for predicting the breast cancer prognosis according to Nottingham Grading System. Pathologists look for tumor areas and select 10 HPF(high power field) images and assign a grade based on the number of mitotic counts. Mitosis detection is a tedious task because the pathologist has to inspect a larger area. The pathologist's views about mitotic cell are also subjective. Because of these problems, an assisting tool for the pathologist will generalize and reduce the time for diagnosis. Due to recent advancements in whole slide imaging, CAD(computer-aided diagnosis) systems are becoming popular. Mitosis detection for scanner images are difficult because of variability in shape, color, texture and its similar appearance to apoptotic nuclei, darkly stained nuclei structures. In this paper, the mitotic detection task is carried out with state of the art object detector (Faster R-CNN) and classifiers (Resnet152, Densenet169, and Densenet201) for ICPR 2012 dataset. The Faster R-CNN is used in two ways. In first, it was treated as an object detector which gave an F1-score of 0.79 while in second, it was treated as a Region Proposal Network followed by an ensemble of classifiers giving an F1-score 0.75.

Keywords: Breast cancer, mitosis, FasterR-CNN

1. INTRODUCTION

According to the World Health Organization (WHO), breast cancer is the most common cancer among women worldwide. The WHO recommends the Nottingham Grading System (NGS) for tumor grading. It is a modification of Scarff, Bloom and Richardson grading system. It is obtained from the assessment of three morphological features: tubule formation, nuclear pleomorphism, and mitotic count. Among these, the mitotic count is an important indicator of invasive ductal carcinoma. During a biopsy, the tissue samples are stained with Haematoxylin and Eosin (HE) stain which is the standardized technique for visualizing the tissue components. The Haematoxylin stain enhances the nuclei with purple/blue color while the eosin enhances the cytoplasm with pink color. To grade the tumor, the pathologist visually inspects the microscopic slides usually with 40x magnification images known as High Power fields (HPF). In NGS, a score is given by counting the number of mitotic cells in 10 consecutive HPFs. The scores given for the range of mitotic count are as follows 1:0-9, 2:10-19 and 3:>19. The lack of consistency in identifying mitotic cells between pathologists will affect the diagnosis. And also, identifying mitotic cells in a whole slide can be time-consuming for a pathologist. This makes it necessary to have a computer-aided diagnosis (CAD) which can assist pathologists. Recent advancement of whole slide scanner technology has made this CAD possible. The mitosis detection is a challenging problem due to following three reasons:

- The mitotic cells are a rare event compared to non-mitotic cells.
- It has a similar appearance to other structures such as apoptotic nuclei, lymphocyte nuclei, and dust particles.
- There is a high variation in shape and texture, as the mitotic cell division is a complex biological process which undergoes various morphological transformations.

Therefore, the main aim of our work is focused on automatic detection of mitotic cells from histopathology image which will assist the pathologist.

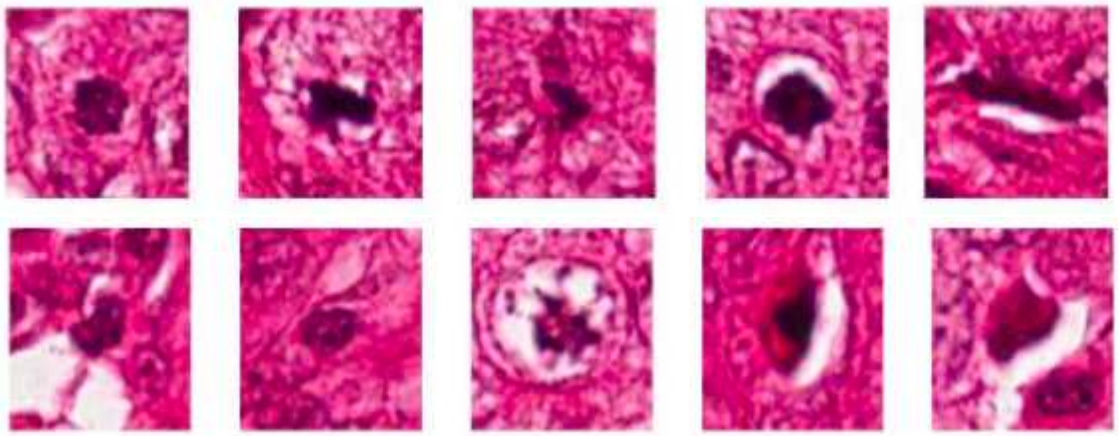

Figure 1. *First row* : Mitotic cells, *Second row* : Non-mitotic cells

2. METHODS

The detection of mitotic cell in an image cane be done by three possible approaches:

- The problem is considered as classification. A standard grid size of 100 x 100 is selected and the grid is moved over the image by a pixel. Dataset is collected with classes mitosis and non-mitosis based on whether grid contains mitotic cell or not. Machine learning and deep learning classifiers are used to differentiate between the cells. The drawback with this kind of approach is the high computation time as grid has to cover the whole image.
- The problem is treated as an object detection. Here mitosis is considered as an object and object detection algorithms can be used.
- The problem is looked as a segmentation task. This kind of approach involves two steps. In the first step, mitotic segmentation is carried out. Once the segmentation mask is created, the region of interest is obtained. Different types of classifiers can be used to differentiate the cell inside region of interest as mitotic or not.

In our paper, we have taken approaches similar to method 2 and have added additional classifiers.

2.1 Dataset

The dataset is used from 2012 ICPR MITOSIS detection contest. The images in the dataset are taken from Aperio XT scanner, resolution of the scanner is 0.2456 μm per pixel. The HPF image has an area of 512 x 512 μm^2. The dataset consists of 35 train and 15 test images. The images are of dimension 2084 x 2084. Each image contains random number of mitotic cells. The total number of mitotic cells in train, test images are 226 and 101 respectively. Some sample of mitotic and non-mitotic cells are shown in Figure 1.

2.2 Data preprocessing

In order to have uniform color/intensity between images, color normalization is done using Macenko stain normalization. As can be seen from the dataset description, the images are of dimension 2084 x 2084 and mitotic cells generally cover a maximum of 150x150 pixels. In deep learning literature, the images are resized to certain dimension and given to the network. This kind of transformation will result in complete loss of mitotic cells. The relative size of the mitotic cell makes the detection difficult when considering the original dimension. So to handle this difficulties, image patches are created each of dimension 512x512 with a stride of 32. This helps in passing the image to the network without any geometric transformations and along with that it also increases the available data. While creating image patches, the same is repeated for mask to obtain corresponding mask

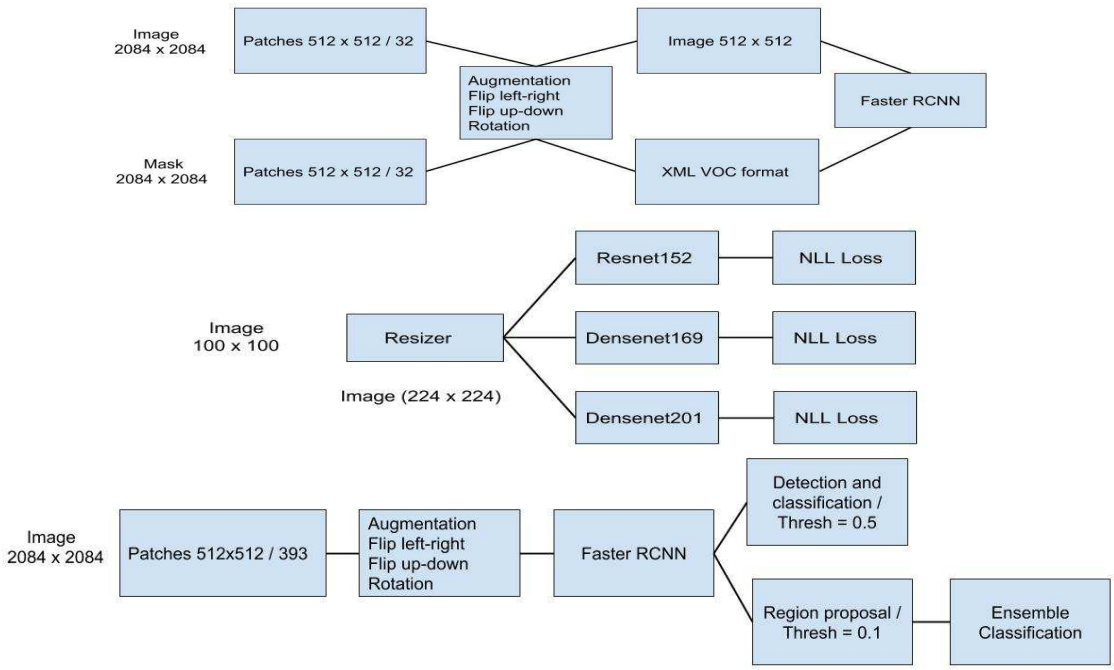

Figure 2. *First row* : Faster RCNN training , *Second row* : Classifiers training, *Third row* : Test stages

for each image. The images without mitotic cells and images in which the whole mitotic cell is not present are removed. Having image, mask as a pair helps in creating bounding box in Pascal VOC format. In order to populate the images even further, simple data augmentation techniques like flip left/right, flip up/down and random rotation between -5 to 5 degrees are followed.

2.3 Detection and classification

Faster RCNN[1] is the recent state of the art object detection network. Faster RCNN consists of two networks region proposal network (RPN) and object detection network. The object detection network contains regressor and classifier to regress the bounding box and classify the object in the bounding box. Multi-task loss function is used, cross entropy loss for classification and smooth L2 loss for regression. Faster RCNN is used in two ways:

- Selecting the confidence threshold at which the F1-score is maximum.
- Keeping the confidence threshold to a minimum at which Recall is maximum.

State of the art networks for ImageNet challenge Resnet152, Densenet169 and Densenet201 are chosen for the problem of classification. The overall pipeline of training/testing and detection/classification is shown in Figure 2.

2.3.1 Train procedure

Faster RCNN is configured to have resnet-101 backbone, anchor scales of 0.25,0.5,1.0,2.0 , aspect ratio of 0.5,1.0,2.0, batch size of 1. Using the trained model, two results are taken, one with the highest F1-score and the one with the highest Recall. The obtained regions from highest recall are split into mitotic and non-mitotic based on the ground truth. The obtained dataset split is used to train Resnet152, Densenet169 and Densenet201 separately with a batch size of 4, SGD optimizer and Negative Log Likelihood loss. The model is built using Tensorflow, PyTorch and run on GeForce GTX 1060/6GB.

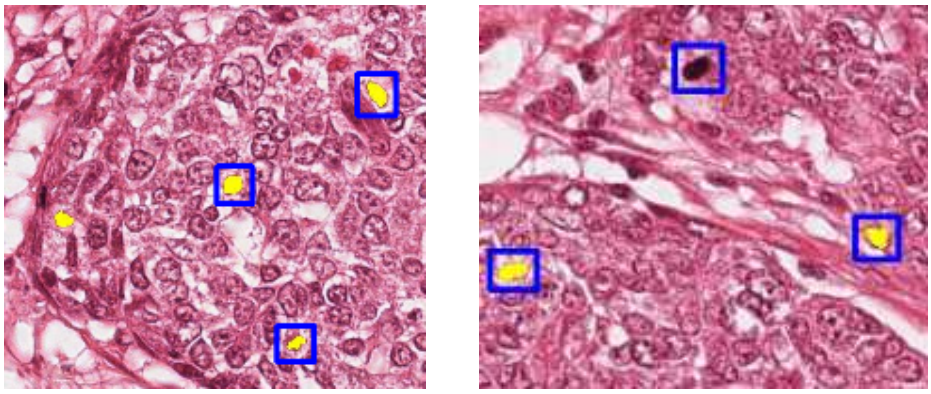

Figure 3. Sample results

2.3.2 Test Procedure

The images are split by 512 x 512 with a stride of 393 to compensate for the overlap regions. During the test phase, the image patch is taken and tested for normal, flip up/down and flip left/right to not miss a mitotic cell. The overlapping bounding boxes obtained by detection are removed by non-maximum suppression. The test process is done in two ways, one is considering the output of the Faster RCNN itself, other is taking the region proposals and passing to an ensemble of classifiers. Both this procedures will be faster than moving a grid of size 100 x 100 with stride 1. In the first case, Faster RCNN provides results at a higher rate. In the second case, combining the region proposal with an ensemble of classifiers give fewer regions to process.

Method	Precision	Recall	F-Score
DeepDet	0.854	0.812	0.832
RRF	0.835	0.811	0.823
Our Model(th=0.5)	0.856	0.735	**0.790**
CasNN	0.804	0.772	0.788
HC+CNN	0.84	0.652	0.735
Our Model(RPN)(th=0.1)+Classifier	0.761	0.732	**0.746**
IPAL	0.698	0.74	0.718
SUTECH	0.70	0.72	0.709
NEC	0.75	0.59	0.659
Our Model(RPN)(th=0.1)	0.213	**0.92**	0.341

Table 1. Performance Comparison of Our Model with other competing approaches on the ICPR 2012 Dataset.

3. RESULTS

In reference to Table 1, Our model with a confidence threshold of 0.5 achieves 79% F1 Score while inferring with a confidence threshold of 0.1 results in a recall of 92%. This model is used as a Region Proposal Network to the ensemble classifiers, achieving an F1 Score of 74.6%. Sample outputs can be seen in Figure 3. yellow marks represent a mitotic cell, blue bounding box represent the detections.

4. CONCLUSION

In this work, we have studied how state of the art classifiers and object detectors can be used in mitotic cell detection. In future, we have planned to perform join segmentation and classification task to get a better F1-score and also to extend the procedures to other publicly available datasets.

REFERENCES

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