TIPTEKNO'19
TIP TEKNOLOJİLERİ KONGRESİ
MEDICAL TECHNOLOGIES CONGRESS
3-5 Ekim 2019
Kuşadası / Aydın
İZMİR KÂTİP ÇELEBİ ÜNİVERSİTESİ

Mitosis Detection in Multispectral Histopathological Images with Deep Learning

Sardor Hazratov and Gokhan Bilgin
Department of Computer Engineering
Yildiz Technical University
34220 Istanbul, Turkey
serdarjan1995@gmail.com, gbilgin@yildiz.edu.tr

***Abstract*—In this study, segmentation of cellular structures in the multispectral histopathological images and possibility of the discrimination within normal and mitotic cells have been investigated. In histopathological images, it is very challenging task to extract the mitotic cells from the histopathological image. In the first stage of the study, 'discriminative images' are obtained using linear discriminant analysis. The discriminative images found are used to screen mitotic cell candidates and train them with deep learning networks. Since mitotic cells are usually dark pixels, the discriminating images are first filtered to obtain dark areas. Then, two-clustered k-means algorithm was used to differentiate background and mitotic candidates. With the help of convolutional neural networks, it is aimed to find the mitotic and non-mitotic areas with the classification approach. In experimental studies, ICPR-2012 dataset is used in both training and prediction stages and the training of deep artificial neural network architecture is carried out with samples of mitotic and non-mitotic regions. As a result, the F-measure for the data set is found as 0.760, the recall is 0.723 and the sensitivity is 0.802.**

Keywords*—Multispectral, histopathological images, mitosis detection, segmentation, classification.

I. Introduction

According to World Health Organization (WHO) data, breast cancer is the most common type of cancer among women. The number of patients with breast cancer and related deaths have increased significantly. The standard approach for breast cancer diagnosis relies on visual inspection of histopathological (HP) samples stained with Hematoxylin and Eosin (H&E). Traditional approach of detecting mitotic cells (MC) is manually analyzing H&E stained tissue using high-power microscopy [1].

Within the scope of this study, only the detection of mitotic cells is carried out. Mitotic count is an important parameter in breast cancer grading as it gives an evaluation of the aggressiveness of the tumour. The main phases of a mitosis are interphase, prophase, metaphase, anaphase and telophase. Detection of mitosis is a very challenging task since they appear as tiny objects in images which have a large variety of shapes. The shape of the nucleus varies depending on the phase of the mitosis. On its last stage, the telophase, a mitosis has two distinct nuclei, but they are not yet full individual cells. A mitosis in telophase must be counted as one single mitosis, it should not be miscounted as two mitosis [2]. Mitosis detection is exhausting and complex process of diagnosing every cell. Automatizing this process using novel image processing and pattern recognition techniques could reduce the effort, time and its costs making it more affordable.

978-1-7281-2420-9/19/$31.00 ©2019 IEEE

II. Related Studies

Studies for automatic detection of mitosis on H&E stained biopsies began thanks to the introduction of scanners for whole slide imaging on glass slides. Previous studies applied domain-specific handcrafted features to describe the morphological, statistical or textural characteristics of mitosis [3]–[10].

In the study [3] trained Neural Network (NN) to differentiate patches with a mitotic nucleus close to the center from all other windows. In the study [4] focused on the intensity and texture of the object in the LDA generated discriminative image space to differentiate the MCs and other cytological components and the performance of this study is F-measure 0.4790. In the studies [5], [6], textural features of histopathologic images (HPI) and Local Binary Pattern were used to recognize MC. In [7], MC was determined with the advantages of CNN using two models. The first model retrieves the mitosis candidates. Then retrieved candidates are fed into the second model for further discrimination of mitoses and mimics with similar appearance. In the study [8], has been taken approach based on the simultaneous consideration of spatial and spectral relationships in the detection of MC in digital multispectral HPI. For classification problem was developed different clusters using support vector machines (SVM), random forests (RF), naive Bayes (NB), and k-Nearest Neighbor classification methods. The highest F-measure gained with SVM classification (with 30-fold cross-validation) is 0.5465.

III. Experimental Histopathological Image Data

According to mitosis detection contest reference paper [2], 129 teams have been registered to the ICPR 2012 contest. However, only 17 teams submitted their detection of mitotic cells. And only 4 teams submitted multispectral image evaluation. The highest F-measure along them gained 0.5890. Detection MC on multispectral images is challenging than detection MC on images captured by scanner A and H. The

Multi-spectral image dataset itself has 10 spectral bands. The spectral bands are all in the visible spectrum.

Mitosis detection is difficult because mitosis are small objects with a large variety of shapes, and they can thus be easily confused with some other objects or artefacts present in the image. ICPR 2012 contest train dataset contains a total of 226 mitotic cells on images from microscopes Aperio and Hamamatsu, and 224 mitotic cells on the multispectral microscope. The full dataset is made up of 50 high power fields (HPF) coming from 5 different slides. There are 10 HPFs per slide and has a size of 512μm x 512μm. The train dataset contains only 35 HPFs. The camera attached on the top of the multispectral microscope generates images of 1360x1360 pixels. However, to cover an area of 512μm x 512μm, 2767x2767 pixels are needed. Therefore, four images used to cover the same area as the A and H scanners. However, these four images do not cover completely the 512μm x 512μm area, 47 pixels are missing in width and in height to cover fully the area. Each image, covering a quarter of a scanner image, is labeled a, b, c or d depending on its position in the scanner image.

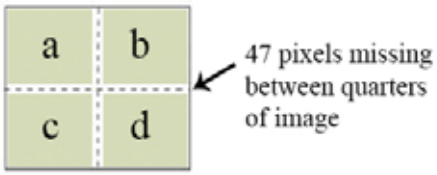

Figure 1: Locations of quarters a, b, c and d of the multispectral microscope in scanner image

Figure 1 shows the location of each quarter a, b, c, d. As the quarters do not cover completely the 512μm x 512μm area, compared to the scanner images, there is a small gap on the borders and between quarters a, b, c and d [2].

IV. Methods

Multispectral images contain more information than three-channel RGB images. However, applying image processing techniques on multispectral images is a very exhaustive job. Combining all bands of the multispectral image could help us detect MC regions easily. By using LDA (Linear Discriminant Analysis) discriminative image (DI) was acquired as described in [4]. DI was applied a filter to distinguish darker regions since mitotic regions are mainly dark regions. Applying k-means with two clusters would unify all darker pixels separating white background. The next step is applying contour analysis on the image. These contours will provide a bounding box of candidate regions for classification. As bounding boxes are acquired we can match these regions on ten-band multispectral image, so that CNN will extract features and predict whether the region is MC or non-MC.

A. Implementation of Discriminative Image

The LDA technique is a supervised technique widely used in multi-label data analysis, pattern recognition, and classification. The LDA aims to find a projection of the high-dimension data into a lower dimensional space such that the best discriminant between two or more classes is achieved [4].

The DI is generated using the following equation:

$$I_D = AI = [a_1, ..., a_K][I_1, ..., I_K]^T = \sum_{i=1}^{K} a_i I_i \quad (1)$$

where a_i is the coefficient for each spectral image, K is the number of spectral bands, and I_i is a spectral image (i is the spectral index). Using this technique requires to find a projection vector A. In order to obtain this vector firstly pixels in C1 (MC class) and C2 (non-MC class) classes are separated. Then, mean intensity (M_{C1}, M_{C2}) and variant ($\sum_{C1}, \sum_{C2}$) of pixels are calculated for every band.

$$M_{C1} = [\mu_{C1,1}, \mu_{C1,2}, ..., \mu_{C1,K}] \quad (2)$$

$$M_{C2} = [\mu_{C2,1}, \mu_{C2,2}, ..., \mu_{C2,K}] \quad (3)$$

$$\Sigma_{C1} = [\sigma_{C1,1}, \sigma_{C1,2}, ..., \sigma_{C1,K}] \quad (4)$$

$$\Sigma_{C2} = [\sigma_{C2,1}, \sigma_{C2,2}, ..., \sigma_{C2,K}] \quad (5)$$

Finally the projection vector A is obtained as below:

$$A = (\Sigma_{C1} + \Sigma_{C2})^{-1}(M_{C1} - M_{C2}) \quad (6)$$

Projection vectors have been calculated in over 100 annotated images. Average of these vectors, which is one vector with discriminative values will be used in generating all DI using (1)

B. Convolutional Neural Networks (CNNs)

CNN is a neural network based DL algorithm which is proposed by LeCun & Bengio [11]. CNN uses a non-linear method to find the most representative features of data like other DL algorithms. CNN basically accepts two-dimensional input data unlike other DL algorithms. CNN architecture consists of convolutional layer, pooling layer and fully-connected layer connected to the output. In convolutional layer, different number of kernels (in size of k x k) are convolved with the input image to obtain feature maps. Obtained feature maps are then used at the next layers. The selected kernel types of each convolutional layer can be similar or different. After each convolutional layer, the pooling layer may be placed. Essentially, the pooling layer takes the blocks created from the previous convolutional layer and applies sub-sampling to produce a single output from each block. Averaging or getting the maximum values are two different approaches in pooling.

In this study, unlike the RGB image multispectral images have 10 different channels. The CNN model architecture used on the training dataset is shown on Figure 2 as part of the flowchart. The input layer has dimension of 60x60x10 images. The Conv1 layer has 96 filters with 7x7 kernel. Next the Conv2 layer has 384 filters with 5x5 kernel size. The Conv3 layer has 128 filters with 3x3 kernel followed by 2x2 max-pooling layer. The Conv4 layer has 256 filters with 3x3 kernel. And the last Conv5 layer has 96 filters with 3x3 kernel followed by 2x2 max-pooling layer. After convolutional layers begin fully-connected layers with 64 followed by 32 Dense. The final layer with softmax activated Dense has 2 output that is prediction of MC and non-MC region.

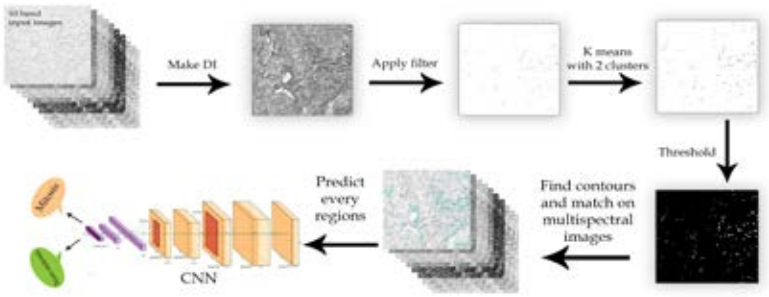

Figure 2: General flowchart of mitotic detection framework

C. General overview of the proposed technique

Firstly, multispectral images are given as input reduced to one dimension image called DI. Then DI is applied 2D filter. The result of filtered DI is image with only darker pixels. After distinguishing dark pixels k-means applied to separate white background and unify values of all darker pixels. The next step is applying threshold in order to get contours of ROI. This ROI matched in multispectral images and resized 60x60x10 as input of CNN. Then CNN predicts whether given ROI mitotic or not. Figure 2 shows the flowchart of the proposed steps in predicting MC. To train CNN set with 2 classes that are MC (C1) and non-MC (C2) generated over images.

V. Generation of Training Data for CNN

The image data used in this paper are obtained from publicly available ICPR-2012 dataset, which includes 35 high-resolution multispectral images. All images have been manually examined by pathologists and a total of 232 MCs have been labeled. The images were acquired using a ten-band multispectral microscope.

C1 class obtained with annotated MC pixels and resized to 60x60 with 10 bands. In deep learning tasks, a lot of data is needed to train DNN model. C1 class dataset is not big enough for doing DNN tasks. In order to overcome lack of data C1 class data flipped vertically, horizontally and mirrored (both horizontal and vertical flip), also for every flipped image, regions zoomed by expanding pixels with different size.

C2 class data candidates obtained from filtered DI. The candidate selection process has some steps that firstly DI applied 11x11 filter with values 1/53. This filter picks up dark pixels. Then k-means with two clusters applied to separate background from candidate regions. After that regions bounded with rectangles picked and compared to true MC pixels from the annotation file which comes with dataset itself. If the pixels do not belong to MC, the region annotated as C2 data. All C2 data resized to 60x60 with different expansion values (zooming) and saved as 10 band-image. Since lots of candidates obtained from dark regions there is no need to flip C2 data. Figures 3, 4 and 5 show how C1 and C2 class data looks like.

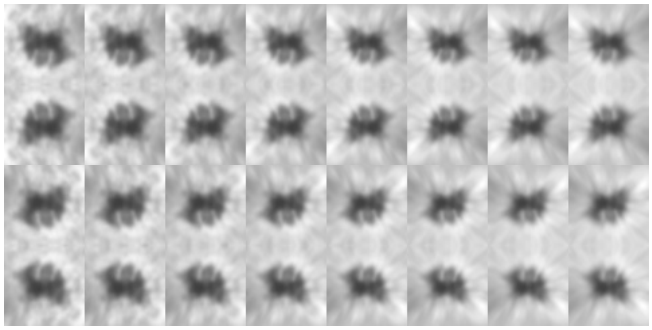

Figure 3: Train data for C1. Flipped and zoomed sample MC on 1 band. Expansion values [8, 10, 12, 14, 16, 18, 20, 21]

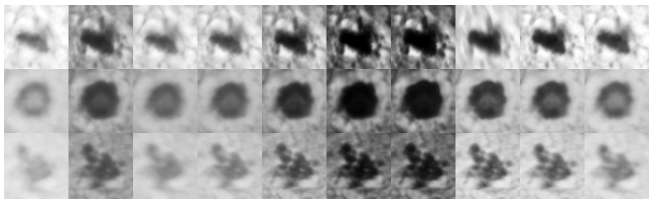

Figure 4: Train data for C1. MC with 10 bands.

VI. Experimental Studies

Approximately 14,000 C1 class data and 50,000 C2 class data have been generated over ICPR-2012 train dataset images. All data has been trained on CNN with 0.15 cross-validation and 30 epochs. The train performance was 0.96 and the validation performance was 0.91. Figure 6 shows the predicted result. On the right image has one False-Positive.

All train data images have been given to CNN to predict mitosis areas and compared to actual mitosis regions by a script. At the candidate extraction stage of the proposed method, some mitotic regions were divided by the filter. Sometimes candidate region did not cover the full area of actual MC area. In this case uncovered area was labeled as False-Negative. While the candidate extraction process pixel expansion value selected as 16 since it had better performance on trained CNN. The confusion table is shown on Table I:

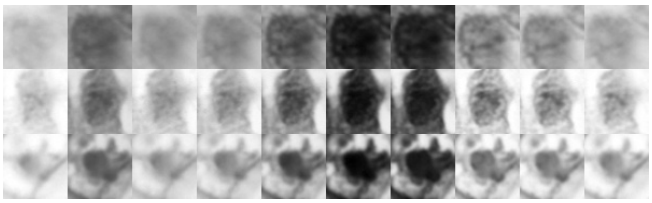

Figure 5: Train data for C2. Non-MC with 10 bands.

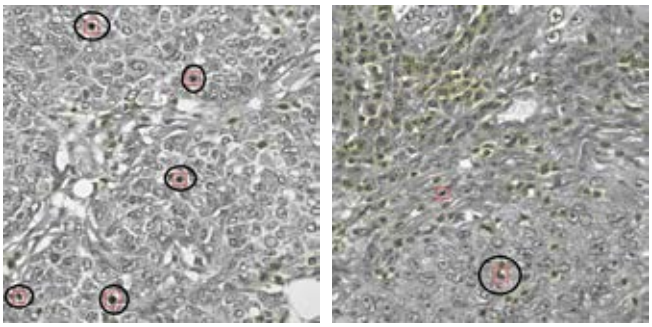

Figure 6: Visual mitosis prediction results. Red squares are predicted by CNN and black circles are actual mitosis areas on the annotated image.

Table I: Confusion table obtained by the proposed framework

	Predicted MC	Predicted Non-MC
Actual MC	TP=191	FN=73
Actual Non-MC	FP=47	TN=9398

Recall (sensitivity) = $\frac{TP}{TP+FN}$ = 0.723

Precision (positive predictive value) = $\frac{TP}{TP+FP}$ = 0.802

F-measure = $2 * (\frac{precision \times recall}{precision+recall})$ = 0.760

VII. Conclusion

In this work, a deep learning based feature extraction method using convolutional neural network is proposed for automated mitosis detection on histopathological images. The proposed method has been tested on ICPR-2012 breast cancer histopathological images dataset. Since the dataset is not enough for deep learning tasks, data augmentation was used. MC class training data were zoomed by expanding pixels around candidate regions and also flipping them horizontally, vertically and both horizontal-vertically. Non-MC class training data were acquired from dark regions on the discriminative image. Approximately 50,000 non-mitotic and 14,000 mitotic regions have been generated from the original 10-band images. The precision, recall and F-measure values are 0.802, 0.723 and 0.760 respectively. These results prove that the proposed technique achieved promising results for mitosis detection on histopathological images. Evaluation of the publicly available dataset and comparison with the existing techniques shows effectiveness of the proposed technique. The proposed technique is expected to reduce the workload of pathologists when they evaluate the cancer grade of biopsy.

References

[1] R. Siegel, D. Naishadham, A. Jemal, "Cancer statistics", CA: A Cancer Journal for Clinicians, vol. 63, no. 1, pp. 11–30, 2013.

[2] L. Roux, D. Racoceanu, N. Loménie, M. Kulikova, H. Irshad, J. Klossa, F. Capron, C. Genestie, G. L. Naour, M. N. Gurcan, "Mitosis detection in breast cancer histological images an ICPR 2012 contest", J. Pathol. Inf., vol.4, no.1, pp. 8, 2013.

[3] H. Chen, Q. Dou, X. Wang, J. Qin, P.A. Heng, "Mitosis detection in breast cancer histology images via deep cascaded networks", In Proceedings of the 30th AAAI Conference on Artificial Intelligence, pp. 1167–73. Palo Alto, USA: 2016.

[4] C. Lu, M. Mandal, "Toward automatic mitotic cell detection and segmentation in multispectral histopathological images", IEEE Journal of Biomedical and Health Informatics, vol. 18, no. 2, 2014.

[5] A. Albayrak, G. Bilgin, "Detection of mitotic cells in histopathological images using textural features", IEEE 21st Signal Processing and Communications Applications Conference, SIU'13, pp 1–4, 2013.

[6] I. O. Sığırcı, A. Albayrak, G. Bilgin, "Detection of mitotic cells using completed local binary pattern in histopathological images", IEEE 23nd Signal Processing and Communications Applications Conference, SIU'15, pp. 1078-1081, 2015.

[7] D. C. Cireşan, A. Giusti, L. M. Gambardella, J. Schmidhuber, "Mitosis detection in breast cancer histology images with deep neural networks", Proceedings of the 2013 Medical Image Computing and Computer-Assisted Intervention Conference, pp. 411–18. Berlin: Springer, 2013.

[8] H. Çukur, G. Bilgin, "Detection of mitotic cells in multispectral histopathological images", IEEE 25th Signal Processing and Communications Applications Conference, SIU'17, pp. 1-4, 2017.

[9] M. Üstüner, G. Bilgin, "Mitosis detection on histopathological images using statistical detection algorithms", IEEE 23nd Signal Processing and Communications Applications Conference, SIU'15, pp. 540-543, 2015.

[10] C. Sommer, L. Fiaschi, F. A. Hamprecht, D. W. Gerlich, "Learning-based mitotic cell detection in histopathological images", Proceedings of the 21st International Conference on Pattern Recognition, ICPR2012, Tsukuba, Japan pp. 2306-2309, 2012.

[11] Y. Le Cun, Y. Bengio, "Convolutional networks for images, speech, and time series", The Handbook of Brain Theory and Neural Networks, vol.3361, no.10, p. 1995, 1998.

[12] A. Paul, A. Dey, D. P. Mukherjee, J. Sivaswamy, and V. Tourani, "Regenerative random forest with automatic feature selection to detect mitosis in histopathological breast cancer images", International Conference on Medical Image Computing and Computer-Assisted Intervention, pp 94-102, 2015.

[13] M. Veta, J. P. W. Pluim, P. J. van Diest, M. A. Viergever, "Breast Cancer Histopathology Image Analysis: A Review", IEEE Transactions on Biomedical Engineering, vol.61, issue 5, pp 1400-1411, 2014.

[14] H. Irshad, L. Roux, D. Racoceanu, "Multi-channels statistical and morphological features based mitosis detection in breast cancer histopathology", Annual International Conference of the IEEE Engineering in Medicine and Biology Society, pp. 6091-6094, 2013.

[15] M. Saha, C. Chakraborty, D. Racoceanu, "Efficient deep learning model for mitosis detection using breast histopathology images", Computerized Medical Imaging and Graphics, vol 64, pp 29-40, 2018.

[16] T. Wan, X. Liu, J. Chen, Z. Qin, "Wavelet-based statistical features for distinguishing mitotic and non-mitotic cells in breast cancer histopathology", IEEE Int. Conference on Image Processing, pp 2290-2294, 2015.

[17] N. Wahab, A. Khan, Y. S. Lee, "Two-phase deep convolutional neural network for reducing class skewness in histopathological images based breast cancer detection", Computers in Biology and Medicine, vol 85, pp 86-97, 2017.

[18] H. Irshad, A. Gouaillard, L. Roux, D. Racoceanu, "Multispectral band selection and spatial characterization: Application to mitosis detection in breast cancer histopathology", Computerized Medical Imaging and Graphics, vol 38, issue 5, pp 390-402, 2014.