The Effect of Hyper Parameters on the Classification of Lung Cancer Images Using Deep Learning Methods

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Abstract

Cancer is a fatal disease arised from the formation of abnormal cells as a result of random growth in the human body. Lung cancer is the frequently encountered cancer type and causes abnormal growth of lung cells. Diagnosis at an early stage substantially enhances the chance of survivability of the patient, as well as prolongs the survival time. There may even be a complete recovery. For this reason, it is of vital importance to support the diagnosis and detection of doctors and enables them to diagnose more easily and quickly. In this paper, it is aimed to detect lung cancer disease with the help of Alexnet and Resnet50 architectures, which are deep learning architectures, by using computed tomography images. In addition, the performances of the hyper-parameters of maximum epoch and batch size, which are of great importance in training the models, have been compared. According to the results obtained, the highest overall accuracy in automatic detection of lung cancer has been achieved with the AlexNet architecture. The highest overall accuracy value obtained as a result of the simulations is found to be 98.58% with the highest cycle value and the batch size are 200 and 64, respectively.

Keywords: Lung cancer, Alexnet, Resnet50, epoch, mini batch size.

Derin Öğrenme Yöntemleri Kullanılarak Akciğer Kanseri Görüntülerinin Sınıflandırılmasında Hiper Parametrelerin Etkisinin İncelenmesi

Öz

Kanser, insan vücudunda rasgele büyüme sonucunda normal olmayan hücrelerin oluşması ile meydana gelen ölümcül bir hastalıktır. Akciğer kanseri ise oldukça yaygın olan bir kanser türü olup, akciğer hücrelerinin anormal büyümesine neden olmaktadır. Hastalığın erken evrede teşhisi, hastanın yaşama şansını büyük oranda artırmanın yanı sıra sağ kalım süresini uzatmaktadır. Hatta tamamen iyileşme bile söz konusu olabilmektedir. Bu sebeple, doktorların tanı ve tespitini destekleyerek daha kolay ve hızlı bir şekilde teşhis edebilmelerine olanak sağlanması hayati öneme sahiptir. Bu çalışmada, bilgisayarlı tomografi görüntüleri kullanılarak derin öğrenme mimarilerinden olan Alexnet ve Resnet50 mimarileri yardımıyla akciğer kanseri hastalığının teşhis edilmesi amaçlanmaktadır. Ayrıca, modellerin eğitiminde büyük öneme sahip en yüksek devir ve parti boyutu hiper parametrelerinin performansları karşılaştırılmıştır. Elde edilen sonuçlara göre, akciğer kanserinin otomatik tespitinde en yüksek genel doğruluk değeri AlexNet mimarisi ile sağlanmıştır. Yapılan benzetimler sonucu, en yüksek genel doğruluk değeri, devir değeri 200 ve parti boyutu 64 ile %98.58 olarak elde edilmiştir.

Anahtar Kelimeler: Akciğer kanseri, Alexnet, Resnet50, devir sayısı, parti boyutu.

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1. Introduction

Cancer is a deadly disease in which some cells in the body multiply randomly and uncontrollably and insidiously spread to different areas of the body (Khanmohammadi et al., 2020). Cancer can occur in almost any cell. For this reason, tumors can occur with the growth and proliferation of damaged cells, which are harmful in any part of the body. The important thing is to detect whether these tumors are benign or malignant. While benign tumors do not spread to other tissues, malignant tumors can insidiously and dangerously spread to other tissues and prevent the person from performing their life functions. Lung, breast, prostate, bladder, skin, stomach are the most frequently encountered cancer types. In addition, among these, lung cancer which is the most frequently encountered in men causes the most deadly in the World Health Organization (WHO) report (Huang et al., 2017; Stapelfeld et al., 2020). According to the worldwide statistics of lung cancer incidence and death in 2020, there are an estimated 2.2 million new patients and 1.8 million deaths (Sung et al., 2020). It has been stated that in Turkey human deaths from lung cancer are higher than from other types of cancer (Demirkazık, 2014).

The most important causes of lung cancer; high body mass index, smoking and excessive use of alcohol, genetic predisposition, radiation exposure, air pollution, vitamin deficiencies, and exposure of the body to heavy metals. Since lung cancer starts to show some symptoms after a certain period, it is difficult to detect those who have the disease at an early stage. The most common symptoms are; shortness of breath, coughing up blood, and rapid weight loss (Jameson et al., 2004). For the definitive diagnosis of the disease, chest X-ray and computed tomography (CT), which are current methods, are mostly requested from the patients at the initial detection stage. However, a biopsy is required to determine the type of the tumor. Lung cancer, which is a difficult and tiring process and even the name must scare, can be detected at an early stage with the least effort. Early detection will not only save the life of the patient but also increase the standard of living. Hence, the need for computer-aided detection systems (CAD) is increasing day by day in the literature (Xiuhua et al., 2011). In addition, given the cases that radiologists face every day, it is inevitable that they need a fast and reliable system to support their analysis of large amounts of data. In this context, deep learning models, which are important approaches in solving big data problems, are highly preferred. In the literature, there are many studies on automatic diagnosis and detection of different diseases and cancer types through X-ray, CT, and pathological images utilizing deep learning (Al-Antari et al., 2020; Fanti et al., 2021; Narin and Kefeli, 2020).

There have been diversified researches in the current literature to detect lung cancer on CT automatically. Zhao et al. presented a detection sensitivity of 84.2% by utilizing a CAD system to identify small lung nodules automatically with the aid of multislice CT (MSCT) (Zhao et al., 2003). Sun et al. compared the performance of support vector machines (SVM) and other classification algorithms on 3- dimensional (3D) CT images for the diagnosis of lung cancer (Sun et al., 2013). Tan et al. used a CADx method that describes nodules with the help of filters and then they presented a novel classifier by using genetic algorithms and artificial neural networks (Tan et al., 2011). In addition, Alilou et al. have suggested a new

CADx to detect the pulmonary nodules by using thoracic CT images and they also have automated the whole lung segmentation process and detection of candidate nodules (Alilou et al., 2014). Çevik and Dandıl (2019) performed classification on 1218 CT images taken from 23 different patients using a convolutional neural network (CNN) with a transfer learning method.

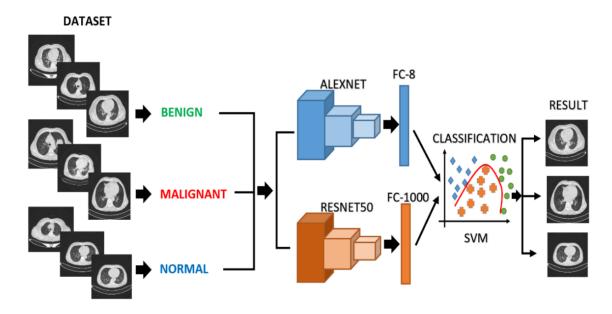


Figure 1. Schematic representation of lung cancer detection with deep learning

This paper studies the automatic detection of lung cancer by using pre-trained CNNs on CT images as shown in Figure 1. In addition, the roles of maximum epoch and batch size parameters, which significantly affect the performance of deep learning methods used for diagnosing lung cancer, were investigated.

The highlights of this study compared with the ones in the literature can be explained as follows:

i) The performances of AlexNet with a shallow architecture and ResNet50 with a deeper architecture have been compared.

ii) The results have been obtained on a hybrid system classified by the SVM algorithm using the features acquired from two different convolutional neural network architectures.

The rest of the paper is arranged as follows. Section 2 details the data set used, convolutional neural network models, and feature extraction and performance measures.

In Section 3, the results obtained in the experimental studies are presented. The last section concludes the paper by comparing the study with related ones in the literature.

2. Material and Methods

2.1. Data set

The lung cancer data set of the Iraq-Oncology teaching hospital/national cancer diseases center (IQ-OTH/NCCD) presented in 2019 is used in this study. This publicly available dataset can be reached from the Mendeley Data page (Al-Yasriy) and Kaggle's page (Kareem). The data set consists of CT data belonging to three different classes which are benign, malignant, and normal, as shown in Figure 2 and includes 1097 total images that represent CT scan slices from 110 individuals (15 benign, 40 malignant, 55 normal). These images were acquired in DICOM format via Siemens SOMATOM browser. Thereafter, it was saved in the data set in JPG format and made available for use.

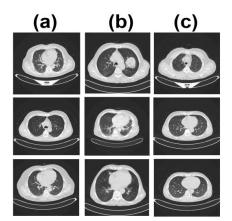


Figure 2. Examples of the used CT images a) Benign, b) Malignant, and c) Normal.

2.2. Deep feature extraction based on convolutional neural networks

A CNN is a special case of deep neural networks. The CNN architecture is based on the organization of the visual cortex and is similar to the connection structure of neurons in the human brain (Lindsay, 2021). This structure, which takes its name from the convolution process, is very effective and useful in the case of increasing data sizes and approaches related to the analysis of big data. CNN architecture generally consists of three main structures that are convolution, pooling, and fully connected layers. In the convolution layer, where convolution operations are performed, feature maps are created by filtering incoming patterns with filters of different sizes. By shifting these filters on the pattern, multifarious features emerge. As the number of convolution layers increases, the obtained deep features increase. In the pooling layer, operations are performed to derogate the size and number of feature maps and network parameters. In the fully connected layer, the obtained feature maps are converted to one-dimensional vectors (Ari and Hanbay, 2018). Interconnections of fully connected layers are weighted. Additionally, layers such as normalization layers, dilution layers are also used (Gray et al., 2017). Generally, with these operations, feature extraction processes are performed on the pattern given as input. Classification operations can be performed on the last layer of the fully connected layer (Yamashita et al., 2018). In addition,

hybrid models can be realized with the help of feature maps obtained from the layers before the last layer and different classifier algorithms (Çınar and Yıldırım, 2020). In this paper, AlexNet and ResNet50 models, which are CNN architectures, were used.

2.2.1. AlexNet model

AlexNet has eight layers with learnable parameters. The model consists of five layers with maximum pooling pursued by a combination of 3 fully connected layers and uses Relu activation in each of these layers except the output layer. AlexNet was designed by Alex Krizhevsky and her colleagues in 2012 and won a very high success in a large-scale competition called "Imageneté" in the same year (Krizhevsky et al., 2012).

2.2.2. ResNet50 model

Differently from classical methods, in the ResNet50 model, residual values and the blocks that feed the next layers (residual blocks) are added to the model. ResNet50 architecture is a model that consists of 50 layers (Russakovsky et al., 2015). Convolution operations include 1×1 , 3×3 , and 1×1 convolution stages that are responsible for different operations (Hu et al., 2018).

In this paper, the features gotten out of the fully connected layers in the AlexNet and ResNet50 models of the classification stage were used. The fully connected layers from which the features are extracted are "fc8" for AlexNet and "fc1000" for ResNet50.

2.3. Support vector machines algorithm

Support vector machines (SVM) is a statistical-based algorithm developed by Vapnik to solve the pattern recognition and classification problems from machine learning approaches (Weston et al., 2000). It is aimed to determine the surface with the highest separation between the classes while classifying the patterns. For this, support vectors are determined first. Identifying the separating surfaces that will separate two or more classes is one of the stages of the education process. Various different combinations can be obtained without changing the success of the separating surface on the dataset. Thanks to SVM, the separating surface is at the same distance and maximum distance to both classes. In the realization of this operation, the Lagrangian method has been used (Xie et al., 2021). In this paper, the results were obtained by using the linear functions of the SVM algorithm (Agner et al., 2011).

2.4. Performance metrics

The performances of the models used in the study were evaluated with four different criteria that are Accuracy, Recall, Precision, and F1-Score values, whose mathematical expressions are given in Equations (1)- (4).

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN}$$
(1)

$$Recall = \frac{TP}{TP + FN}$$
(2)

$$Precision = \frac{TP}{TP + FP}$$
(3)

$$F1 - score = \frac{2 x Recall x Precision}{Recall + Precision}$$
(4)

In the above equations, TP, FN, TN, and FP represent the number of correctly classified positive patients, the number of positive patients falsely classified as non-patient, the number of correctly classified non-patients, and the number of patients falsely classified as patients but not actually sick, respectively (Narin et al., 2017).

3. Results and Discussion

3.1. Results

In this study, the MATLAB 2020A program was used to establish the model and obtain the results. In experimental studies, a computer with Intel(R) Core(TM) i7-3632QM CPU @ 2.20GHz processor was used. The performances of the features extracted using AlexNet and ResNet50 from CNN architectures were determined with the help of the SVM algorithm. In addition, the effects of epoch and batch size, which are network parameters that significantly change the performance of deep learning approaches, are analyzed and their roles in lung cancer detection are examined. Here, the results were found using 70% of the data set for training and 30% for testing. Accuracy values of three different batch sizes obtained for AlexNet architecture according to five different epoch numbers are given in Figure 3.

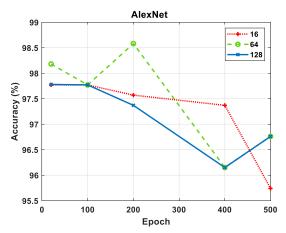


Figure 3. The variation of Accuracy values of three different batch sizes for AlexNet according to five different epoch numbers.

Figure 3 indicates that the increment in the epoch number causes a downward trend in the general performance values for AlexNet. The highest Accuracy value is obtained when the batch size is 64 and the number of epochs is 200. Recall, Precision, and F1-Score values, which are other performance criteria, are calculated for these parameter values where the highest Accuracy value is obtained and given in Table 1.

Table 1 points out that people with malignant lung cancer have an overall accuracy of 99.70% and images belonging to the malignant class are detected with 100% recall. The Accuracy values of three different batch sizes (batch size) obtained for the ResNet50 architecture which is another CNN model used in the study, according to five different epoch numbers, are shown in detail in Figure 4.

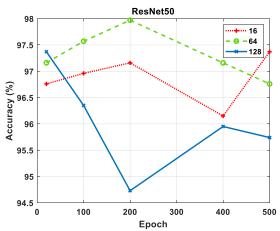


Figure 4. The variation of accuracy values of three different batch sizes for ResNet50 according to five different epoch numbers

In Figure 4, with a large batch size, an increase in the number of epochs causes a decrease in the overall accuracy and the highest accuracy of 97.97% is achieved for the ResNet50 architecture, with a batch size of 64 and an epoch of 200. Table 2 presents the detection performances of the classes for the highest accuracy value obtained over the ResNet50 architecture.

When the results obtained in Table 2 are

evaluated, an overall accuracy of 99.39% was achieved in the detection of images belonging to the malignant class, and moreover, in 99.40%, it is possible to detect images belonging to the malignant class.

If the results obtained for both models used in the study are examined, it can be seen that AlexNet exhibits higher performance than ResNet50. In addition, batch size and epoch parameters also significantly affect the detection performance of lung cancer types.

3.2. Discussion

Studies that use deep learning methods and are conducted on lung cancer diagnoses are given in Table 3. The results obtained from this study were compared with the ones that are based on deep learning in the literature and carried out using the same data set. Al-Yasriy et al. have suggested a CAD to aid for lung cancer detection from normal, benign, or malignant images with the convolutional neural network using AlexNet architecture in chest tomography images. They succeed 93.55% accuracy rate with the proposed model (Al-Yasriy et al., 2020). In another research, Hamdalla et al. applied image enhancement, image segmentation, and feature extraction methods including three preprocessing steps to determine lung cancer in the same data set. They utilized SVM for classification to diagnose three classes of lung cancer that are normal, benign, or malignant, and the highest accuracy achieved was 89.89% (Hamdalla et al., 2021). In the comprehensive study of Prarthana and Bhavani malignant, normal, and benign lung nodules were classified with more images than previous studies, and they were trained using CNN and Artificial Neural Network (ANN) to compare all the results obtained (Prarthana and Bhavani, 2021). As a result

Classes	ТР	TN	FP	FN	Accuracy (%)	Recall (%)	Precision (%)	F1-score (%)
Benign	32	291	2	4	98.18	88.89	94.12	91.43
Malignant	168	160	1	0	99.70	100	99.41	99.70
Normal	122	200	4	3	97.87	97.60	96.83	97.21
Average					98.58	95.50	96.78	96.14

Table 1. The performance measures for AlexNet with batch size 64 and epoch 200.

Table 2. The performance measures for ResNet50 with batch size 64 and epoch 200.

Classes	ТР	TN	FP	FN	Accuracy (%)	Recall (%)	Precision (%)	F1-Score (%)
Benign	30	291	2	6	97.57	83.33	93.75	88.24
Malignant	167	160	1	1	99.39	99.40	99.40	99.40
Normal	122	197	7	3	96.96	97.60	94.57	96.06
Average					97.97	93.45	95.91	94.66

they obtained the highest general accuracy of 98% and 71% with CNN and ANN, respectively.

Table 3. The comparison with the studies conducted with the same data set in the literature

Author(s)	Accuracy(%)
Al-Yasriy et al. (2020)	93.55
Hamdalla et al. (2021)	89.89
Prarthana and Bhavani (2021)	98.00
This Study	98.58

4. Conclusion

In this study, AlexNet and ResNet50 models from CNN architectures have been used and a higher general accuracy value has been obtained than many studies in the literature. The classification was performed with the SVM algorithm and the highest accuracy value was obtained with AlexNet as 98.58%. In addition, the effects of epoch and batch size, which are network parameters that significantly change the performance of deep learning approaches, were studied and their effects for lung cancer diagnosing were investigated.

It is estimated that the performance will increase significantly by increasing the data set used in the study. Future studies can be carried out in more detail using different CNN models and parameters. In addition, other current deep learning-based approaches in the diagnosis of lung cancer will be investigated, and it is planned to work on popular deep learning techniques, hybrid methods, and more data.

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Authors' Contributions

TÖO supervised the findings of this work. TÖO and DN carried out the study and committed to the paper. Both authors read and approved the final manuscript.

Competing Interests

The authors declare that they have no competing interests.

Ethics in Publishing

There are no ethical issues regarding the publication of this study.

References

- Agner, S.C., Soman, S., Libfeld, E., McDonald, M., Thomas, K., Englander, S., Madabhushi,
 A. 2011. "Textural Kinetics: A Novel Dynamic Contrast-enhanced (DCE)-MRI Feature for Breast Lesion Classification", Journal of Digital Imaging, 24(3), 446-463.
- Al-Antari, M. A., Han, S. M., Kim, T. S. 2020. "Evaluation of Deep Learning Detection and Classification Towards Computer-aided Diagnosis of Breast Lesions in Digital X-ray Mammograms", Computer Methods and Programs in Biomedicine, 196, 105584.
- Alilou, M., Kovalev, V., Snezhko, E., Taimouri, V. 2014. "A Comprehensive Framework for Automatic Detection of Pulmonary Nodules in Lung CT Images", Image Analysis & Stereology, 33(1), 13-27.
- Alyasriy, H.F. "The IQ-OTHNCCD Lung Cancer Dataset", https://data.mendeley.com/datasets/bhmdr45bh2/1, Last accessed: 10.08.2021
- Al-Yasriy, H. F., Al-Husieny, M. S., Mohsen, F. Y., Khalil, E. A., Hassan, Z. S. 2020.
 "Diagnosis of Lung Cancer Based on CT Scans Using CNN", IOP Conference Series: Materials Science and Engineering (ISCAU), Thi-Qar, Iraq, 928(2), 022035.
- Ari, A., Hanbay, D. 2018. "Deep Learning Based Brain Tumor Classification and Detection System", Turkish Journal of Electrical Engineering & Computer Sciences, 26(5), 2275-2286.
- Çevik, K., Dandıl, E. 2019. "Classification of Lung Nodules Using Convolutional Neural Networks on CT Images", 2nd International Turkish World Engineering and Science Congress, Antalya, 27-35.
- Çinar, A., Yildirim, M. 2020. "Detection of Tumors on Brain MRI Images Using the Hybrid Convolutional Neural Network Architecture", Medical Hypotheses, 139, 109684.

- Demirkazık, B. F. 2014. "Akciğer Kanserinde Bilgisayarlı Tomografi ile Tarama: Güncel Bilgiler", Türk Radyoloji Seminerleri, Hacettepe Üniversitesi Tıp Fakültesi, Radyoloji Anabilim Dalı, 290-303.
- Fanti, S., Goffin, K., Hadaschik, B. A., Herrmann, K., Maurer, T., MacLennan, S., Daniela, E. O-L. 2021. "Consensus Statements on PSMA PET/CT Response Assessment Criteria in Prostate Cancer", European Journal of Nuclear Medicine and Molecular Imaging (EJNMMI), 48(2), 469-476.
- Gray, S., Radford, A., Kingma, D. P. 2017. "Gpu Kernels For Block-sparse Weights", Technical Report.
- Hamdalla, F. K., Al-Huseiny, M. S., Mohsen, F. Y., Khalil, E. A., Hassan Z. S. 2021. "Evaluation of SVM Performance In the Detection of Lung Cancer in Marked CT Scan Dataset", Indonesian Journal of Electrical Engineering and Computer Science (IAES), 21(3), 1731-1738.
- Huang, C. Y., Ju, D. T., Chang, C. F., Reddy, P. M., Velmurugan, B. K. 2017. "A Review on the Effects of Current Chemotherapy Drugs and Natural Agents in Treating Non–Small Cell Lung Cancer", Biomedicine, 7(4), 12-23.
- Hu, J., Shen, L., Sun G. 2018. "Squeeze-and-excitation Networks", IEEE Conference on Computer Vision and Pattern Recognition, Salt Lake City, UT, USA, 7132-7141.
- Jameson, J. L., Fauci, A. S., Kasper, D. L., Hauser, S. L., Longo, D. L., Loscalzo, J. (2004). "Harrison's Principles of Internal Medicine", Mc Graw Hill, 506–516.
- Kareem, H. F. "The IQ-OTHNCCD Lung Cancer Dataset", https://www.kaggle.com/hamdallak/the-iqothnccd-lung-cancer dataset/metadata, Last accessed: 10.08.2021
- Khanmohammadi, A., Aghaie, A., Vahedi, E., Qazvini, A., Ghanei, M., Afkhami, A., Bagheri, H. 2020. "Electrochemical Biosensors for the Detection of Lung Cancer biomarkers: a review", Talanta, 206 (1), 120251.
- Krizhevsky, A., Sutskever, I., and Hinton, G. E. 2012. "Imagenet Classification with Deep Convolutional Neural Networks", Advances in Neural Information Processing Systems, 25, 1097-1105.
- Lindsay, G. W. 2021. "Convolutional Neural Networks As a Model of the Visual System: Past, Present, and Future", Journal of Cognitive Neuroscience, 33(10), 2017–2031.
- Narin, A., Kefeli, S. K. 2020. "Meme Kanseri Tespitinde Evrişimsel Sinir Ağı Modellerinin Performansları", Karaelmas Science and Engineering Journal, 10(2), 186-194.
- Narin, A., Özer, M., İşler, Y. 2017. "Effect of Linear and Non-linear Measurements of Heart Rate Variability in Prediction of PAF Attack", 25th Signal Processing and Communications Applications Conference (SIU), Antalya, 1-4.
- Prarthana, K. R., Bhavani, K. 2021. "Lung Cancer Classification Techniques", International Journal of Engineering Science and Computing (IJESC), 11(6), 28054-28058.
- Russakovsky, O., Deng, J., Su, H., Krause, J., Satheesh, S., Ma, S., Fei-Fei, L. 2015. "Imagenet Large Scale Visual Recognition Challenge", International Journal of Computer Vision, 115(3), 211-252.
- Stapelfeld, C., Dammann, C., Maser, E. 2020. "Sex-specificity in Lung Cancer Risk", International Journal of Cancer, 146 (9), 2376-2382.

- Sun, T., Jingjing, W., Xia, L., Pingxin, L., Fen, L., Yanxia, L, Qi, G., Huiping, Z., Xiuhua, G. 2013. "Comparative Evaluation of Support Vector Machines for Computer Aided Diagnosis of Lung Cancer in CT Based on a Multi-dimensional Data Set", Computer Methods and Programs in Miomedicine, 111(2), 519-524.
- Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., Bray, F. 2021. "Global cancer statistics 2020 (GLOBOCAN)", A Cancer Journal for Clinicians, 71(3), 209-249.
- Tan, M., Deklerck, R., Jansen, B., Bister, M., Cornelis, J. 2011. "A Novel Computer-aided Lung Nodule Detection System for CT Images", Medical Physics, 38(10), 5630-5645.
- Weston, J., Mukherjee, S., Chapelle, O., Pontil, M., Poggio, T., Vapnik, V. 2000. "Feature Selection for SVMs", Advances in Neural Information Processing Systems (NIPS), 12, 668-674.
- Xie, W., She, Y., Guo, Q. 2021. "Research on Multiple Classification Based on Improved SVM Algorithm for Balanced Binary Decision Tree", Scientific Programming, 2021, 1-11.
- Xiuhua G., Tao, S., Zhigang, L. (2011). "Prediction Models for Malignant Pulmonary Nodules Based-on Texture Features of CT Image", InTech, 63-76.
- Yamashita, R., Nishio, M., Do, R. K. G., Togashi, K. 2018. "Convolutional Neural Networks: An Overview and Application In Radiology", Insights into İmaging, 9(4), 611-629.
- Zhao, B., Gamsu, G., Ginsberg, M. S., Jiang, L., Schwartz, L. H. 2003. "Automatic Detection of Small Lung Nodules on CT Utilizing a Local Density Maximum Algorithm", Journal of Applied Clinical Medical Physics, 4(3), 248-260.