A Deep Learning Based Framework for Accurate Segmentation of Cervical Cytoplasm and Nuclei

Youyi Song, Ling Zhang, Siping Chen, Dong Ni, Baopu Li, Yongjing Zhou, Baiying Lei* and Tianfu Wang*

***Abstract*—In this paper, a superpixel and convolution neural network (CNN) based segmentation method is proposed for cervical cancer cell segmentation. Since the background and cytoplasm contrast is not relatively obvious, cytoplasm segmentation is first performed. Deep learning based on CNN is explored for region of interest detection. A coarse-to-fine nucleus segmentation for cervical cancer cell segmentation and further refinement is also developed. Experimental results show that an accuracy of 94.50% is achieved for nucleus region detection and a precision of 0.9143±0.0202 and a recall of 0.8726±0.0008 are achieved for nucleus cell segmentation. Furthermore, our comparative analysis also shows that the proposed method outperforms the related methods.**

I. Introduction

Cervical cancer is one of the most widely spread cancer for woman's morbidity and mortality [1]. Detection of the cervical cancer cell has played a very important role in clinical practice. Currently, the popular diagnosis utilizes the cytology screening to prevent cervical cancer at an early stage, which depends heavily on the clinician's experience for accurate diagnosis. It is time-consuming and error-prone to perform such diagnosis even for an experienced doctor. To address this issue, low-cost and labor-saving methods are more desirable than the doctor's experience especially in the under-privileged countries. It is also an effective way to eliminate the psychological fatigue of manual inspection, and hence misdiagnosis and missed diagnosis can be reduced. Consequently, development of new automated diagnosis techniques to prevent cervical cancer has attracted a lot of interest and become a focus [2].

In the recent year, automatic-assisting approaches have achieved great success in cell detection. Since the nucleus and background have relatively high contrast, detection of abnormal cytoplasmic cells is also very critical [3]. In the literature, there are numerous cell segmentation algorithms available [2-7]. Although these methods may work well on their own datasets, the clinical application is still a far way to go. For example, In [7], smoothing is applied to solve the problem of low contrast between background and cytoplasm and strengthen the border. A gradient direction edge enhancement operator was used to enhance the performance. The nucleus contours are refined by nucleus intensity threshold. However, this approach was developed for isolated cell not for multi-cells in a Field-of-View. In [6], Genctav et al. proposed a unsupervised method for cervical cell segmentation using multi-scale watershed. The performance is very promising even under uneven staining, low contrast and overlapping cell condition. However, it is unclear whether this method can work on cervical cancer cells. Recently, Zhang et al [2] proposed to segment the cytoplasm region with a multi-thresholding Otsu method, and segment the abnormal cervical nuclei using a local adaptive graph cuts approach, However, the nucleus segmentation lacks of effective boundary constrain, which might lead to inaccurate segmentation results.

The traditional methods assume the input image contains only a single cell, and hence the image boundary or cytoplasmic borders of the nucleus are considered. However, multiple cells or cells with irregular cross lined leukocytes are quite common. It is more challenging to address the multiple cell issue than the single one. Besides, dust, impurities and uneven illumination increase the difficulty to segment nucleus accurately. Due to these challenges, most of the existing methods cannot achieve very promising results. It is essential to develop a new automatic tool for cervical cancer nucleus segmentation. Based on the observations and limitations of the current methods, a superpixel algorithm [8] for segmentation is developed to segment cervical cancer nucleus. A rough template structure is constructed followed by detecting the nucleus region based on the convolution neural network (CNN) [9]. The use of superpixel guarantees the accuracy of cytoplasm boundary segmentation. The coarse to fine segmentation algorithm is also effective for the nucleus segmentation.

II. Methodology

A. Overview

Figure 1 illustrates the overview of the proposed method. The input image is pre-processed first, and a template is formed for superpixel extraction. The nucleus region is detected based on the CNN method for further segmentation. Finally, coarse to fine segmentation is applied to segment the cervical cancer cell precisely. Figures 2 and 3 show the detailed segmentation procedure visually.

Y. Song, L. Zhang, S. Chen, D. Ni, B. Li, Y. Zhou, B. Lei and T. Wang* are with Department of Biomedical Engineering, School of Medicine, Shenzhen University, National-Regional Key Technology Engineering Laboratory for Medical Ultrasound, Guangdong Key Laboratory for Biomedical Measurements and Ultrasound Imaging, Shenzhen, China.

This work was supported partly by National Natural Science Foundation of China (Nos. 61101026, 61372006, 60871060 61031003 and 81270707), Shenzhen Key Basic Research Project (Nos. 201101013, 201202076, JCYJ20130329105033277, and JSE201109150013A), China Postdoctoral Science Foundation Funded Project (No. 2013M540663) and National Natural Science Foundation of Guangdong Province(No. S2013040014448).
(Corresponding authors' Email:*leiby@szu.edu.cn, *tfwang@szu.edu.cn).

978-1-4244-7929-0/14/$26.00 ©2014 IEEE

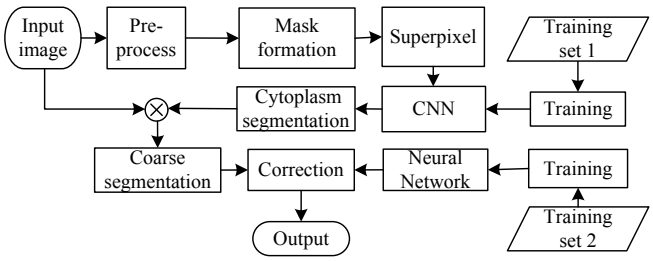

Figure 1. Framework of the proposed method.

B. Pre-process

Normally, the captured image has a great amount of impulse and Gaussian noises, which are mainly generated in the image acquisition process. Cell segmentation requires a certain image quality and noise reduction is necessary. Median filter is very effective to reduce these noises. However, it is proved that trimmed mean filter is more effective to eliminate them than the median filter [7]. Assuming C_k is the color value in the $m \times m$ window, trimmed mean filter is defined as:

$$C = \frac{1}{(1-2\lambda)m^2} \sum_{k=\lambda m^2+1}^{(1-\lambda)m^2} C_k \qquad (1)$$

In our experiment, $\lambda = 0.4$, window size is set 11×11 to get the best results.

C. Cytoplasm Mask

The purpose of the template is to provide a rough cytoplasmic region by segmenting an image coarsely, and thus the computation time of superpixel extraction is reduced. Since the cells in the nucleus region must be stained in red tones, whereas the background area is not stained. Therefore, the image is converted from RGB color space to CIE LAB color space to increase the contrast between nucleus and background. To further enhance the contrast, the grayscale range is increased from $[r_{\min}, r_{\max}]$ to [0,255] by:

$$f(x) = \frac{D_m}{2}\{1 + \frac{1}{\sin(\alpha\frac{\pi}{2})}\sin[\alpha\pi(\frac{x}{D_m} - \frac{1}{2})]\}, 0 < \alpha < 1 \qquad (2)$$

where D_m is the maximum value after transformation, x is gray pixel value, α is a weight parameter.

It is shown that cervical cancer cell is very complicated due to inconsistent staining, ill-lightening, inflammatory cells, white blood cells and impurities (i.e. dust and graphite particles), a global threshold is not suitable. High-dimensional Otsu thresholding method is adopted for segmentation. It is found that better coarse segmentation results can be achieved by the obtained threshold than a global threshold. Morphological operations are also applied to smooth boundary. Besides, preliminary filtering based on this area is able to eliminate impurities. An example result of this step is shown in Figure 2b.

D. Superpixel

After coarse segmentation, the nucleus areas containing uneven staining and bad illumination are not well-segmented, especially for the border area. Fine-grained segmentation to correct the coarse segmentation is very necessary and important. It was proved that superpixel algorithm is very promising for the low contrast segmentation [8]. Superpixel had also shown very remarkable performance in blood vessels, optic disc glaucoma, and prostate segmentation. A simple linear iterative clustering (SLIC) algorithm is very attractive for practical applications due to its fast speed, less parameters and reserved boundaries [8]. SLIC makes use of five dimensional feature (CIE LAB of L, A, B, and two dimensional position information) to improve the shape of superpixels. After coarse segmentation, it is observed that around 15 pixels wide are reserved to split the coarse image, and hence morphological dilation is implemented to boost the performance. SLIC is then applied to calculate over the pixel and split the nuclei from the boundary area precisely by high discriminative power (Figure 2c).

E. Convolutional Neural Network

CNN has a shared network similar to the biological neural networks. The complexity of the network model and the number of weights is reduced in this way. CNN is able to learn numerous mappings between input and output to train the known patterns. CNN is applied due to the above mentioned attractive characteristics.

To extract features based on superpixel, size, color, shape and texture descriptor with intensity gradients are selected since these features can represent the cervical cancer cells very well. To distinguish between cells and background, color is very important. A total of 18 color features is included to reduce the amount of computation. It is commonly assumed that spatial relationships between local appearances affect classification of underlying structure. Therefore, the contextual spatial information is also explored to characterize the appearance and shape of each superpixel and its neighborhood.

F. Coarse Nucleus Segmentation

In the actual case, due to cytoplasmic staining or overlapping of inflammatory cells, erroneous nucleus segmentation may occur. To address it, RGB color space is transformed to HSV color space, and the following processing is based on the V channel. In order to enhance the contrast between the nucleus/inflammatory cells and cytoplasm, transformation is applied as well. V channel in image undergoes the morphological top-hat transformation. In order to obtain a better image binarization, a new nucleus template is constructed to enhance the segmentation performance. Let $L(x, y)$ be the pixel value, $G_\sigma(x, y)$ be the Gaussian mask, sobel edge operator is first applied to locate the edges. An adaptive threshold segmentation method is designed as:

$$T(x, y) = L(x, y) * G_\sigma(x, y) - b \qquad (3)$$

The nucleus border region is smoothed by morphological operations. The corresponding template area is thresholded by

a specified value.

G.Fine Nucleus Correction

Most of the nucleus has been split accurately after a coarse segmentation. Due to uneven staining, weak staining of abnormal nucleus, the nucleus segmentation performance needs to be further improved. Therefore, R, G, B values of in both non-nucleus region and nucleus region are selected as features. Both non-nucleus and nuclei data are randomly selected and cross-validated by neural network. The coarse segmented area is enlarged by 5 pixels. The final nucleus is obtained by the updated nucleus with point-based pixel value in each test.

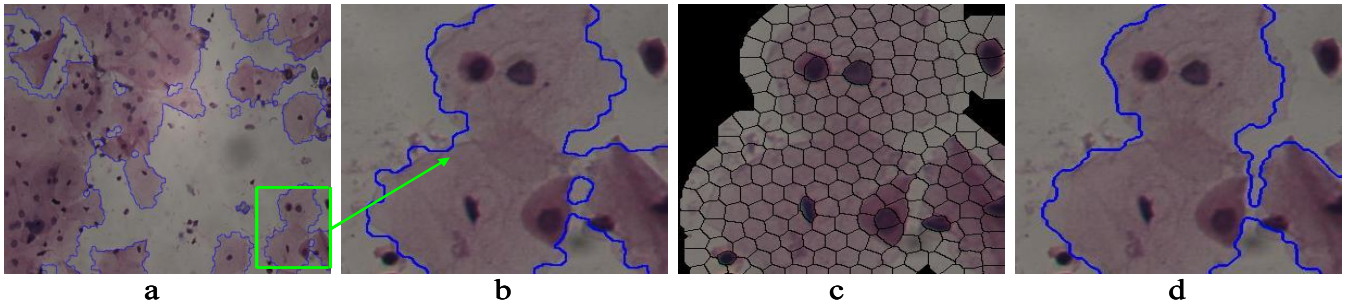

Figure 2. Illustration of cytoplasm segmentation; a. Cytoplasm boundaryafter coarse segmentation; b. Image of the area in the green frame of Figure 1a; c. Superpixel extraction for Figure 1b; d. Cytoplasm boundary after fine segmentation.

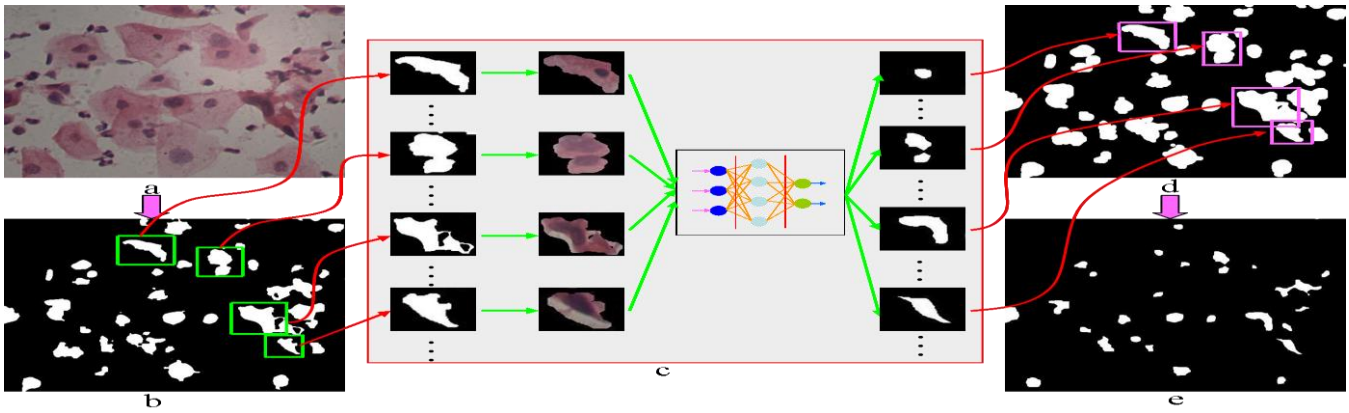

Figure 3. Illustration of segmeantion; a. Input image b. Coarse segmentation,c. Segmentation correction; d. Fine segmentation, e. Final segmentation results.

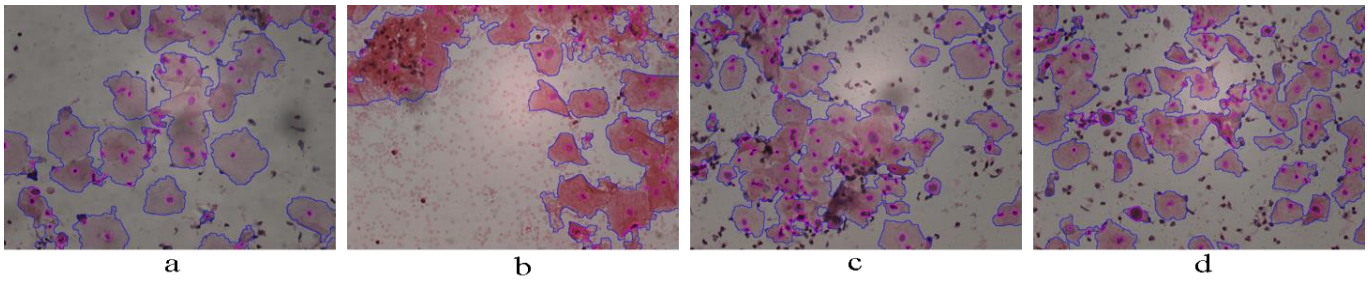

Figure 4. Representative image after segmentation (blue line denotes cyptclosm boundary and pink line denotes nucleus boundary).

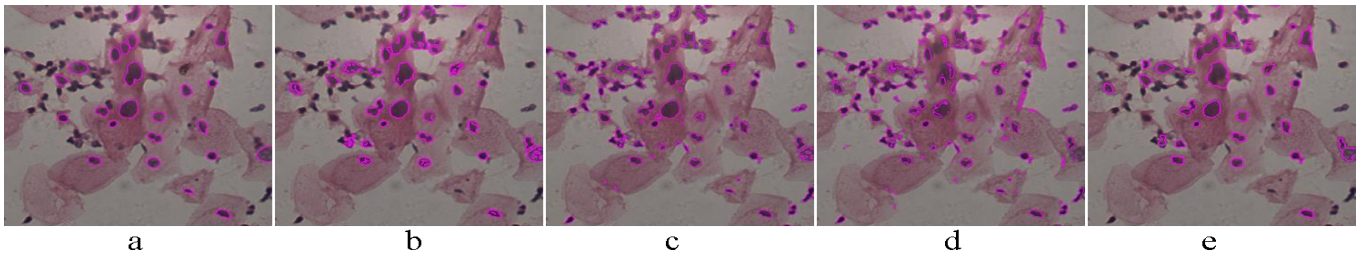

Figure 5. Comparison of segmentation methods; a Ground truth; b Canny method; c Otsu method; d Method in [2]; e) The proposed method.

III. EXPERIMENTAL RESULTS

A. Materials and Experimental Setup

Our experiments are based on 200 women subjects aged 22-64 from the Sixth People's Hospital of Shenzhen. A total of 53 slides are collected using the Olympus BX43 microscope at a magnification rate of 40. 21 images (15 images contain abnormal, and 6 images contain normal nuclei only) are utilized for performance evaluation. H&E stain is simple to use, inexpensive, and clinical-acceptable, and hence it is chosen in our study. All slides were prepared using manual liquid-based cytology (MLBC) technique stained with H&E, and confirmed by biopsy. It should be noted that all the materials used in this experiment were approved by the Ethics Committee of the Sixth People's Hospital of Shenzhen. A total of 1400 cell samples are collected for background data, CNN utilizes 1200 cell samples for each train, and the remaining 200 cell samples is used for test data. For an image size of 1024×1360, the total processing time for segmentation is around 50s (3.39GB RAM, CPU (3.20GHz Intel i5-3470)).

B. Evaluation of Detection Performance

Since accurate evaluation of every cytoplasm cell is very difficult, the cytoplasm evaluation is mainly based on experience and observation. In total, we had collected 1400 background data and 1200 of them are used for training, and the rest are for testing. Detection performance evaluation is based on accuracy, sensitivity and specificity. To compare the performance with different algorithms, CNN, backward propagation neural network (BPNN), probabilistic neural networks (PNN), support vector machine (SVM), and learning vector quantization (LVQ) algorithms are selected for performance comparison. BPNN is a supervised method, which adjusts weights of each layer by minimizing the objective function using a gradient method. Accuracy, sensitivity, specificity and F1 measure are employed for detection performance evaluation quantitatively. Table 1 summarizes the detection performance of different algorithms. Based on the quantitative results, CNN is found to outperform other algorithms, which demonstrates that deep learning is very effective for nucleus and cytoplasm detection. Obviously, the detection performance is high enough for the following cervical cancer nuclei segmentation.

TABLE I. NUCLEUS REGION DETECTION RESULTS.

Algorithms	Accuracy	Sensitivity	Specificity	F1 measure
BPNN	0.8900	0.8578	0.9286	0.8947
PNN	0.8775	0.8912	0.8647	0.8753
SVM	0.8975	0.8841	0.9119	0.8993
LVQ	0.9000	0.9124	0.8883	0.8985
CNN	**0.9450**	**0.9406**	**0.9495**	**0.9453**

C. Evaluation of Cytoplasmic and Nucleus Segmentation

As to segmentation performance evaluation, the popular F1 measure, precision and recall are utilized for performance comparison. The comparison of the manual and automatic segmentation results for nucleus identification is illustrated in Figure 4. It is observed that the automatic segmentation is very desirable compared to the ground truth based on doctors' experience. The quantitative results of the segmentation are shown in Table 2. It can be seen that the segmentation performance is very promising. The comparison of segmentation results in terms of different methods demonstrates that the proposed method has achieved the best segmentation result. We can see that the proposed segmentation result outperforms the state-of-the-arts method in [2] in terms of nucleus segmentation.

Figure 5 shows the final segmentation results. It can be observed that cytoplasm and nucleus are accurately extracted by the proposed method. Our segmentation method can work well even under dyed shades, uneven illumination, dust blocking and abnormal nuclei.

TABLE II. SEGMENTATION RESULTS (MEAN±STANDARD DEVIATION).

Method	F1 measure	Precision	Recall
Canny	0.5488±0.0215	0.9084±0.0008	0.4094±0.0202
Otsu	0.5622±0.0202	0.5073±0.0292	0.6837±0.0284
ALGC [2]	0.8732±0.0015	0.8497±0.0047	0.9016±0.0004
Our method	**0.8951±0.0215**	**0.9143±0.0202**	**0.8726±0.0008**

IV. CONCLUSION

In this paper, superpixel and CNN techniques are investigated for accurate cytoplasm and nucleus segmentation in the cervical cancer image. Our experimental results indicate that both superpixel partitioning and CNN are highly effective for cervical cancer cell segmentation. The achieved remarkable segmentation results demonstrate that the proposed method could be possible used for automatic cervical cancer detection and diagnosis.

REFERENCES

[1] A. Jemal, F. Bray, M. M. Center, J. Ferlay, E. Ward, and D. Forman, "Global cancer statistics," *CA: a cancer journal for clinicians,* vol. 61, pp. 69-90, 2011.

[2] L. Zhang, H. Kong, C. Ting Chin, S. Liu, X. Fan, T. Wang, *et al.*, "Automation‐assisted cervical cancer screening in manual liquid‐based cytology with hematoxylin and eosin staining," *Cytometry Part A,* 2013.

[3] Y. Marinakis, G. Dounias, and J. Jantzen, "Pap smear diagnosis using a hybrid intelligent scheme focusing on genetic algorithm based feature selection and nearest neighbor classification," *Computers in Biology and Medicine,* vol. 39, pp. 69-78, 2009.

[4] O. Lezoray and H. Cardot, "Cooperation of color pixel classification schemes and color watershed: a study for microscopic images," *IEEE Transactions on Image Processing,* vol. 11, pp. 783-789, 2002.

[5] M.-H. Tsai, Y.-K. Chan, Z.-Z. Lin, S.-F. Yang-Mao, and P.-C. Huang, "Nucleus and cytoplast contour detector of cervical smear image," *Pattern Recognition Letters,* vol. 29, pp. 1441-1453, 2008.

[6] A. Gençtav, S. Aksoy, and S. Önder, "Unsupervised segmentation and classification of cervical cell images," *Pattern Recognition,* vol. 45, pp. 4151-4168, 2012.

[7] S.-F. Yang-Mao, Y.-K. Chan, and Y.-P. Chu, "Edge enhancement nucleus and cytoplast contour detector of cervical smear images," *IEEE Transactions on Systems, Man, and Cybernetics, Part B: Cybernetics,* vol. 38, pp. 353-366, 2008.

[8] R. Achanta, A. Shaji, K. Smith, A. Lucchi, P. Fua, and S. Susstrunk, "SLIC superpixels compared to state-of-the-art superpixel methods," *IEEE Transactions on Pattern Analysis and Machine Intelligence,* vol. 34, pp. 2274-2282, 2012.

[9] A. Krizhevsky, I. Sutskever, and G. E. Hinton, "ImageNet Classification with Deep Convolutional Neural Networks," in *NIPS*, 2012, p. 4.