

Automated classification of histopathology images using transfer learning[☆]

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ABSTRACT

Early and accurate diagnosis of diseases can often save lives. Diagnosis of diseases from tissue samples is done manually by pathologists. Diagnostics process is usually time consuming and expensive. Hence, automated analysis of tissue samples from histopathology images has critical importance for early diagnosis and treatment. The computer aided systems can improve the quality of diagnoses and give pathologists a second opinion for critical cases. In this study, a deep learning based transfer learning approach has been proposed to classify histopathology images automatically. Two well-known and current pre-trained convolutional neural network (CNN) models, ResNet-50 and DenseNet-161, have been trained and tested using color and grayscale images. The DenseNet-161 tested on grayscale images and obtained the best classification accuracy of 97.89%. Additionally, ResNet-50 pre-trained model was tested on the color images of the Kimia Path24 dataset and achieved the highest classification accuracy of 98.87%. According to the obtained results, it may be said that the proposed pre-trained models can be used for fast and accurate classification of histopathology images and assist pathologists in their daily clinical tasks.

1. Introduction

Pathologists examine tissue samples manually using a microscope to determine diseases. The biopsy procedure is used to examine tissue samples for diagnosis of pathological diseases [1]. The extracted tissue sections are stained to reveal high-level structures. Therefore, tissue samples are placed on a glass slide to analyze morphological characteristics [2].

In recent years, microscopes have been replaced by digital scanners. The entire histology slide is scanned by a digital whole slide scanner and saved as a whole slide image (WSI). The analysis of tissue characteristics from WSI has opened a new era in digital pathology [3]. Computer-aided diagnostic (CAD) systems can be used to detect and classify diseases using WSI. However, diagnosis of digital pathology images is a tedious task because of large image size. The high-resolution WSIs are usually divided into partial patches and the analyses are performed separately on each sample.

In the analysis of histopathological images, different interpretations can be seen among different pathologists [4]. Since WSIs are very large in size, it is not easy to diagnose diseases examining all available patches. CAD systems can overcome these problems. Hence, there is a strong demand for the development of CAD tools which can reduce the workload of pathologists and help them for fast and precise diagnosis [5].

In the last few years, CNN have been increasingly used in the field of

medical image analysis such as detection [6–10] and classification [11,12]. Talo et al. [13] proposed transfer learning technique to classify brain MR images into two classes (normal and abnormal). They used Resnet-34 pre-trained CNN model and the proposed model yielded the best classification accuracy of 100%.

The CNN architectures have an end-to-end structure, which learn high-level representations from raw data [14]. Deep learning models have also achieved tremendous success in histopathology image processing, such as mitosis detection [15], tissue grading (classification) [16], and nuclei segmentation [17] from high-resolution images. In histopathology image analysis, color and texture based features of histopathology images have been used for segmentation and classification tasks [18].

Several studies have been conducted to diagnose diseases from histopathology images using deep learning approaches. Saha et al. [19] used a deep learning based model for automated detection of mitoses from breast histopathology WSIs. Their model achieved 92% precision and 88% recall. Han et al. [20] have implemented a structured deep learning model to classify breast cancer histopathology images. Their method achieved average accuracy of 93.2% to classify subclasses of breast cancer images into three classes (lobular carcinoma, ductal carcinoma, and fibroadenoma). Zheng et al. [21], developed a CNN to classify breast cancer images into two classes (benign and malignant). The proposed CNN model has yielded 96.6% classification accuracy. The authors also tested the proposed model on a 15-class breast tumor

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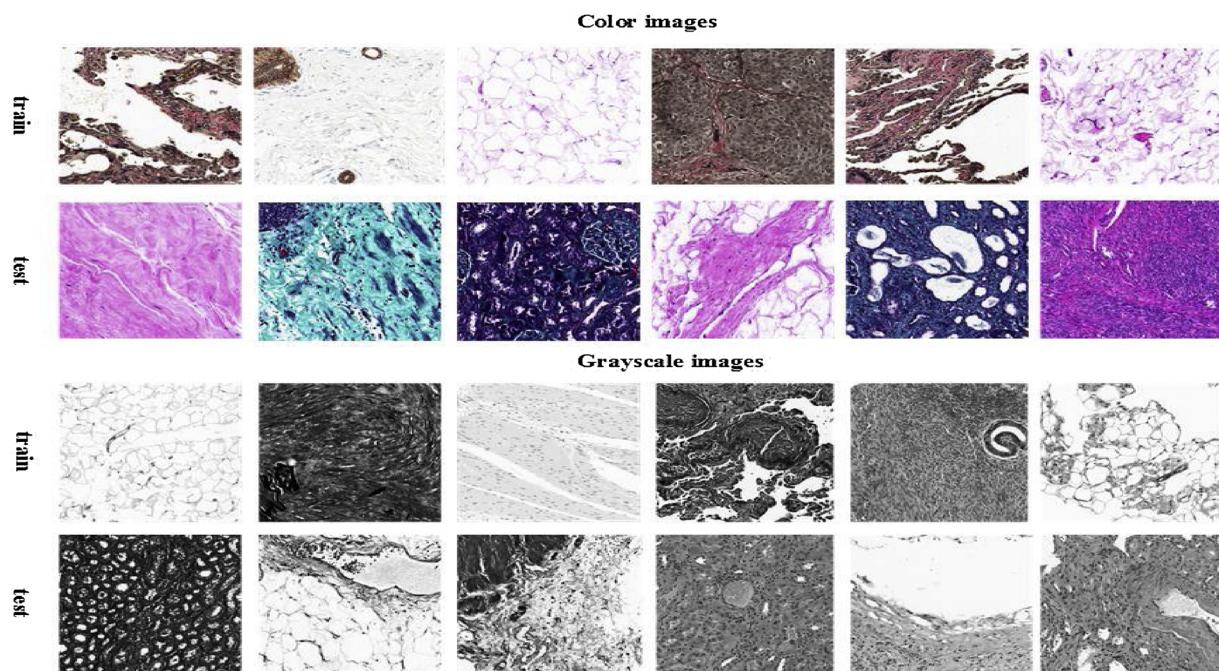


Fig. 1. Sample color and grayscale images from the Kimia Path24 dataset. Each row demonstrates few color and grayscale images from the training and test datasets.

dataset. The proposed model has yielded average classification accuracy of 96.4%.

Jia et al. [22] implemented a fully connected network using multiple instance learning algorithms to segment cancerous regions in histopathological images. Xu et al. [23] used CNN to segment and classify histopathology images using transfer learning technique. Shi et al. [24] applied a deep hashing model for the retrieval and classification of histopathology images. The authors implemented the proposed model on a lung cancer image dataset. Their model achieved the highest classification accuracy of 97.49%.

Beevi et al. [25] proposed VGG pre-trained CNN model to detect mitosis from breast histopathology images using transfer learning technique. Khan et al. [26] applied GoogleNet, VGGNet, and ResNet pre-trained CNN architectures to classify breast cancer images into benign and malignant classes using transfer learning approach. Vo et al. [27] used an ensemble of deep convolutional neural networks (DCNN) to classify breast histopathology images into two (carcinomas, and non-carcinomas) and four (normal, benign, invasive carcinomas and *situ* carcinomas) classes. The authors also used gradient boosting trees algorithm and DCNN architecture with majority voting strategy to increase the performance of the model. In 2019, Yan et al. [28] proposed a hybrid deep neural network using Inception-V3 and long short-term memory (LSTM) models to classify breast cancer images into four classes (normal, benign, invasive carcinoma, and *in situ* carcinoma) and achieved an average classification accuracy of 91.3%.

In 2019, Sudharshan et al. [29] used multiple instance learning (MIL) approach to classify histopathology breast cancer images into two classes (malignant and benign). They compared the performance of various MIL types (MIL-CNN, citation-kNN, diverse density, MI-SVM, APR) to classify biopsy images on the BreakHis dataset. The highest classification accuracy was obtained with MIL-CNN approach. The other work by [30], used DeCAF deep features for breast cancer classification. Song et al. [31,32] applied deep transfer learning technique for histopathology image classification. The authors employed Fisher Vector (FV) encoder to extract features from histopathology images and used a CNN model to classify malignant and benign breast cancer tumors. In [33], a cell-based semi-supervised hashing method used to extract image representations. The obtained representations, then fed into a support vector machine to classify lung cancer histopathology

images into two categories. Their method has reached 87.88% classification accuracy using 800 test images with five labeled images. Gecer et al. [34] used a CNN model for automated classification of whole slide breast biopsy images into five classes.

In this study, we have proposed deep CNN models using transfer learning technique for the classification of histopathology images. Two well-known pre-trained CNN models, ResNet-50 and DenseNet-161, have been used as deep models. The ResNet-50 and DenseNet-161 were trained on the large scale ImageNet database to provide high classification performance. The proposed approach in this study does not require any preprocessing or hand-crafted feature extraction/selection techniques. The classification and feature extraction operations were performed automatically in an end-to-end structure using raw histopathology images as input. Therefore, we have selected CNN models to classify histopathology images. The main contributions of the present study can be summarized as follows:

- The ResNet-50 and DenseNet-161 pre-trained CNN models are proposed to classify histopathology images automatically.
- The color and grayscale histopathology images are classified into 24 categories using all available data in the Kimia Path24 dataset.
- The classification performances of proposed pre-trained models are examined using both color and grayscale histopathology images.
- The ResNet-50 and DenseNet-161 pre-trained models demonstrated a better classification accuracy than the existing studies in the literature.

- The proposed approach is powerful and state-of-the-art method that can be used to classify histopathology images in the field of medicine.

2. Material and methods

2.1. Dataset

In this study, publicly available Kimia Path24 histopathology dataset was used. The dataset was released by Babaie et al. [35], which contains 24 whole-slide tissue images. The dataset shows various body parts with different texture patterns. The images in the Kimia Path24 dataset were obtained by TissueScope LE 1.0. The dataset contains a total of 23,916 images and 1325 of these images used for testing. We

have used all available histopathology images from the Kimia Path24 database. All images have an equal size of 1000×1000 pixels. The selected test patches were removed from WSIs and their locations were stained white on scans. Therefore, the use of test patches in the training set was prevented.

The previous studies conducted on the Kimia Path24 dataset were converted the color images to grayscale and the classification process was performed on grayscale images. In this study, the classification of images was carried out using both color and grayscale images to benefit from the color and texture features. Few sample grayscale and color images from Kimia Path24 are shown in Fig. 1.

2.2. Deep transfer learning

CNN automatically learn best representative features from raw data instead of using traditional machine learning techniques that benefit from handcrafted features. A typical CNN consists of a series of building blocks such as convolutional, pooling, and fully-connected (dense) layers. The shallow CNN architectures have been constructed stacking several building blocks together such as AlexNet [36] and VggNet [37]. However, modern CNN architectures are deeper than shallow architectures and use progressively more complex connections among alternating layers, such as ResNet [38] and DenseNet [39].

In this study, ResNet-50 and DenseNet-161 CNN architectures were employed to classify digitalized pathology images. The ResNet and DenseNet architectures have been used in the construction of new models. The Resnet-50 and DenseNet-161 models were trained on a part of the ImageNet database which contains more than one million images belong to 1000 classes.

2.2.1. ResNet

The residual neural networks (ResNet) was developed by He et al. [38], got the first place in MS COCO 2015 and ILSVRC 2015 image detection and segmentation challenges. The authors used a 152-layer deep CNN architecture in ILSVRC 2015. The ResNet architecture popularized the idea of using deeper layers as compared to AlexNet, which has eight layers and VggNet with up to 19 layers. The ResNet architecture introduced skip connections, also known as residual connections to avoid information loss during training of deep networks. Skip connections enable to train very deep networks and boost the performance of the networks. Using residual connections in the ResNet architecture, the authors were able to train a 1001-layer deep CNN model. ResNet architecture mainly composed of residual blocks. In shallow neural networks, consecutive hidden layers are linked to each other, however, in ResNet architecture, there are also connections among residual blocks. The main compelling advantage of residual connections in ResNet architecture was the connections among residual blocks. They preserve gained knowledge during training and speed up the training of the model by increasing the capacity of the network. A block diagram of the pre-trained ResNet-50 model used in this study is shown in Fig. 2.

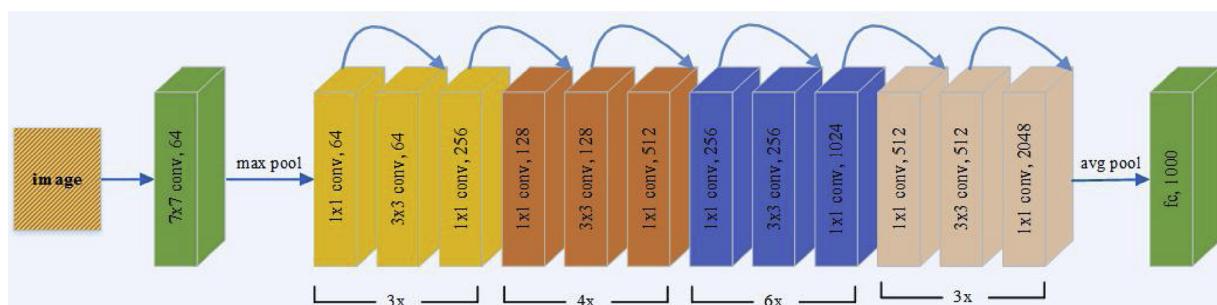


Fig. 2. A block diagram representation of pre-trained Resnet-50 architecture.

2.2.2. DenseNet

Dense convolutional networks (DenseNet) developed by Huang, Liu and Maaten [39] had the best classification accuracies on publicly available image datasets (CIFAR-10 and ImageNet) in 2017. The DenseNet architecture used dense connections in the construction of the model as in ResNet architecture. DenseNet was built with a structure that connects each layer to the later layers. Hence, important features learned by any layers of the network were shared within the network. In other words, the extra links among the layers of DenseNet boost information flow through the whole network. In this way, training of the deep network becomes more efficient and the performance of the model increases. The DenseNet architecture used fewer parameters than similar CNN architectures (ResNet) for the training of the network. Additionally, using dense connections alleviate overfitting problem for the models which have small datasets. A block diagram of DenseNet-161 having four dense blocks is presented in Fig. 3.

Training deep architectures with millions of parameters can take weeks using random weights initialization technique. A large amount of data and powerful computer hardware (GPUs) are required to train CNN from starch. The transfer learning technique is commonly used to elevate these problems. With this technique, a CNN model is trained on a huge dataset then the features learned from this model transfer to the current model. In the transfer learning technique, the fully connected layer of the model is removed and the remaining layers of the architecture are used as a feature extractor for the new task. Therefore, only the dense layers of the proposed model are trained.

CNN try to discover patterns performing various convolutions on images. The proposed CNN models which trained on a large dataset (ImageNet) learn small patterns such as lines and diagonals in the first few layers, and then combine these pieces in the consecutive layers to learn complex features. In the final layer, the models learn meaningful structures such as doors, arms, cats, dogs, etc. using the patterns learned in the previous layers. Using the transfer learning method, we have transferred the knowledge (weights value) of the basic structures learned in the first and middle layers to the new model. The essential structures that pre-trained models have learned to identify different objects in the ImageNet dataset are used to classify histopathology images. Therefore, transfer learning technique accelerates the training process and speeds up the construction of new CNN models. The schematic representation of transfer learning technique used in this study to classify histopathology images is given in Fig. 4.

3. Experiments and results

The Resnet-50 and DenseNet-161 pre-trained CNN architectures were employed to classify histopathology images into 24 classes. The number of training and test images in the official Kimia Path24 dataset are 23,916 and 1325, respectively. In this study, 80% of the training images used for training and the rest of the training images (20%) allocated for validation in order to have a separate validation set. The performances of the proposed pre-trained CNN models were evaluated on the test set.

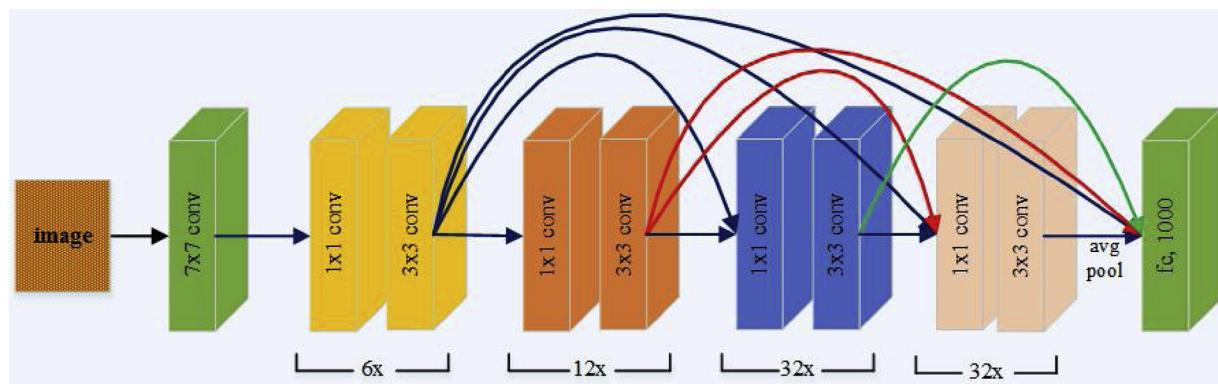


Fig. 3. A block representation of DenseNet-161 architecture.

PyTorch [40] library and Fastai [41] framework were used to train the proposed pre-trained models. PyTorch and Fastai libraries are open source and build on Python programming language for machine learning tasks. The training and testing of ResNet-50 and DenseNet-161 pre-trained models were performed on NVIDIA GeForce GTX 1080 TI using 11 GB graphics card.

3.1. Experimental setups

In this study, transfer learning technique was applied to ResNet-50 and DenseNet-161 pre-trained CNN architectures. The fully connected layer of DenseNet-161 and ResNet-50 were removed and the convolutional layers of the pre-trained models were used as a *base network* in new architectures. Two sets of batch normalization, dropout, and fully connected layers were respectively added to the base network. The addition of two batch normalization layers was due to the rapid training of the pre-trained models. The dropout layers were attached to the base network to alleviate the overfitting problem. In overfitting problem, deep models fail to generalize on unseen test data. Further, in the last layer of proposed models, the softmax activation function was used to classify digital pathology images into 24 classes. The overall framework of the customized CNN architecture is given in Fig. 5.

Each of the pre-trained models was trained independently on color and grayscale image datasets. DenseNet-161 and ResNet-50 models were trained for the same number of epochs. The training of the networks was carried out only using the newly attached layers. In this way,

the computation cost of the network in the training process was decreased.

The stochastic gradient descent (SGD) with momentum, namely RMSprop was employed to optimize the parameters of the networks during training. The learning rate value was randomly chosen to be 1e-3. The dropout ratios were selected as 0.25 and 0.50, respectively, to regularize the deep models. The batch normalization values were selected as 0.1 for momentum and 1e-5 for epsilon.

The accuracy calculation protocol established by [35] was followed in this study to compare the results of this work to other studies conducted on the Kimia Path24 dataset. The test patches belonged to 24 distinct sets. Let R represent the retrieved images for an experiment and let $\Gamma_s = \{P_s^i | s \in S, i = 1, 2, \dots\}$, where $s = 0, 1, \dots, 23$, the *patch-to-scan accuracy*, η_p is described in Eq. (1),

$$\eta_p = \frac{1}{n_{tot}} \sum_s |R \cap \Gamma_s| \quad (1)$$

and the *whole-scan accuracy*, η_w , formulized in Eq. (2).

$$\eta_w = \frac{1}{24} \sum_s |R \cap \Gamma_s| \quad (2)$$

The *total accuracy* is obtained multiplying whole-scan accuracy by patch-to-scan accuracy as given in Eq. (3) [35].

$$\eta_{total} = \eta_p \times \eta_w \quad (3)$$

The Python code is publicly available for the accuracy calculations



Fig. 4. The transfer learning method used to classify histopathology images.

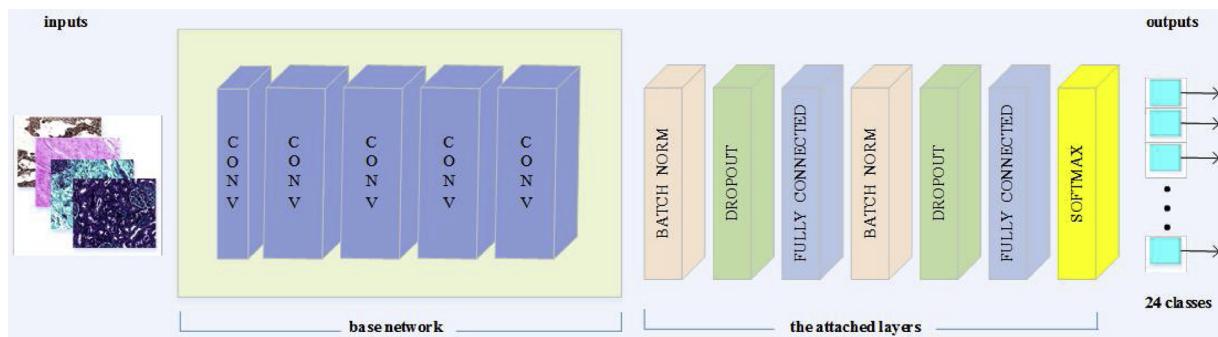


Fig. 5. An illustration of the customized CNN architecture. The first five feature extractor convolutional blocks are used as the base of networks. The rest of the layers are added to the base networks.

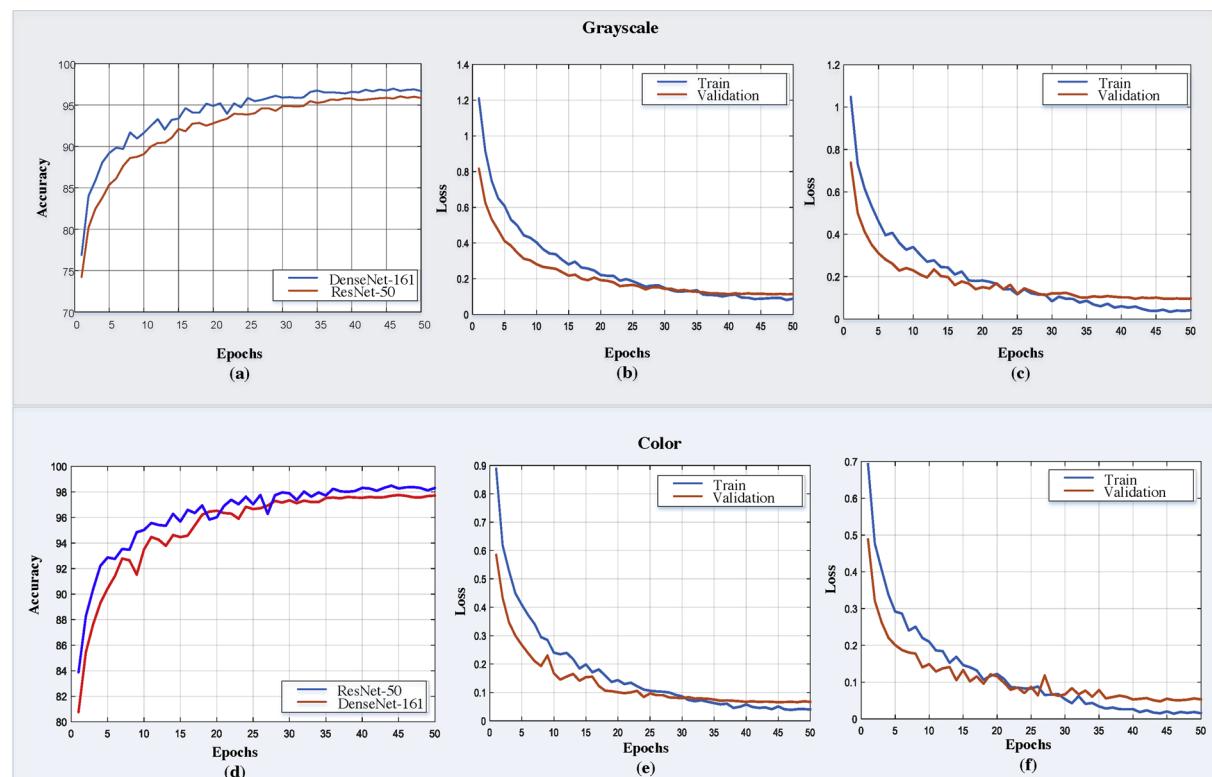


Fig. 6. The performance graphs of DenseNet-161 and ResNet-50 architectures on grayscale and color datasets: (a) validation accuracies of DenseNet-161 and ResNet-50 on grayscale images, (b) training and validation loss of ResNet-50 for grayscale images, (c) training and validation loss of DenseNet-161 for grayscale images, (d) validation accuracies of ResNet-50 and DenseNet-161 on color dataset, (e) training and validation loss of ResNet-50 for color images, (f) training and validation loss of DenseNet-161 for color images.

and can be obtained from the Kimia Lab website [42].

3.2. Results

The attached layers of the ResNet-50 and DenseNet-161 models were trained to classify histopathology images for 50 epochs. Each pre-

Table 1

The results obtained using DenseNet-161 and ResNet-50 models on grayscale and color datasets.

Models	Image format	Training Time (hour : min : sec)	η_p (%)	η_w (%)	η_{total} (%)
DenseNet-161	grayscale	4:14:37	97.89	97.86	95.79
ResNet-50	grayscale	3:01:49	96.08	96.38	92.60
DenseNet-161	RGB	4:23:50	98.64	98.63	97.28
ResNet-50	RGB	4:03:34	98.87	98.89	97.77

trained models was trained separately on color and grayscale images. For the grayscale and color images, the validation accuracy and the training and validation loss graphs of ResNet-50 and DenseNet-161 are shown in Fig.6.

The performances of DenseNet-161 and ResNet-50 were evaluated for color and grayscale test images. Table 1 shows patch-to-scan (η_p), whole scan (η_w), and total (η_{total}) accuracies on test data and the training time of models.

According to the evaluation results, DenseNet-161 has provided better classification accuracy than ResNet-50 for the classification of grayscale images. The DenseNet-161 architecture has introduced the idea of shortcut connection among the layers of the network. The DenseNet-161 network has more layers than ResNet50. However, in the classification of grayscale images, ResNet-50 pre-trained CNN model has provided better accuracy than DensNet-161. The confusion matrixes obtained using ResNet-50 and DenseNet161 models for grayscale and color test datasets are shown in Fig.7.

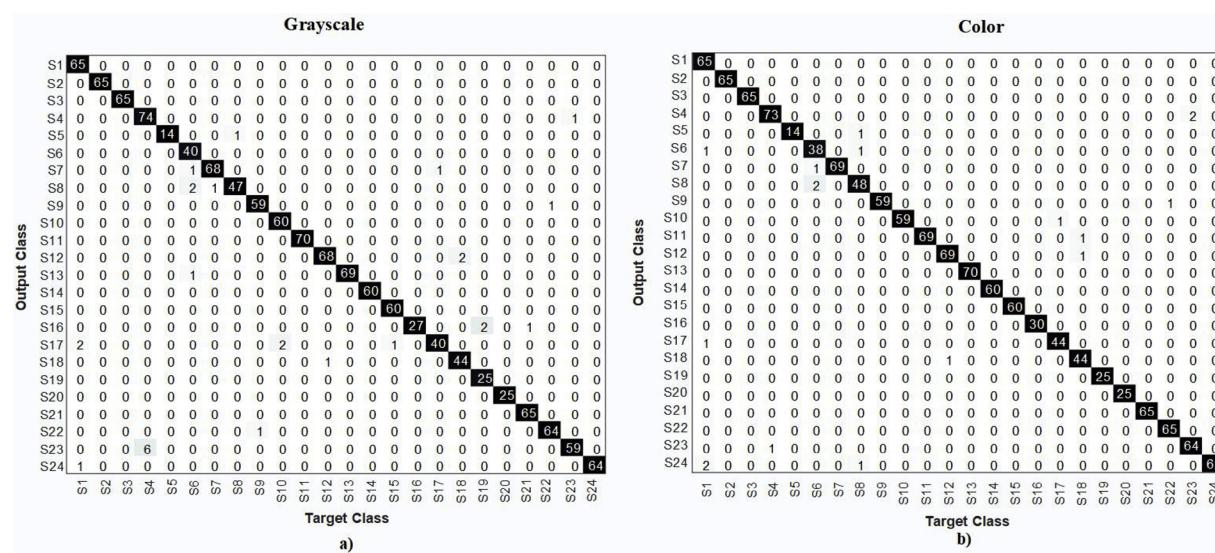


Fig. 7. The confusion matrixes for the grayscale and color test datasets: (a) DenseNet-161, (b) ResNet-50.

Table 2

The classification report for DensNet-161 model using the grayscale test dataset.

Classes	Precision (%)	Recall (%)	F1-score (%)	Amount of Data
s1	0.96	1.00	0.98	65
s2	1.00	1.00	1.00	65
s3	1.00	1.00	1.00	65
s4	0.93	0.99	0.95	75
s5	1.00	0.93	0.97	15
s6	0.91	1.00	0.95	40
s7	0.99	0.97	0.98	70
s8	0.98	0.94	0.96	50
s9	0.98	0.98	0.98	60
s10	0.97	1.00	0.98	60
s11	1.00	1.00	1.00	70
s12	0.99	0.97	0.98	70
s13	1.00	0.99	0.99	70
s14	1.00	1.00	1.00	60
s15	0.98	1.00	0.99	60
s16	1.00	0.90	0.95	30
s17	0.98	0.89	0.93	45
s18	0.96	0.98	0.97	45
s19	0.93	1.00	0.96	25
s20	1.00	1.00	1.00	25
s21	0.98	1.00	0.99	65
s22	0.98	0.98	0.98	65
s23	0.98	0.91	0.94	65
s24	1.00	0.98	0.99	65

The DenseNet-161 model misclassified 25 out of 1325 images in the grayscale test dataset. However, ResNet-50 pre-trained model incorrectly classified only 18 out of 1325 images in the color test dataset. The precision, sensitivity, specificity, and F1-score values of DenseNet-161 using the grayscale test dataset is given in Table 2 for detailed performance analysis.

The average precision, recall, and F1-score values were 98% for DenseNet-161 which used the grayscale test images. But for the same evaluation criterions, ResNet-50 has yielded 99% for the color test images. When the performances of the pre-trained models were evaluated, it was observed that the performances of both pre-trained models on the color images were better than the grayscale images. This may be due to the reason that, for color images, the pre-trained models learned both color and textual features during training. However, the proposed models only learned textual representations on the grayscale data.

4. Discussion

There are few important studies used the Kimia Path24 dataset to classify histopathology images. In these studies, different CNN models, pre-trained networks, and feature extraction approaches were used to classify histopathology images. Table 3 presents the comparison of this study and state-of-the-art studies used the same dataset (Kimia Path24).

In 2017, Babaie et al. [35] proposed bag of words (BoW), local binary pattern (LBP) histograms, and a CNN model to classify grayscale histopathology images. The total accuracy value (η_{total}) for BoW, LBP and CNN approaches were reported as 39.65%, 41.33%, and 42.07%, respectively. Their proposed CNN model has yielded the highest classification accuracy of 42.07% using 40,513 patches for the training of the network. Kieffer et al. [43] used data augmentation and transfer learning techniques to train Inception-v3 and VGG-16 CNN models to classify histopathology images. The Inception-v3 pre-trained CNN model achieved the highest accuracy of 74.87% for grayscale images. In 2018, Zhu et al. [44] proposed a BoW and a variant of BoW with multiple dictionaries (MBow) approaches to classify grayscale histopathology images. The authors excluded patches that have a bright background and used the rest of 25,390 images for training. The Bow and MBow methods have reached 88.07% and 89.21% classification accuracies, respectively.

It can be seen from Table 3 that the proposed DenseNet-161 pre-trained CNN model outperformed other methods in all performance metrics for the classification of grayscale images. The DenseNet-161 has yielded 95.79% total accuracy for the grayscale test images. ResNet-50 pre-trained model achieved 97.77% total accuracy to classify the color images.

The main advantages of this study can be summarized as follows:

I Most of the studies in the literature performed classification of histopathology images for only several classes. However, the proposed deep learning models have classified histopathology images into 24 classes and achieved high performance for the color and grayscale images. Additionally, Resnet-50 and DenseNet-161 CNN models have better classification accuracy than other studies that used the Kimia Path24 dataset in the literature.

II The proposed models do not require any hand-made feature extraction technique, i.e., they have a fully automated end-to-end structure.

III The performance of pre-trained Resnet-50 and DenseNet-161 are compared for color and grayscale images.

Table 3

The performance comparison for histopathology image classification studies using the same dataset.

Papers	Year	Image Format	Method	η_p (%)	η_w (%)	η_{total} (%)
Babaie et al. [29]	2017	Grayscale	BoW	64.98	61.02	39.65
Babaie et al. [29]	2017	Grayscale	LBP	66.11	62.52	41.33
Babaie et al. [29]	2017	Grayscale	CNN	64.98	64.75	42.07
Kieffer et al. [37]	2017	Grayscale	VGG-16	65.21	64.96	42.36
Kieffer et al. [37]	2017	Grayscale	Inception-v3	74.87	76.10	56.98
Zhu et al. [38]	2018	Grayscale	BoW	88.07	84.50	74.41
Zhu et al. [38]	2018	Grayscale	MBoW	89.21	85.30	76.09
The proposed	2019	Grayscale	DenseNet-161	97.89	97.86	95.79
The proposed	2019	RGB	ResNet-50	98.87	98.89	97.77

IV All histopathological images in the Kimia Path24 database were used.

The main disadvantage of this study is the limited number of histopathology images used for the training of deep learning models. However, we have overcome this problem by using transfer learning technique. In future studies, we will perform patient-level classification on sufficiently large histopathology datasets using different deep learning models.

Histopathological images, given as an input to the proposed deep learning models, can be automatically classified with high performance. The use of deep CNN models in the clinical setting gives experts a second opinion and increases the rate of more accurate diagnosis. The accurate diagnoses can protect the patient from harmful and expensive procedures such as radiotherapy and chemotherapy.

5. Conclusion

The automated classification of histopathology images by computer aided systems is of great importance in the field of medical image analysis. Microscopic analysis of histopathological images is challenging and time-consuming. Automated diagnosis of histopathology images relieves the workload of pathologists and allows them to focus on more critical cases. In this study, a deep transfer learning technique has been proposed for automated classification of histopathology images. The current DenseNet-161 and ResNet-50 CNN models have been used to classify grayscale and color images in the Kimia Path24 dataset. According to the experimental results, the proposed pre-trained models outperformed the existing studies in the literature.

Declaration of Competing Interest

None.

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