An Efficient Method of Histological Cell Image Detection Based on Spatial Information Convolution Neural Network

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ABSTRACT
As an important research direction in the field of medical images, histopathological cell image detection has been widely used in computer-aided diagnosis, biological research fields. With the rise of deep learning, neural network is applied to medical image analysis, which can realize the automatic detection and classification of histological cell images. In order to solve the problem that the output of the existing neural network is affected by spatial information factors in its topological domain, on the basis of the traditional convolution neural network. Combined with the spatial position information, an improved convolution neural network model for histological cell image detection is proposed. Taking the traditional convolution neural network as the carrier, the convolution neural network model based on spatial information is constructed, which makes the model has the ability to fuse spatial information and eigenvector. Histopathological cell images were preprocessed by color deconvolution. Finally, a model verification experiment based on colorectal cancer image dataset is designed. The model proposed in this paper shows better performance than the state-of-the-art methods in four different categories (more than 20000 experimental images): the experimental accuracy is 75.8%, and the recall rate is 82.3%. F1 reached 80.1%.

CCS Concepts
•Computing methodologies → Image processing

Keywords
Cell nuclei detection; Convolutional neural network; Spatial information.

1. INTRODUCTION
Qualitative and quantitative analysis of tumor cells plays a decisive role in the process of tumor analysis. Tumor tissue is composed of parenchyma and stroma, and tumor parenchyma is the main component of tumor, which has tissue source specificity. It determines the biological characteristics of the tumor and the particularity of each tumor. The mainstream cell detection method in biology is to use multiple protein markers to label different cells in cancer tissue. On the basis of this method, combined with the characteristics of cell morphology, the automatic detection of nucleus is designed and realized.

At present, the main factors affecting nuclear detection are as follows: (1) there are a large number of problems in the preparation of nuclear images, such as poor fixation, poor staining, failed digital focusing of images, and the quality of medical cell images is low; (2) the internal structure of nucleus is complex and it is difficult to extract features. In order to solve the above problems, some scholars design cell detection methods by manually extracting cell features.

With the development of deep learning, the design of histopathological cell detection model based on neural network has achieved good results, and it has been proved that the method of deep learning is generally better than the traditional nuclear detection method. Xu *et al.* [1] used stacked sparse autoencoder to learn a high-level representation of nuclear and non-nuclear objects in an unsupervised fashion. Yuan *et al.* [2] classified nuclei into cancer, lymphocyte or stromal based on the morphological features in H&E stained breast cancer images. This requires accurate segmentation of all the nuclei which is not straight forward due to the complex micro-architecture of tumor. Cosatto *et al.* [3] proposed to use Gaussian difference and Hough transform to find radial symmetrical shapes to detect nuclei. This makes it easier to find abnormally enlarged nuclei, but by using a single feature for detection, this will significantly degrade performance on large datasets. AI Kofahi *et al.* [4] used the graphic cutting method of image response Gauss-Laplacian operator filter to obtain good performance in the detection of nucleus, but when the nucleus is too large, the problem of over-segmentation will occur. Kuse *et al.* [5] used the method of local phase bilateral symmetry to detect nuclei. This method has proved its effectiveness in detecting β cells in mouse pancreatic sections and lymphocytes in breast histological images, but the accuracy is not high. Similarly, Veta *et al.* [6] rely on the direction of gradient to determine the center of the nucleus. This method has good performance in detection accuracy, but may not be able to detect fusiform nuclei and irregular malignant epithelial nuclei. Arteta *et al.* [7] used the most stable extremum region for detection. This method has high accuracy in the detection of chromatin structure regular nuclei, but it does not perform well in the detection of weakly stained nuclei or nuclei with irregular chromatin structure. Ali *et al.* [8] proposed an active contour method based on shape model to detect and segment filter kernels and achieve good results. However, under the detection of tumor nucleus, this method will become unstable. Vink *et al.* [9] use an adaptive lifting algorithm (Adaboost) classifier to train two detectors, one using pixel-based features and the other using features based on

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Hal transform. The results of combining the two detectors to detect the nuclei in the immune histochemical staining of breast tissue images have a high accuracy, but the effect of this method in detecting slender fibroblasts and small nuclei is limited.

However, the limitation of CNN, especially about the ignorance for spatial information, restricts the development of nuclei image detection. Xie *et al.* [10] proposed structural regression CNN capable of learning a proximity map of cell nuclei and was shown by the authors to provide more accurate detection results. Another closely related deep learning work is by Xie *et al.* [11], which localizes nucleus centroids through a voting scheme.

To sum up, the cell detection method depends on the stability of the shape and characteristics of the nucleus for cell detection. However, the existing in-depth learning methods for histiocytology nuclear detection do not take the spatial location information into account, which has a certain impact on the improvement of detection performance.

In this paper, a new deep learning method based on spatial position information is proposed, which is based on convolution neural network (Convolutional Neural Network for short CNN). A method for the detection of nuclei in histopathological images of colorectal adenocarcinoma by conventional hematoxylin-eosin staining. We propose a spatial constrained convolution neural network, which is a new network model based on the traditional convolution neural network, which includes parameter estimation layer and spatial constraint layer. The confidence used to predict the centroid position of the nucleus and whether they correspond to the true centroid. The advantage of this is that the center of the nucleus can be given a high probability of being detected by us.

The structures of this paper are as follows: in section 1, we introduce the background of our research and related significant works; section 2 illustrates the methodology, including proposed convolutional neural network and proposed nuclei cell image detection framework; sections shows the results of our method and make analysis and comparisons with state-of-the-art methods; in section 4, conclusion is given.

2. METHOD

The existing detection methods focus on the improvement of convolutional neural networks (including layers setting, parameters setting, etc.,), neglecting the functional meaning about CNN, which results in the low-accuracy of detection and classification, especially in special items. As illustrated in Equation 1, a CNN is a composition of a sequence of *L* function or layers that maps an input *x* to an output *y*.

$$y = f\left(X; W_1, \ldots, W_L\right) = f_L\left(\bullet; W_L\right) \circ f_{L-1}\left(\bullet; W_{L-1}\right) \circ \cdots \circ f_2\left(\bullet; W_2\right) \circ f_1\left(X; W_1\right) \quad (1)$$

where *y* represents the output vector, *x* represents the input vector, the *f* represents the CNN, f_L represents the *l*th layer CNN, W_L represents weight and bias vector for the *l*th layer f_L.

As shown in Equation 1, in regression analysis, given a pair of input *x* and output *y*, the task is to estimate a function g that represents the relationship between both variables. However, CNN function only consider the information contained in *x*. In medical image processing, *x* do not record spatial information, which is essential to medical image detection. As a result, classical CNN cannot excavate well, limiting the development of medical image processing.

In order to tackle this problem, we let Ω be the spatial domain of *y*, and define a new CNN model. We suppose that the spatially regression model g is known a priori, and is of the form $y=g\left(\Omega; \theta\left(x\right)\right)$ where is an unknown parameter vector. We can employ CNN to estimate $\theta\left(x\right)$ by extending the standard CNN such that the last two layers $\left(f_{L-1}, f\right)$ of the network are defined as

$$\theta\left(x\right) = f_{L-1}\left(X_{L-2}; W_{L-1}\right) \quad (2)$$

$$y = f_L\left(\Omega; \theta\left(x\right)\right) = g\left(\Omega; \theta\left(x\right)\right) \quad (3)$$

where X_{L-2} is an output of the *(L-2)*th layer of the network, equation 2 is the new parameter estimation layer and equation 3 is the layer imposing the spatial constraints.

Based on the alteration above, we design a novel frameworks to do cell nuclei detection, as shown in Figure 1.

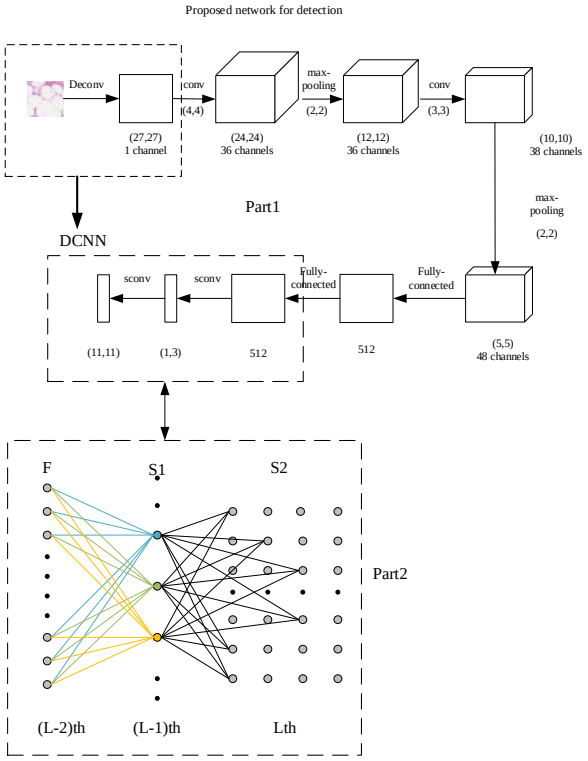


Figure 1.Proposed network for detection

The whole detection frame structure is shown above. The whole process is divided into two parts. In the first part, aiming at the problem of input, the processed cell image is transformed into hematoxylin strength value. For details, please refer to [12]. In this process, The aim is to transform the stained nuclei into quantifiable indicators in the cell image and to prepare for the next step. The second part is the core of this paper, a detailed description of the proposed network structure, from the input to

the traditional convolution neural network, to the full connection layer, and then to the parameter estimation layer, and finally through the spatial constraint layer output.

The last three layers of the spatial CNN are shown as part2. Here, F is the fully connected layer, in which each of these neurons represents medical image information without spatial information; S1 is the new parameter estimation layer, in which each of these neurons represents estimated position information. In S1, we let $Z \in \Omega$ to estimated center. The parameters $Z = (u_m, v_m)$ are estimated in the parameter estimation layer. We define u_m, v_m as

$$u_m = (H-1) \bullet sigm\left(W_{L-1,u_m} \bullet x_{L-2} + b_{u_m}\right) + 1 \quad (3)$$

$$v_m = (W-1) \bullet sigm\left(W_{L-1,v_m} \bullet x_{L-2} + b_{v_m}\right) + 1 \quad (4)$$

Where W_{L-1,u_m}, W_{L-1,v_m} denote the weight vectors and b_{u_m}, b_{v_m} denote the bias variables, and $sigm(\bullet)$ denotes the sigmoid function. S2 is the spatially constrained layer, and L is the total number of layers in the network, in which each neuron represents medical image information with spatial parameter information. The detailed parameters of the convolution are shown in Table 1:

Table 1. Architectures of the proposed network for nucleus detection

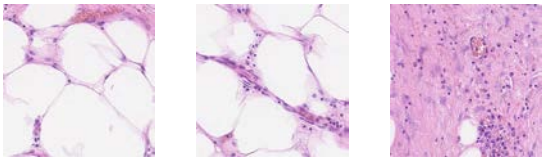
Layer	Type	Filter Dimensions	Input/Output Dimensions
0	I		27×27×1
1	C	4×4×1×36	24×24×36
2	M	2×2	12×12×36
3	C	3×3×36×48	10×10×48
4	M	2×2	5×5×48
5	F	5×5×48×512	1×512
6	F	1×1×512×512	1×512
7	S1	1×1×512×3	1×3
8	S2		11×11

The networks consist of input(I), convolution(C), max-pooling(M), fully-connected(F), parameter estimation(S1), and spatial layers(S2).

3. EXPERIMENT AND RESULTS

3.1 Dataset

Our experiment involved 100 cases of histological images of large intestine pancreas. The common size of all images is 500 times 500 pixels. A total of 29756 nuclei were labeled in the cell image, and the nuclear types labeled as inflammation included lymphocyte plasma, neutrophils and eosinophils. Nuclei that do not belong to the first three categories (epithelial cells, inflammatory cells, and fibroblasts), such as adipocytes, endothelial cells, mitosomes, and necrotic (that is, dead) cells, are labeled as heteronuclear. In the dataset, there were 7722 epithelial cells, 5712 fibroblasts, 6971 inflammatory nuclei, 2039 miscellaneous nuclei and the remaining 7312 cells were unlabeled. The cell data set is the benchmark data set for the detection and classification of medical tissue cells. The following is shown:



(a) Original drawing 1 (b) Original drawing 2 (c) Original drawing 3

Figure 2. Partial original diagram of dataset

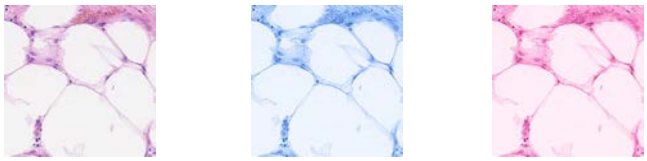
3.2 Experimental Setting

The input feature is set to W*H= 27*27, and the output patch size is set to W*H=11*11. We initialize the ownership weight with the 0 average and the 10^{-2} standard deviation Gaussian random number. All deviations are set to 0. The random gradient descent with momentum 0.9 and weight attenuation 5×10^{-4} is used to train the network with 120 cycles. We adjusted the learning rate, starting 10^{-2} times in the first 60 cycles, 10^{-3} times in the next 40 cycles, and 10-4 times in the last 20 cycles. We use 20% of the training data for validation. According to the mean square error and classification error on the verification set, the optimal network of proposed network is selected.

3.3 Experimental Results

3.3.1 Color Deconvolution

The multi-stained images are separated according to the color deconvolution theory, and the separated images can be used for density and texture analysis. Experiments were carried out on the original cell map according to the staining method of H&E, and the experimental results were shown in Fig. 3:



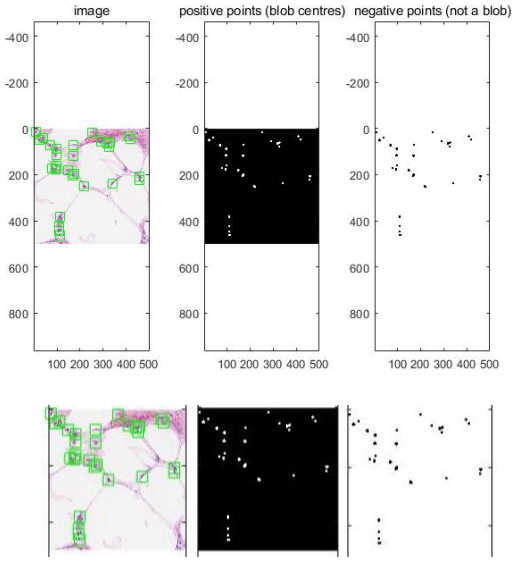
(a) (b) (c)

Figure 3. H&E dyeing separation effect. (a) Dye original image (b) Hematoxylin staining component image (c) Eosin staining component image

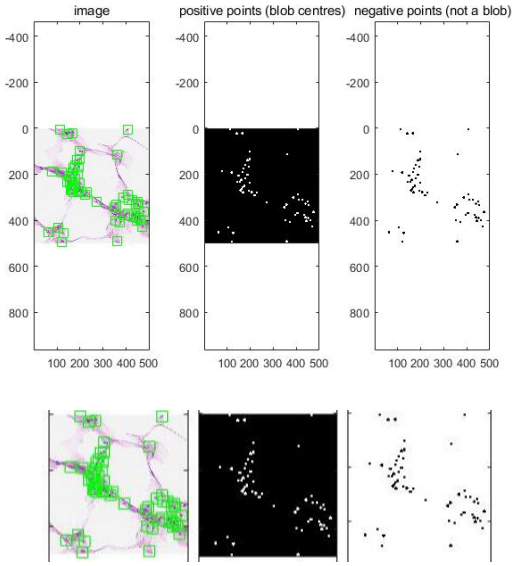
The nucleus of the separated hematoxylin staining component image was blue, and the cytoplasm and cytoplasm of the eosin staining component image were pink. After color deconvolution of pathological images in this dataset, the effect of nuclear and cytoplasmic separation is very good. It can be seen from the figure that the color deconvolution method can be used as an image preprocessing method in this chapter.

3.3.2 Nuclei Detection Results

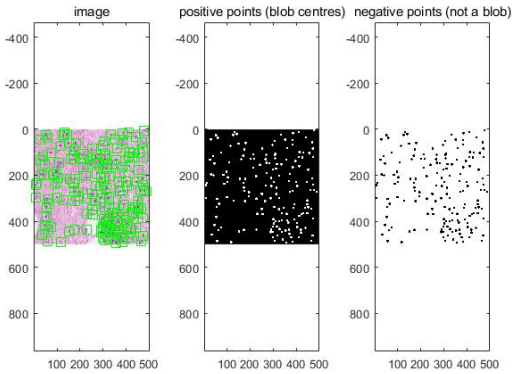
The following is a picture of the effect after the end of the test:

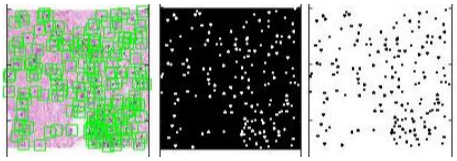


(a) Original figure 1 detection result



(b) Original figure 2 detection result



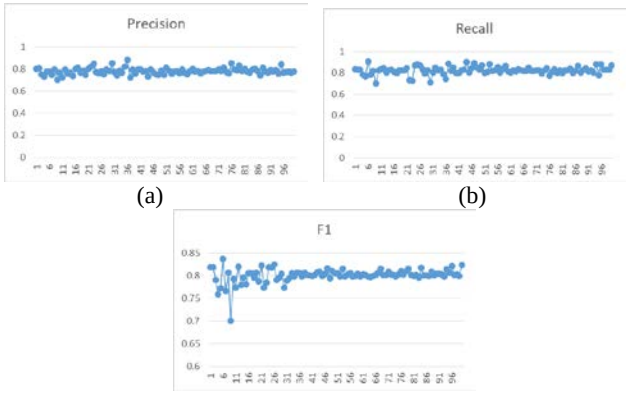


(c) Original figure 3 detection result

Figure 4. Nuclear detection results

The detected cell image shown in figure 4abc corresponds to the original cell image a, b, c in figure 4. The green box indicates the location of the detected nucleus, and the center of the detected nucleus is clearly located in the middle and right of each image. This shows that the proposed method proposed network has a good effect on the detection and localization accuracy of nucleus. The results of the three images are consistent, indicating that the method is stable, and can be accurately detected for images with fewer cells and more cells, indicating that the method is generalized and widely used.

The following are the recall rates, exact values, and F1 values for the test:



(a) (b)

(c)

Figure 5. Quantitative analysis of each index of nuclear detection

Figure 5a shows the accuracy curve of the detection of 100 images, the curve range is between 0.7093 and 0.9076, stable around 0.78, and the average value of the curve is 0.781. Figure 5b shows the recall rate curve for the detection of 100 images, which ranges from 0.7002 to 0.8823, stabilizes around 0.82, and the average value of the curve is 0.823. Figure 5c shows the F1 value curve for the detection of 100 images, the curve range is between 0.70065-0.836947, stable around 0.8, and the average value of the curve is 0.802.

In order to verify the superiority of the method, the comparative experiment is specially designed, the comparative methods are SRCNN, SSAE, LIPSyM, CRImage four methods, and the experimental environment experimental software is consistent. Finally, the experimental results are as follows:

Table 2. Experimental comparison results

Method	Precision	Recall	F1 score
Proposed Network	0.781	**0.823**	**0.802**
SR-CNN[10]	**0.783**	0.804	0.793
SSAE[1]	0.617	0.644	0.630
LIPSyM[5]	0.725	0.517	0.064

CRImage[2]	0.657	0.461	0.542

In this experimental comparison, the accuracy of the proposed network method is slightly lower than that of the SR-CNN method by 0.002 percentage points, but it is at least 1 percentage point higher than that of the SSAE, CRImage method, and obviously higher than that of the LIPSyM method. The recall rate and F1 value of proposed network were significantly higher than those of the other four methods. The results show that the proposed network method has obvious advantages in the detection of nuclei in cell images.

4. CONCLUSIONS

In this study, a depth learning method for spatial constraints was proposed for the detection of nuclei in conventional stained histological images of colorectal pancreas. The evaluation was carried out on a large dataset containing more than 20000 annotation cores. The experimental results show that the proposed CNN nuclear detection method based on spatial constraints has a significant effect on the detection of nuclei in histological images. This method can bring more accurate detection effect in the analysis of nucleus in the future, and will promote the further development of cell image analysis.

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