

A Novel Histological Dataset and Machine Learning Applications

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Abstract: Histology has significant importance in the medical field and healthcare services in terms of microbiological studies. Automatic analysis of tissues and organs based on histological images is an open problem due to the shortcomings of necessary tools. Moreover, the accurate identification and analysis of tissues that is a combination of cells are essential to understanding the mechanisms of diseases and to making a diagnosis. The effective performance of machine learning (ML) and deep learning (DL) methods has provided the solution to several state-of-the-art medical problems. In this study, a novel histological dataset was created using the preparations prepared both for students in laboratory courses and obtained by ourselves in the Department of Histology and Embryology. The created dataset consists of blood, connective, epithelial, muscle, and nervous tissue. Blood, connective, epithelial, muscle, and nervous tissue preparations were obtained from human tissues or tissues from various human-like mammals at different times. Various ML techniques have been tested to provide a comprehensive analysis of performance in classification. In experimental studies, AdaBoost (AB), Artificial Neural Networks (ANN), Decision Tree (DT), Logistic Regression (LR), Naive Bayes (NB), Random Forest (RF), and Support Vector Machines (SVM) have been analyzed. The proposed artificial intelligence (AI) framework is useful as educational material for undergraduate and graduate students in medical faculties and health sciences, especially during pandemic and distance education periods. In addition, it can also be utilized as a computer-aided medical decision support system for medical experts to minimize spent-time and job performance losses.

Key words: Classification, computer-aided diagnosis, histological image, image processing, machine learning.

Yeni Bir Histoloji Veriseti ve Makine Öğrenmesi Uygulamaları

Öz: Histoloji, tıp alanında ve sağlık hizmetlerinde mikrobiyolojik çalışmalar açısından önemli bir yere sahiptir. Histolojik görüntülere dayalı doku ve organların otomatik analizi, gerekli araçların olmaması nedeniyle açık bir sorundur. Ayrıca hücrelerin bir araya gelmesiyle oluşan dokuların doğru tanımlanması ve analizi, hastalıkların mekanizmalarını anlamak ve tanı koymak için çok önemlidir. Makine öğrenmesi (MÖ) ve derin öğrenme (DÖ) yöntemlerinin etkin performansı çeşitli son teknoloji tıbbi sorunlara çözüm sağlamıştır. Bu çalışmada Histoloji ve Embriyoloji Anabilim Dalında hem laboratuvar derslerinde öğrenciler için hazırlanan hemde kendimizin elde ettiği preparatlar kullanılarak yeni bir histoloji veriseti oluşturulmuştur. Hazırlanan veriseti kan, bağ, epitel, kas ve sinir dokusundan oluşmaktadır. Kan, bağ, epitel, kas ve sinir dokusu preparatları insan dokularından veya dokuları insana benzer çeşitli memeli hayvanlardan farklı zamanlarda alınmıştır. Sınıflandırmada kapsamlı bir performans analizi sunmak amacıyla çeşitli MÖ teknikleri test edilmiştir. Deneysel çalışmalarda AdaBoost (AB), Yapay Sinir Ağları (YSA), Karar Ağacı (KA), Lojistik Regresyon (LR), Naive Bayes (NB), Rastgele Orman (RO) ve Destek Vektör Makineleri (DVM) yöntemleri analiz edilmiştir. Geliştirilen yapay zekâ (YZ) uygulaması, özellikle pandemi ve uzaktan eğitim dönemlerinde, tıp fakülteleri ve sağlık bilimlerindeki lisans ve lisansüstü öğrencileri için bir eğitim materyali olarak faydalı olmaktadır. Ayrıca, bu uygulama tıp uzmanlarının harcadığı zamanı ve iş performans kayıplarını en aza indirmek amacıyla bilgisayar destekli tıbbi karar destek sistemi olarak da kullanılabilir.

Anahtar kelimeler: Bilgisayar destekli teşhis, görüntü işleme, histolojik görüntü, makine öğrenmesi, sınıflandırma.

1. Introduction

Histology is a term derived from the Greek words histos (tissue) and logia (science) and refers to the science of the structure and function of tissues. Physicians' basic science education makes a significant contribution to the accuracy of the decisions they make in their profession.

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Histology knowledge is critical in medical science because accurate identification and analysis of tissues are necessary for comprehending disease mechanisms and diagnosing patients. The recent global pandemic has had a significant impact on medical education, particularly on face-to-face education practices. Histology education, in particular, is severely lacking in the process of face-to-face laboratory applications, in which students learn to differentiate tissue types.

From this vantage point, the effectiveness of ML methods has provided the solution to numerous state-of-the-art medical problems. AI frameworks may be beneficial as educational material for undergraduate and graduate students studying histology, medicine, and health sciences, particularly during distance education and pandemic periods. Additionally, it can be also utilized as a computer-assisted medical decision support system for medical experts to help them save time and perform better on the job.

AI has rapidly emerged method of choice for medical image analysis applications. Classification [1], detection [2-3], segmentation [4], etc. problems in the medical field can be solved more easily due to the fast and robust side of the AI approaches. In the literature, computer-aided analysis of histological and histopathological tissues and organs has been performed using different AI techniques. Codella et al. [5] studied lymphoma recognition in hematoxylin and eosin (H&E) stained histopathology slides. Each of the over 200 descriptors has been trained by non-linear SVMs. They demonstrated a 38.4% reduction in residual error over the current state-of-the-art dataset. Mazo et al. [6] developed a framework to categorize normal cardiovascular tissues and organs from histological images using a transfer learning mechanism. Convolutional Neural Network (CNN) architectures trained to recognize visual objects in natural images were fitted and modified for this problem. They claimed the idea that CNNs are very suitable for improving tissue and organ classification. Niemann et al. [7] compared various image segmentation techniques which are texture-based clustering, filter and threshold-based segmentation, and DL for histologic images of intracranial aneurysms. Finally, they analyzed the performance of the approaches depending on the experimental results. Xu et al. [8] proposed an unsupervised Tissue Cluster Level Graph Cut (TisCut) approach for histological image partition using three different histology image sets with different color staining methods. They proved that TisCut can effectively partition the histological images into meaningful compartments. Sato et al. [9] proposed an unsupervised approach combining CNNs and a visualization algorithm to cluster the images of the glomerulus of kidney biopsy samples stained with (H&E). Taylor-Weiner et al. [10] described an ML-based method for liver histology assessment to characterize disease severity and heterogeneity. They measured key histological features such as steatosis, inflammation, hepatocellular ballooning, and fibrosis. Varalakshmi et. al [11] proposed a classification and prediction model based on the XGBoost algorithm which is an ensemble learning algorithm that uses a gradient boosting framework. The proposed model has been compared with other classification algorithms such as AB, DT, Gradientboost, and NB. They classified osteosarcoma with an accuracy of 94.84%.

Normal fundamental tissues are analyzed by histology experts or others with a similar background. However, there are not enough systems that can recognize tissues automatically. Thanks to the designed AI framework that classifies histological images automatically, people who do not work in the field of histology such as biology, dentistry, and veterinary medicine can utilize and pathological analysis can be performed after determining which image belongs to which tissue. As a result, the designed AI framework has a support system mechanism that can be used by students and experts in the medical faculty minimizing the loss of time and energy.

The rest of this paper is structured as follows. Section 2 describes the created novel histological dataset in detail. Section 3 gives experimental results and discussion of ML applications for the classification of histological images. Finally, Section 4 summarizes the main conclusions of this work.

2. Material and Method

2.1. Histological data

Cell groups that are specialized to perform a specific task with a similar structure in the living body are called tissues. The main structures that make up the tissue are the cells and the substances that lie between the cells. Since tissues perform different tasks, they differ from each other in many respects. There are more intercellular substances, in some tissues, there are fewer. This causes the tissues to be different from each other. The tissue consists of cellular and intercellular elements organized to perform specific functions. There are four basic types of tissue: epithelial, connective, muscle, and nervous. There are samples of these four basic tissues in every organ and there are many subtypes of these four basic tissues [12]. Tissue types are summarized in Figure 1.

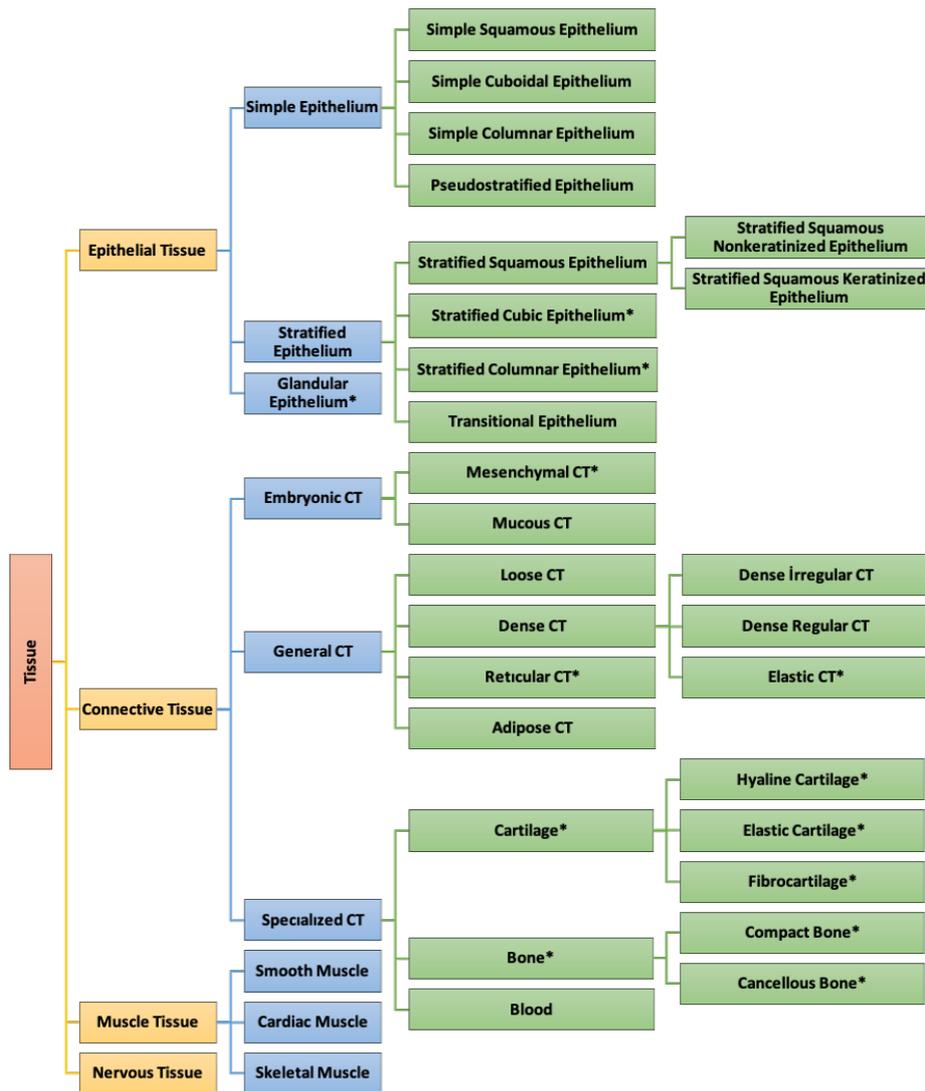


Figure 1. Tissue types (* Tissue types are excluded from the dataset).

Four basic tissue types are present in almost all organs, with different subtypes and in varying amounts. However, the locations of some specialized tissue subtypes are specific. For example, smooth muscle, which is a subtype of muscle tissue, is located on the walls of visceral organs, while the cardiac muscle is specific to the heart [13]. Epithelial tissue serves as a protective covering for the body and organs by covering the inner surface of all lumen organs as well as the exterior surface of the body and organs [14]. Connective tissues comprise the majority of the body's structural components. While specific connective tissue types, such as bone, cartilage, and blood, play significant functions in the skeletal and circulatory systems, general connective tissue types provide support for all organs [15]. While the majority of nervous tissue is concentrated in the central nervous system, which serves as the decision-maker, the peripheral nervous system also includes the nerve network that extends throughout the body to gather information and transmit commands [16]. The need for histological image classification can be expressed as follows:

- To analyze pathological images known as abnormal tissue, histological images must be analyzed first. After determining which image belongs to which tissue, pathological analysis can be performed.
- There is a system that can be easily utilized by people who do not work in the field of histology. It provides convenience in some areas such as biology, dentistry, and veterinary medicine to identify histological images.

- AI frameworks have a support system mechanism that can be used by students and experts in the medical faculty. These kinds of systems minimize the loss of time and energy.

All of the tissue subtypes that can be detected using standard staining and are not exceedingly rare were photographed at various microscope magnifications and transferred to digital media in this histological data set. Tissue types marked with an * in Figure 1 are excluded from the dataset.

The dataset was generated using educational slides prepared for the laboratory courses of Selcuk University Faculty of Medicine, Department of Histology and Embryology. The preparations were obtained from human tissues or tissues from various human-like mammals at different times. Tissues were fixed with formaldehyde, embedded in paraffin, and stained with H&E. Blood preparations were taken as smears and stained with Wright-Giemsa (WG). Figure 2 shows the dissection of the visceral organs in the rat and Figure 3 demonstrates the dissected rat cerebrum and cerebellum. In the continuation of this section, the process of obtaining histological images is explained in detail.



Figure 2. Dissection of the visceral organs in the rat.



Figure 3. Dissected rat cerebrum and cerebellum.

2.1.1 Data preparation processes

2.1.1.1. Preparation of slides

The basic steps in the preparation of tissues were fixation, washing, dehydration, clearing, embedding, sectioning, and attaching sections to slides. These steps can be summarized as follows:

1. Fixation: Tissues were taken into 10% formaldehyde solution with a fixative/tissue ratio of 10/1 and fixed at +4 °C for 24 hours.
2. Washing: Tissues were washed under running tap water for 1 night.
3. Dehydration:
 - Sections were dehydrated by soaking in 50-60-70-80-90% alcohol, for 45 minutes each.
 - Then, 96% and 100% alcohol for 45 minutes each.
4. Clearing:
 - 20 minutes in alcohol+xylene (1/1),
 - 1 hour in xylene,
 - Tissues were cleared by soaking in the second xylene for 1.5 hours.
5. Embedding:
 - Sections were kept for 20 minutes in xylene+paraffin (1/1) in an oven at 57 °C.
 - Then kept in paraffin in an oven at 57 °C for 15 minutes.
 - Then the tissues were embedded in paraffin blocks in metal cassettes and allowed to cool at room temperature. Figure 4 displays the tissue cassette embedded in paraffin.
6. Sectioning: Sections of 4-5µm thickness were taken from the tissues embedded in paraffin blocks with a microtome device as shown in Figure 5.
7. Putting the sections on the slide: The 4 µm sections taken were left in the water pool, left to open, and labeled on the slides with lysine.

To prepare blood tissue preparations:

1. A small drop of blood was placed on the midline, 1 cm from one end of the slide. Then the lamella is brought in front of the drop at an angle of 30-45° and after contacting the drop backward, it is driven forward with a smooth and rapid movement of the hand.
2. The smear was dried in the air for 5-10 minutes.



Figure 4. The tissue cassette embedded in paraffin.



Figure 5. Microtome device.

2.1.1.2. Staining of preparations

For the prepared preparations, the dying phase was started. At this stage, the tissues were first freed from paraffin, then rehydrated and made ready for staining. After the staining steps, the sections were made transparent again and closed with entellan and made ready for imaging. The H&E protocol is summarized below:

1. Deparaffinization:
 - Tissue sections were deparaffinized by incubating at 57 °C overnight,
 - And keep it in xylene at room temperature for 2x30 minutes.
2. Rehydration: Sections were passed through a series of ethyl alcohol in decreasing concentrations (96%, 90%, 80%, 70%, 60%). (2 minutes each) and 5 minutes under running tap water.
3. Staining:
 - Sections were kept in hematoxylin for 5 minutes and washed under running tap water for 5 minutes.
 - Sections were dipped in acid alcohol for a few seconds and washed under running tap water for 5 minutes.
4. Sections were kept in eosin for 2-3 minutes and washed under running tap water for 2 minutes.
5. Sections were passed through a series of increasing concentrations of alcohol.
6. Clearing: Sections were kept in xylene for 1 hour.
7. Mounting: 1 drop of entellan was dropped on the tissue and closed with a coverslip.

Smear and dried blood preparations were stained with WG according to the following protocol:

1. Wright's dye was poured on the preparation and left for 1 minute.
2. Washed with distilled water.
3. Giemsa paint was poured on the preparation and left for 7 minutes.
4. The paint was poured from the preparation and left in an upright position to dry.
5. For the preparations to be used for a long time, entellan was dripped onto the tissue and covered with a coverslip.

The produced preparations for various tissue classes are depicted in Figure 6.

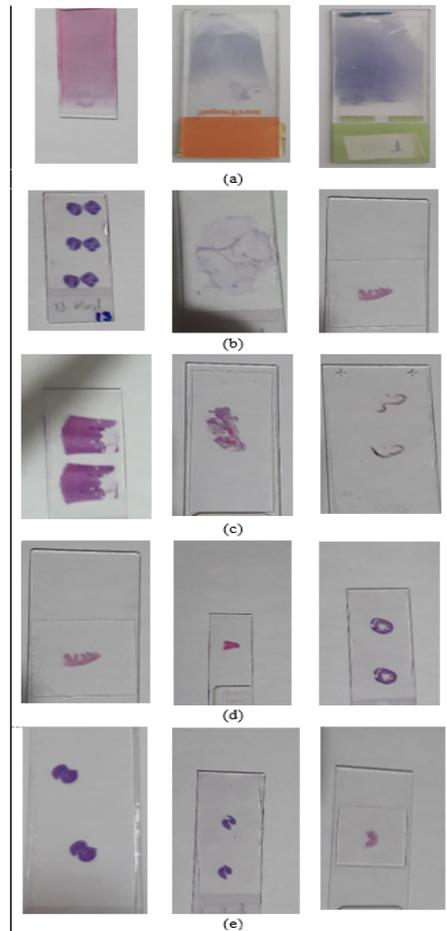


Figure 6. Prepared samples of preparations for histological tissue classification (a: Blood, b: Connective, c: Epithelium, d: Muscle, e: Nerve).

2.1.1.3. Digital display of slides

The prepared and stained preparations were viewed using an Olympus BX51 microscope and a data pool was created by photographing all sections at 4x, 10x, and 40x magnifications using the Olympus DP72 camera and Olympus DP2-BSW program. Since the general evaluation of blood tissue preparations was made with 100x magnifications, photographs were taken with 100x magnifications as well as 4x, 10x, and 40x magnifications. The Olympus BX51 microscope, the Olympus DP72 camera, and the Olympus DP2-BSW program used to digitize the images are shown in Figure 7. Photo examples of histological data classes at 4x, 10x, 20x, 40x, and 100x magnification are shown in Figure 8.

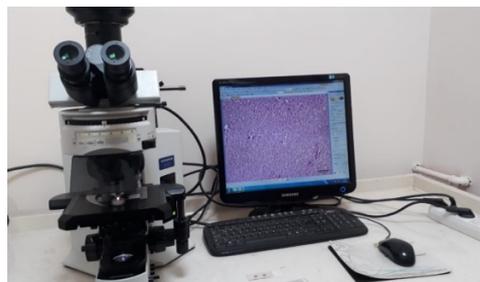


Figure 7. The Olympus BX51 microscope, the Olympus DP72 camera, and the Olympus DP2-BSW program.

2.1.1.4. Dataset description

In this paper, a novel histological RGB image dataset that involves blood, connective, epithelium, muscle, and nerve tissue images was created to perform various medical image analysis tasks such as classification, detection, localization, and semantic segmentation. Sample images of the histological tissues are depicted in Figure 9. As listed in Table 1, the dataset consists of 4031 blood tissue, 4118 connective tissue, 4063 epithelium tissue, 4023 muscle tissue, and 4113 nerve tissue images.

The ethics committee report for the experimental studies was taken from the Histology and Embryology Department of Faculty of Medicine at Selcuk University with the date and number 26.06.2019 and 2019/175.

The proposed histological image dataset is not publicly available due to ethical restrictions. However, some information about the previous studies that use this dataset can be explained as follows: In the first study, detection and classification of leucocyte types on the histological blood tissue images were performed. The positions and types of leucocytes were determined and the classification process was carried out [17]. In the second study, a novel three-dimensional image filter-based CNN approach which is based on three-dimensional object images with different perspectives was developed. The efficiency of the filter generation approach was proved on the proposed histological dataset [18].

Table 1. Distribution of the dataset.

Tissue class	Number of images
Blood	4031
Connective	4118
Epithelium	4063
Muscle	4023
Nerve	4113

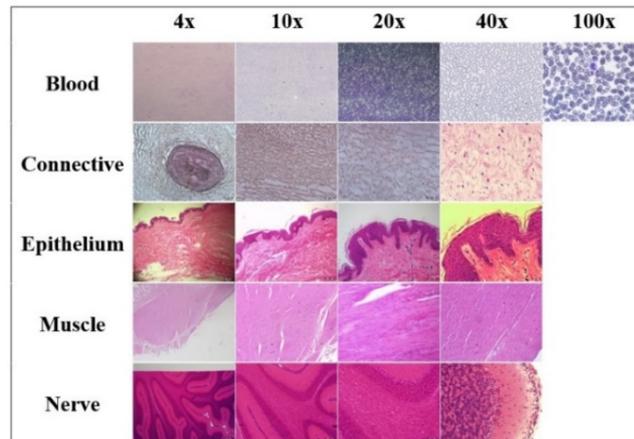


Figure 8. Photo examples of histological data classes at 4x, 10x, 20x, 40x, and 100x magnifications.

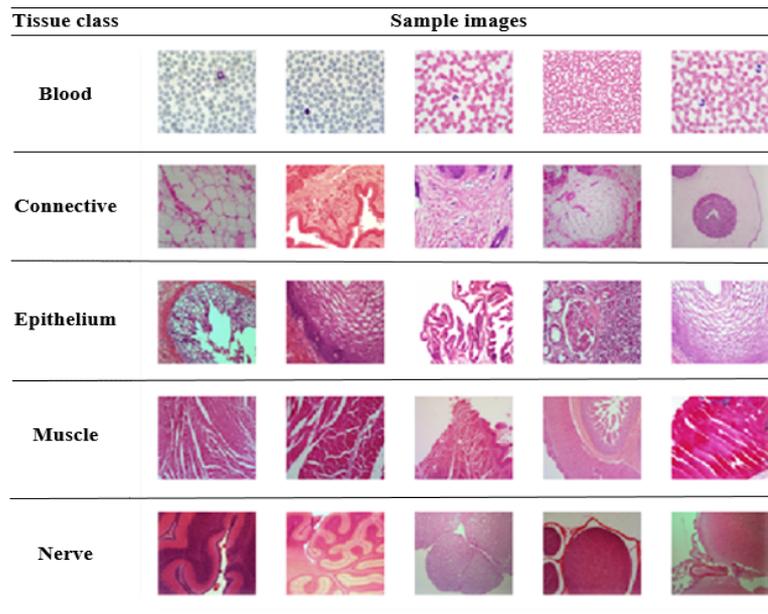


Figure 9. Histological image samples.

2.2. ML methods

ML aims to design models which enable computer systems to mimic the learning process of human beings from the available data. The main task of designing an ML system is to fit the data to the model by tuning the model's hyperparameters. Unlike the DL approaches, ML methods have less learnable parameters. Considering both training and testing processes and computational complexity, ML methods are preferable approaches.

To provide a comprehensive performance analysis in the classification problem, frequently used seven various ML techniques which are AB, ANN, DT, LR, NB, RF, and SVM were discussed. Successful implementation of feature extraction directly affects the classification result. Therefore, features should summarize most of the information of the original dataset. The parameters of the methods used during the training are given in Table 2 in detail, the pseudocode for comparing ML models to make the designed system more understandable is given below.

```

import the histology dataset
scale the dataset
store various ML models in a variable 'models'
set scoring equal to accuracy, precision, recall, f1-score
set name as name of the ML models
for name, model in models:
    store value of model_selection using 10 splits in a variable
    calculate and store results using cross_val_score method of model_selection (train and test data)
    append results in a list of existing results
    calculate the mean of the performance metrics
end for

```

3. Experimental Results and Discussion

The analysis of medical images on time is extremely important to get treatment on time and maintain a healthy lifestyle. In particular, the manual classification of large dimensions of medical image data by medical experts is tiring, time-consuming, and prone to error. With ML prediction, the time that medical professionals will devote to diagnosis, prognosis, image examination, and treatment processes is increased. With discoveries in AI and ever-increasing technological development, ML techniques can analyze medical data efficiently.

3.1. Results

To show the efficiency of classification performances of ML methods, AB, ANN, DT, LR, NB, RF, and SVM methods experimented. Training parameters of the ML methods are listed in Table 2.

Table 2. ML methods and training parameters.

ML method	Training parameters
AB	The number of estimators: 100
	The initial learning rate: 0.01
	The classification algorithm: Stagewise Additive Modeling using a Multi-class Exponential for Real
ANN	Loss function for regression: Linear
	Hidden layer count: 40
DT	The activation function: Rectified Linear Unit (ReLU)
	The optimization algorithm: Stochastic Gradient Descent
LR	The number of iterations (maximum): 80
	The number of instances in leaves (minimum): 2
NB	The tree depth limit (maximum):100
	L1 normalization
RF	-
	The number of trees: 35
SVM	The split limit for subsets smaller than: 5
	SVM with Radial Basis Function (Gaussian kernel)
	The number of iterations: 350

The feature extraction process directly affects the classification result. Therefore, the features of the experimental histological image dataset should summarize most of the information of the original dataset. For this study, SqueezeNet model trained on ImageNet dataset was used for the feature extraction process with Orange Data Mining software. The feature matrix that consists of 1000 image features including five target values (blood, connective, epithelium, muscle, nerve) was obtained using 20348 histological image samples.

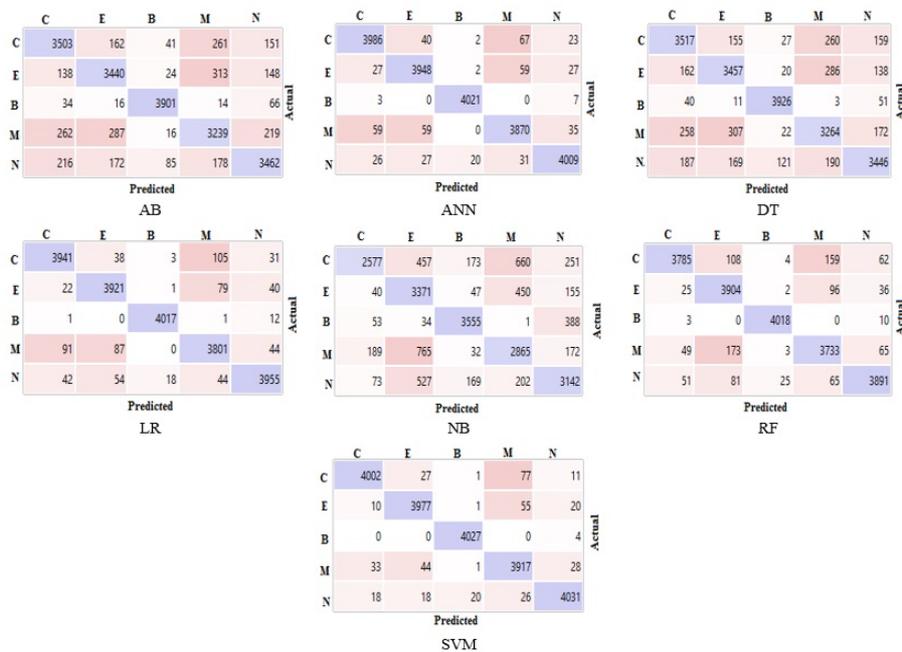


Figure 10. Confusion matrices of ML methods (C: Connective, E: Epithelium, B: Blood, M: Muscle, N: Nerve).

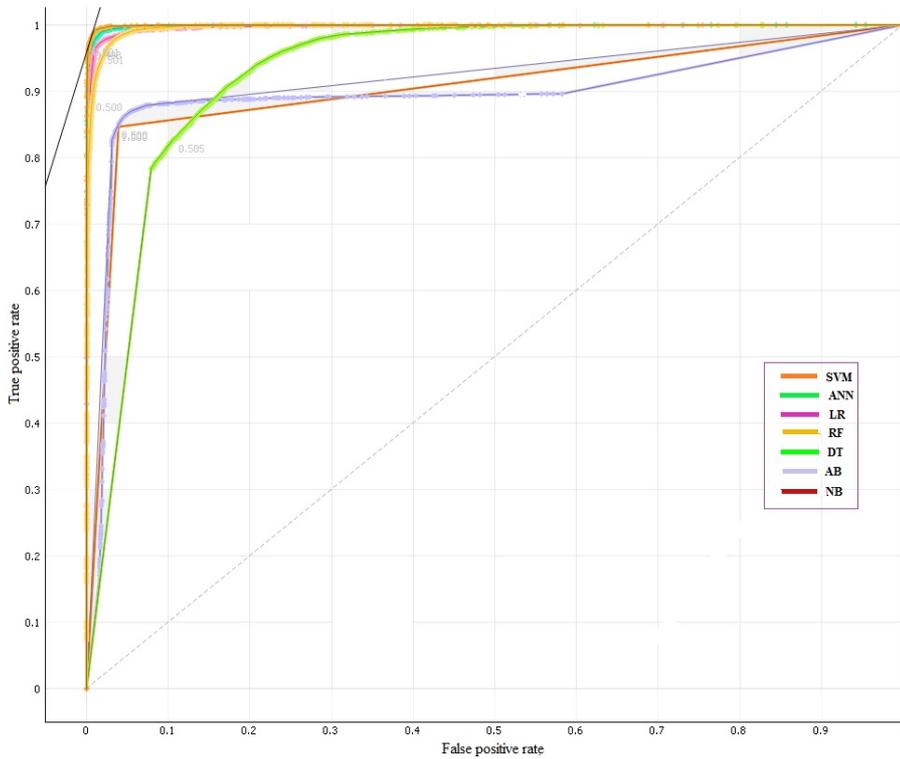


Figure 11. AUC/ROC of ML methods.

The classification performances of ML methods were evaluated using well-known performance metrics such as accuracy, precision, recall, and f1-score. In addition, 10-fold cross-validation was used to improve the validity of the experimental results. Moreover, area under curve (AUC) values and receiver operating characteristic (ROC) curves of all methods were obtained. Figure 10 illustrates the confusion matrices and Figure 11 shows the AUC/ROC of ML methods at the end of the test process.

Table 3. Classification performances of ML methods.

ML method	Measurement metrics (%)				
	Accuracy	Precision	Recall	F1-score	AUC
AB	86.20	86.20	86.20	86.20	91.40
ANN	97.50	97.50	97.50	97.50	99.90
DT	86.50	86.50	86.50	86.50	90.90
LR	96.50	96.50	96.50	96.50	99.70
NB	76.20	77.60	76.20	76.30	93.10
RF	95.00	95.10	95.00	95.00	99.60
SVM	98.10	98.10	98.10	98.10	99.90

Table 3 lists the accuracy, precision, recall, f1-score, and AUC performance metrics of ML methods for the image classification task. SVM outperformed other ML methods with an accuracy of 98.10% as seen in Table 3. Besides, SVM obtained the best values for all calculated performance metrics. SVM obtained a sensitivity of 98.10% with a specificity of 98.10%, which was significantly better than the worst performing method (NB), with a sensitivity of 77.60%, and specificity of 76.20%. SVM is an effective model in high-dimensional spaces and it provides memory efficiency using a subset of training points in the decision function, also called support vectors. The classification accuracy values of ML methods obtained for each class are illustrated in Figure 12.

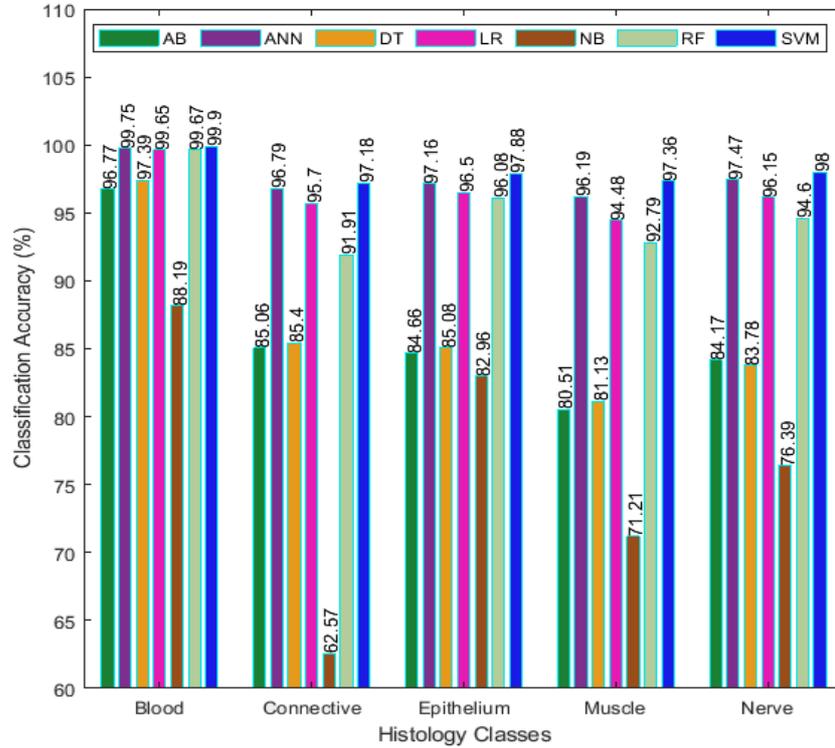


Figure 12. The classification accuracy rates of ML methods obtained for each histology class.

Blood tissue images are the class with the highest classification success. However, connective and muscle tissue images have a structure that can hardly be detected even by most medical experts. While the most successful ML method to classify blood tissue was SVM with an accuracy of 99.90%, the worst classification model was NB with 88.19%. Moreover, ANN has proved that it is a competitive model with an accuracy of 99.75% by taking second place in the classification task.

3.2. Discussion

The proposed approach conducted using real-world data enables a preliminary outline for the clinical studies and the designed AI framework can be utilized as a computer-aided medical decision support system.

The medical image analysis field has complex and massive data and the importance of the decisions made by medical experts makes it one of the fields in which ML techniques can have the greatest impact. Because microscopic examination of histological images is difficult and time-consuming. As seen in this study, histological data were classified with almost 99% success with SVM without needing more complex classification models. In order to analyze the histopathological data, it must first be determined which basic tissue class the image belongs to. After the tissue is determined, more detailed analyzes can be performed. Thanks to this study, the classification of basic tissues can be done quickly. The most important advantage of this study is that ML methods are fast and have a less complex structure compared to DL methods. As a result, the proposed AI framework that provides the automatic classification of histological data, the workload will be alleviated and it will be possible for medical professionals to focus on critical cases.

4. Conclusions

This study presents a novel histological dataset and the implementation of ML methods to analyze histological images. The experimental results of the classification of histological data obtained using ML methods were presented within the scope of this study. The proposed study eliminates the expert's bias with 98% success achieved with the most successful ML model (SVM). Considering the problems such as the fact that the expert's

error is more in real life, and the need for two or more expert evaluations to reduce this error, the proposed AI system has provided a significant advantage.

It is obvious that this dataset will be highly useful in the computer vision field. Among the applications that can be made with the existing dataset, the studies listed below can be given as examples:

- Classification of histological tissues and the classification of the subgroups of each histological tissue
- Detection and grouping of leukocytes in blood tissue
- Detection and classification of histopathological formations in different tissues and organs
- Histological tissue segmentation

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