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# Effects of Histopathological Image Pre-processing on Convolutional Neural Networks

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**Abstract**

In this study, classification performance of histopathological images which are processed by pre-processing algorithms using convolutional neural network structure is examined. The images are divided into four different pre-processing classes with their original state and processed with three different techniques. These classes are; original, normal pre-processing, other normal pre-processing and over pre-processing. Histopathological images of these four classes include cancerous and non-cancerous image patches. For these image classes, cancer patch classification is done using the same convolutional neural network structure. In this view, pre-processing effects on the classification success of the convolutional neural network is examined. For the normal pre-processing algorithm, background noise reduction and cell enhancement are applied. For over pre-processing, thresholding and morphological operations are applied in addition to normal preprocessing operations. At the end of the experiments, the most successful classification results are produced with the normal pre-processing algorithms. This is why the meaningful features of the image are left for the CNN structure that automatically learns the feature. The over pre-processing algorithm removes most of these important features from the image.



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## 1. Introduction

Cancer has become a major health problem all over the world, with the rate of increase in recent years. In a study conducted in 2016 [1] cancer is the second most common cause of deaths in the United States. The most lethal type of cancer among women is breast cancer [2]. In 2017, only 252710 women in the United States are estimated to have breast cancer. It is estimated that 40610 of these cancer cases will result in death [3]. In cancer cases, early detection increases the chance of survival. But when fatigue, inexperience, intense work, and many other factors come together, the decision-making process of experts becomes difficult and long. Computer Aided Diagnosis (CAD) systems have been used extensively in recent years for accelerating this process and for supporting the decision-making process [4]. When the performances of CAD systems are examined, it is seen that they have very inspiring results for many medical applications [5].

With the development of digital imaging systems, CAD systems continue to increase their use and achieve more successful results. This is supported by the availability of medical images captured with cameras and different imaging systems for quality image processing algorithms. Image processing algorithms are used to perceive scenes as human eyes. In this way, many operations can be performed such as detection and recognition of objects in the image, object tracking and so on. With this information, important features can be extracted from the image. The quality of the features extracted from the image directly affects the success of the classification. The ability to obtain appropriate features in high quality depends on the image processing algorithm. For this reason, the proper conditions under which the image processing algorithm can operate as the first job must be specified. Image processing algorithms are adversely affected by noise and various illumination fluctuations. If these negative factors are eliminated, success will increase. Image pre-processing techniques are well suited to this task [6]. Pre-processing methods regulate brightness and contrast variations in the image and suppresses noise. This provides ease of operation for classification algorithms that are very sensitive to brightness and contrast fluctuations. Many researchers have performed successful studies using preprocessing algorithms. Xu et al. [7] use pre-processing techniques for face recognition. Heusch et al. [8] propose new pre-processing method based on local binary patterns. Kalia et al. [9] tested the success of different pre-processing algorithms on SURF. Bernal et al. [10] propose image pre-processing algorithm in order to analyze polyp localization in colonoscopy frames. Adatrao and Mittal [11] analyzed of different image preprocessing techniques for determining the centroids of circular marks. Wang and Zabih [12] use relaxation-based preprocessing techniques for markov random field inference.

Recently, handwritten features have been replaced by algorithms that learn features automatically. Convolutional neural networks have become very popular due to their superior performance in image processing applications like document classification [13], handwritten document recognition [14], speech recognition [15], and traffic signs recognition [16] etc. The main reasons for the success of the convolutional neural network architecture are; the sharing of weights, the protection of the best parameters, and so on. It is useful to use image pre-processing techniques to improve CNN performance [2]. In literature, the effect of different pre-processing methods on CNN performance has been examined with various works [17, 18].

In this study, experiments are carried out on the enhancement of classification performance of histopathological images using CNN structure. For this purpose, the effect of pre-processing on the success of learning CNN structure is studied. First, the image is classified with CNN without any changes in the original images. Then, the gray value fluctuates in the image and various noises are removed. In this case, the image is subjected to a normal pre-processing. These images are classified with same CNN parameters. Finally, an additional threshold is applied over the normal pre-processing method of the image. These images are again classified by the same CNN parameters. In the classification process with CNN, the image patches are divided into two groups as cancerous or noncancerous image. By comparing the classification results of images of these three different pre-processing classes, the effect of pre-processing algorithms on the success of CNN classification is investigated.

## 2. Pre-Processing Techniques

Histopathological images are quite large in size and have a complex structure. For this reason, they are challenging for machine learning algorithms. Because these high-resolution images contain a lot of information about image texture, they provide the most successful diagnosis for almost all types of cancer [19]. Advanced image analysis methods are used to analyze these images. The main objectives of these methods are to assist the expert in the decision-making process, to provide consensus among experts, to gain time for the expert, and to identify the image patterns that specialists are hard to notice [20]. However, analysis of high resolution images takes a long time. At the same time, in the complexity of the background and disturbing factors can slow down the processing speed and decrease the success. Image pre-processing algorithms help prevent this unwanted situation. For this reason, in this study, the same images are passed through 3 different stages and classified. These steps are as follows:

*Original Image without pre-processing:* The use of original images to investigate the effect of pre-processing algorithms on CNN classification success is quite useful for interpreting the results. The success and speed effects of the pre-processing algorithms are evaluated according to the classification results of the original image. In Figure 1, some of the original images in the dataset generated from the image patches are shown.

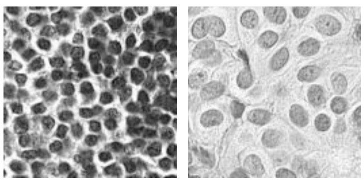


Fig. 1. Original images, a) non-cancerous image patch, b) cancerous image patch

*Normal pre-processing algorithm:* A pre-processing at normal level includes only highlighting the required features of the image and suppressing noises. In this way, more features about the image are provided for machine learning methods. In the first pre-processing method, the gray value fluctuations in the image are determined and remove from the original image. The median value of the view is computed and subtracted from the original image. Then, the final image obtained is extracted from the original image. The method applied is as in Algorithm 1.

**Algorithm 1.** Pre-processing Algorithm 1

**Inputs:** Histopathological image patch

**Outputs:** Pre-processed image

1- Find median value of original image
2- The median value is removed from the original image
3- Apply wiener filter with 3x3 neighbourhood
4- The final image is subtracted from the original image

The image that formed after pre-processing is shown in Figure 2.

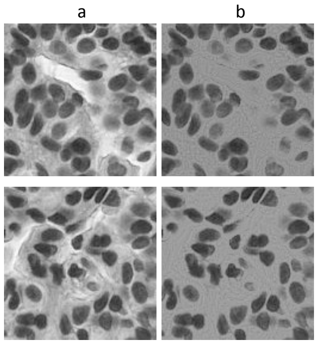


Fig. 2. Pre-processing Algorithm 1, a) original image, b) after pre-processing method

*Second Normal pre-processing algorithm:* In the second preprocessing method, the light gray cells in the image are made darker.First, the image background model is determined by the image opening process. The image is then removed from the original image. Then, H&E paint imbalances in the image are cleaned using a 2D median filter.Finally, adaptive histogram equalization is applied.The method applied is as in Algorithm 2.

**Algorithm 2.** Pre-processing Algorithm 2

**Inputs:** Histopathological image patch

**Outputs:** Pre-processed image

1- Find background using image opening
2- The background is removed from the original image
3- Apply medianfilter with 5x5 neighbourhood
4- Apply adaptive histogram equalization

The image that formed after pre-processing is shown in Figure 3.

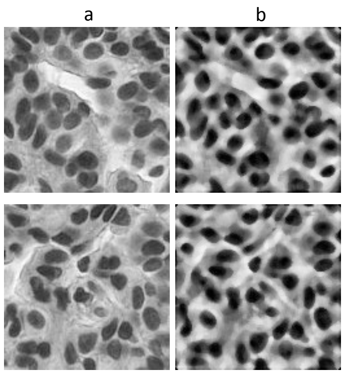


Fig. 3. Pre-processing Algorithm 2, a) original image, b) after pre-processing method

*Over pre-processing algorithm:* In over pre-processing, all information about the image background texture in the image is deleted. Only cells and cell boundaries remain in the image.Reducing a lot of information about the tissue may be useful for some hand-crafted feature extraction methods. However, it is not useful for automatic feature extraction methods.In the third algorithm, the adaptive threshold is applied to the first algorithm.The method applied is as in Algorithm 3.

**Algorithm 3.** Pre-processing Algorithm 3

**Inputs:**Output image of first pre-processing algorithm

**Outputs:** Pre-processed image

1- Apply adaptive threshold
2- Apply medianfilter with 5x5 neighbourhood to remove remain small regions

In Figure 4, some of the original images in the dataset generated from the image patches are shown.

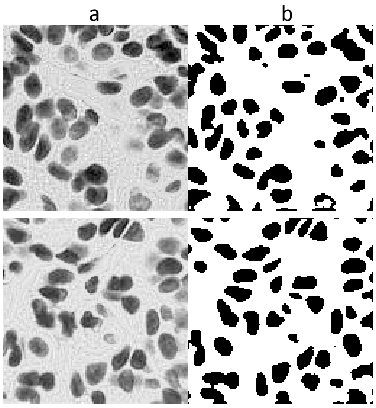


Fig. 4. Pre-processing Algorithm 3, a) original image, b) after pre-processing method

## 3. Experiments

In the experiments, 2000 pieces of histopathological images are used. Of these images, 1000 are composed of cancerous tissue and 1000 are composed of normal tissue. Image patches containing cancerous tissue are labeled as cancerous. Cancer tissue-free image patches are labeled as normal.

Experiments is applied on a computer with Intel Core i7-7700K CPU (4.2 GHz), 32 GB DDR4 RAM and NVIDIA GeForce GTX 1080 graphic card.

### *3.1. CNN Architecture*

After preprocessing, the AlexNet structure is selected for automatic feature extraction and classification. The AlexNet structure [21] has become very popular after winning the ImageNet challenge. A number of CNN structures have been developed in different architectures. CNN is well suited for fast and successful resolution of image processing problems thanks to its advantages over the use of convolution windows. In general, the basic layers of the CNN architecture are the convolution layer, the pooling layer, the ReLU layer and the fully connected layer. In addition, a dropout layer is used to prevent the network from memorizing, and batch normalization is used for fast learning.

The Alexnet structure consists of 5 convolution layers, 3 max pooling layers, 2 normalization layers and fully connected layer with three hidden layers. The size of the first convolution layer filter is 11x11, the second convolutional layer is 5x5, and the other convolutional layers are 3x3 filters. Pooling layers consist of 3x3 pixels.

In the experiments, the AlexNet structure is run on the GPU. Mini batches consisting of 32 images are used in the training process. All parameters of the network have not been changed during the experiments.

### *3.2. Dataset*

The data in the CAMELYON challenge [22] are used in the experiments. The images on the CAMELYON dataset are used for breast cancer detection. A total of 400 whole-slide images are available. These images are obtained from two different sources and drawn with ground truth images. 270 of the images on the dataset are used for training and these images have ground truths. The remaining 130 histopathological images are used for the test. The images in the dataset are placed in image pyramids that contain images of different resolutions.

The images in the Dataset are divided into pieces of image with dimensions of 128x128 pixels. These images are divided into two different classes with cancerous tissue and normal tissue. Images in each class were selected from random whole-slide images. For training, 1000 random samples from the cancerous class and 1000 random samples from the normal tissue class are selected.

### *3.3. Experimental Results*

In the experiments, all images are the same for each pre-processing phase. At the same time, the network parameters are the same for each pre-processing class. For fair comparison of pre-processing methods, both training periods and training curves are compared. The training periods of pre-processing algorithms are shown in Table 1. Table 1 shows no significant difference between the algorithms.

Table 1.Comparison of Training Time

| | Training Time (hours) | Iteration Number |
|---|---|---|
| Original | 22,5 | 500 |
| Normal pre-1 | 22.2 | 500 |
| Normal pre-2 | 22.4 | 500 |
| Over pre | 22.1 | 500 |

As a result of the experiments, the obtained training and validation curves are shown in Figure 5. As can be seen from the curves, preprocessing algorithms make training faster and more successful. In particular, pre-processing at the normal level facilitates learning. In the experiments, training is limited to 500 epochs. However, when Figure 5b and Figure 5c are examined, it is understood that the error tends to continue to decrease. In Figure 5a, where the data are used raw, the validation curve does not change. That is, learning success remained constant at a certain level. In Figure 5d the slope is reduced by a certain epoch, but the slope does not decrease from a certain epoch. As a result, CNN systems are better learned when the complex structure of histopathological images is simplified to a certain extent.

A test data set consisting of 1000 images is created to test the proposed methods. Of these images, 500 have cancerous tissue and 500 have normal tissue. Table 2 shows the test results. For the test operations, each piece of image is processed with the necessary preprocessing algorithm. Then, they are classified by the corresponding pre-trained CNN model. The accuracy values are calculated according to the classification labels.

Table 2. Comparison of Classification Success

| | Accuracy |
|---|---|
| Original | 93.05% |
| Normal pre-1 | 94.1% |
| Normal pre-2 | 94.7% |
| Over pre | 93.4% |

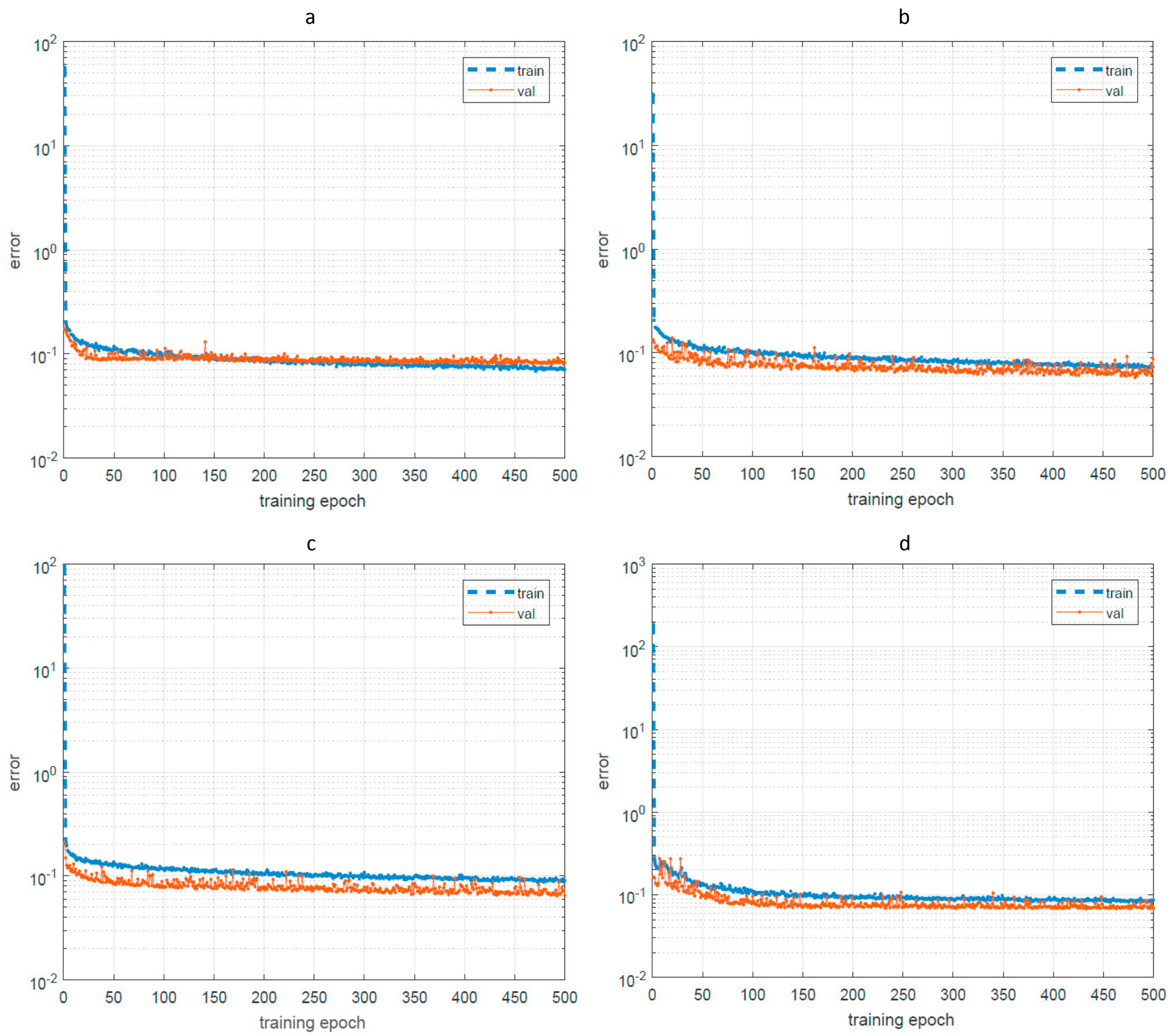


Fig. 5.Training curves of algorithms, a) original images, b) normal pre-processing images, c) other normal pre-processing images, d) over pre-processing images

## 4. Conclusion

In this study, histopathological images are processed using various pre-processing approaches. The processed images are classified using convolutional neural network architecture. The purpose of the study is to determine the effect of the pre-processing steps on the classification success. For this reason, the original image and 3 different preprocessing methods have been tried. When the results are examined, it has been seen that pre-processing methods contribute to learning in a certain extent. This contribution varies depending on the cleaning of the noises and the drying of the properties. If pre-processing is excessive, success cannot reach the desired level. When the curves in Figure 5 are examined, clear information on the state of education is obtained. From these curves, it is clear that appropriate preprocessing is useful in histopathological images.

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