



RESEARCH ARTICLE

Comparative Assessment of Colon Cancer Classification Using Diverse Deep Learning Approaches

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Abstract: Colon cancer is a general form of avoidable cancer, which is also widely spread across the globe. It is also a leading cancer and considered as big killer among all kinds of cancers. In recent times, significant advances are developed in treatment field of this frequently causing disease. In this research, several deep learning techniques, namely convolutional neural network (CNN), recurrent neural network (RNN), transfer learning, AlexNet, and GoogLeNet, are compared for colon cancer classification. Pre-processing is conducted utilizing median filter for removing noises from an input colon cancer image. The filtered image is then segmented using SegNet, which is utilized to segment the affected portions. Finally, classification of colon cancer is conducted employing various deep learning approaches like CNN, RNN, transfer learning, AlexNet, and GoogLeNet. The comparative assessment showed GoogLeNet as the best classifier for colon cancer classification with maximal values of accuracy as 94.165, sensitivity as 97.589, and specificity as 87.359, respectively, for 60% training data.

Keywords: convolutional neural network (CNN), recurrent neural network (RNN), transfer learning, AlexNet, GoogLeNet

1. Introduction

Cancer signifies to a categorization of illness wherein abnormal cells are developed inside human body as an outcome of random alterations (Tasnim et al., 2021). Colon cancer is the third common kind of cancer across the globe. Colon cancer is frequently causes other than rectal cancer, which is commonly occurred in higher income countries but nowadays it is increasing in the middle as well as lower income countries (Labianca et al., 2010). The number of diverse staging condition is utilized for estimating deepness of cancer penetration in colon and extension of extracolonic disease participation. If no prediction is carried out in earlier detection, it causes serious problem to public health conditions (Lannagan et al., 2021). Earlier identification of colon cancer is the significant objective for doctors to evaluate patients at danger. Colonoscopic regimens of observation have been emerged on basis of better evidence, which can improve mortality and morbidity (Zauber et al., 2012). The number of guidance is established for endoscopic observation of high danger groups to identify colon cancer (Freeman, 2013). When healthier cells and lining of colon or rectum expand in an uncontrollable manner, a cancer occurs. This kind of cancer is generally malignant (Ali & Ali, 2021; Lannagan et al., 2021). Adenocarcinoma of colon or rectum generally develops with large intestine lining, beginning in epithelial cells and spreads to other layers (Ali & Ali, 2021).

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Even though, imaging techniques are vital in specifying suspected regions of involvement, entire stage presently needs pathological analysis of resected tissues, especially to define earlier stage of disease (Freeman, 2013). Additionally, upstaging of the colon cancer results from utilization of magnetic resonance imaging (MRI), position emission tomography, computed tomography (CT) (Khan, 2020), and ultrasound with pathological confirmations (Freeman, 2013). In recent times, digital pathology is emerging as vital tool for prognosis and diagnosis of cancers (Gurcan et al., 2009; Kumar et al., 2022). Hence, recent technology progression has been extremely contributed to digital pathology proliferation in diverse applications. Other than classical glass images, the new whole slide images are mathematical copies of stained samples (Pantanowitz, 2010). These images play a main part in a process of pathological diagnosis (Amin et al., 2019; Pantanowitz et al., 2013; Snead et al., 2016) because it enables easier data storing and sharing (Kumar et al., 2022). Presently, a novel intra-operative device utilizing confocal laser microscopy (CLM) is presented, which offers submicrometer image resolutions (Ellebrecht et al., 2019). Nowadays, automated tissue classification has been addressed successfully utilizing deep learning techniques (Fernandis, 2021), such as convolutional neural network (CNN) for the semantic segmentation as well as classification (Gessert et al., 2019a; Litjens et al., 2017). Deep learning-enabled colon cancer diagnosis has been raising prominent probe theme in current years. On the other side, capsule networks are gaining recognition in medical imaging classification owing to

its low weight systems (Afshar et al., 2020; Ali & Ali, 2021; Koresh & Chacko, 2020).

The prime goal of this work is to perform comparative assessment of colon cancer classification using diverse deep learning approaches. Colon is the main constituent of large intestine and colon cancer is an important reason of death in many countries. Here, an input image is considered from specified dataset and given to pre-processing phase. The goal of pre-processing is the enhancement of an image. In pre-processing, the noises are eliminated from an input image utilizing median filter (Gupta, 2011). Thereafter, pre-processed image is given to segmentation stage wherein affected regions in an image are segmented utilizing SegNet (Badrinarayanan et al., 2017). Then, segmented output is passed to classification phase wherein colon cancer classification is carried out utilizing CNN (Gessert et al., 2019b), recurrent neural network (RNN) (Mou et al., 2017), transfer learning (Gessert et al., 2019a), AlexNet (Chen et al., 2022), and GoogLeNet (Sustika et al., 2018). As deep learning has a vast impact in regions like diagnosing cancer and so on, comparative analysis is performed to reveal the best classifier for the classification of colon cancer.

A chief contribution of this work is explained as follows.

Assessment of various deep learning techniques for colon cancer classification: Here, several deep learning techniques like CNN, RNN, transfer learning, AlexNet, and GoogLeNet are compared to prove the efficacy of GoogLeNet for colon cancer classification.

The following sections are arranged in a manner as follows: Section 2 interprets literature overview and Section 3 specifies methodology for comparative assessment. Section 4 elucidates comparative outcomes and Section 5 concludes the assessment.

2. Motivation

Colon cancer is the most general kind of cancer that directs to short period of survival. Therefore, deep learning approaches are required for instant assessment, which motivated this research to compare diverse deep learning techniques to identify the better classifier for colon cancer classification.

2.1. Literature survey

The survey done utilizing the existing deep learning methods is interpreted as follows. Gessert et al. (2019b) utilized CNN to differentiate benign as well as malignant tissue and investigated the possibility of automated classification of colon cancer. This classifier showed detection of cancer from CLM images is possible employing CNN but did not utilize many data. Mou et al. (2017) developed RNN method for classification of hyper-spectral images, which was proved as faster in the testing, though it needs more tolerable time for training as it generates extra channel updates. Gessert et al. (2019a) assessed the possibility of classification from CLM in colon employing transfer learning. The outcomes demonstrated that transfer learning is applicable for identification of cancer tissues with CLM, but it has less features transferability. Sustika et al. (2018) evaluated GoogLeNet for improving the performance, which showed rapid speed but it needs many resources for computation.

2.2. Major challenges

The demerits faced by several classifiers reviewed for colon cancer classification are explained as follows:

- CNN utilized in Gessert et al. (2019b) for automated classification of colon cancer showed the feasibility to detect cancer, but still it failed to investigate malignant tissue detection in colon region.
- In Gessert et al. (2019a), transfer learning was investigated for the possibility of colon cancer classification, though it did not include various classification issues with CLM.
- Diagnosis with usual traditional techniques like CT, MRI, and so on is complicated to classify colon cancer as it requires high resolution.

The proposed technique compares the flaws in literature survey using the metrics like accuracy, sensitivity, and specificity by considering the varying training data percentage.

3. Comparative Assessment Methodology Utilizing Diverse Deep Learning Approaches for Colon Cancer Classification

Colon cancer causes half a million death of people in every year as it frequently occurs. Researchers are working in present days for getting rid of physical investigation and to develop methods to detect colon cancer. Here, diverse deep learning techniques are compared to prove the effectiveness for colon cancer classification. In this assessment, an input image is considered from dataset and fed to pre-processing stage. Median filter is utilized for pre-processing to eliminate noises from input image. Afterwards, filtered image is passed to segmentation phase, where affected regions are segmented utilizing SegNet. Thereafter, segmented output is given to classification stage in which classification of colon cancer is performed utilizing deep learning methods like CNN, RNN, transfer learning, AlexNet, and GoogLeNet. The diagrammatical presentation of comparative assessment methodology for classification of colon cancer is delineated in Figure 1.

3.1. Acquisition of an image

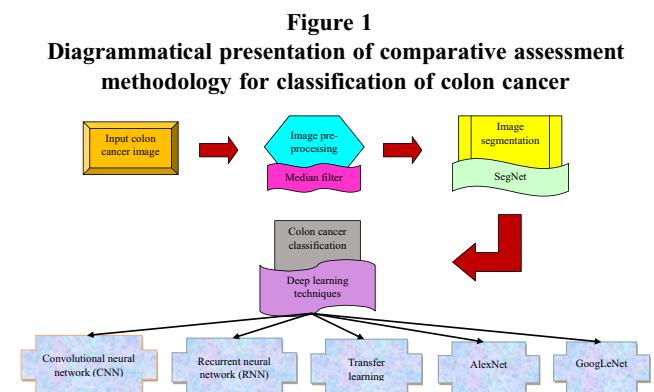
Considering input colon cancer images in database C for classification of colon cancer obtained from certain dataset (Kirby, 2023), it can be represented by

$$C = \{A_1, A_2, \dots, A_g, \dots, A_t\} \quad (1)$$

Here, g^{th} input image is specified by A_g and total image samples in database are implied by A_t .

3.2. Image pre-processing utilizing median filter

An image pre-processing is a valuable stage, which is most significant for discarding noises from an image to process



following phases. In this work, median filter is utilized, which is considered as non-linear filtering method generally employed for rejection of noises. This filter is vastly specified as order statistical filter, which replaces pixel value utilizing gray values median in adjacent pixels. Median filter (Gupta, 2011) is utilized extensively as it offers best noise elimination abilities. An output achieved through image pre-processing method is illustrated by

$$F_g = \underset{(d,e) \in Q_{vw}}{\text{median}} \{n(d, e)\} \quad (2)$$

3.3. Image segmentation utilizing SegNet

The pre-processed image F_g is then fed to segmentation stage wherein segmentation process is achieved effortlessly by means of SegNet. The major contribution of SegNet is mapping low-level contrast features for categorization in pixel-wise. This kind of depiction delivers the features, which are high desirable to boundary location. SegNet (Badrinarayanan et al., 2017) is consisted of three kinds of layers, namely encoder, decoder, and softmax or pixel-wise classification layer. For attaining higher contrast feature maps, the fully connected layer is eliminated. It also minimizes the count of parameters at an encoder network. The decoder outcome is passed to softmax for providing class possibilities.

3.3.1. Encoder network

An encoder network consists of 13 convolutional layers and operates convolutional functions with strainer bank for providing set of feature maps. These feature maps are thereafter batch-stabilized and element-wise function is applied utilizing Rectified Linear Unit (ReLU). Then, max pooling is performed and after that outcome is sub-sampled having parameter of about 2. The max-pooling is utilized for attaining translation unchanging, where sub-sampling is used for resulting larger spatial window.

3.3.2. Decoder network

The decoder network has 13 convolutional layers like encoder network. The major operation of decoder is up-sampling of forthcoming feature maps utilizing max-pooling indices that results in a sparse feature maps, and it executes convolution operation with trained decoder strainer bank for resulting concentrated feature maps. The next phase is the operation of batch normalization procedure on each of the feature maps.

3.3.3. Soft-max classifier

The larger dimension feature attained at decoder is subjected to softmax, which classifies each pixel individually. The softmax result is a segmented image indicated by N_g .

3.4. Colon cancer classification using deep learning techniques

Colon cancer pathological performance fails to predict the repetition accurately and no gene expressive sign is proven trustworthy for prediction in medical practices, maybe because colon cancer is the heterogeneous disease. Here, several deep learning techniques like CNN, RNN, transfer learning, AlexNet, and GoogLeNet are utilized for colon cancer classification to prove efficient classifier. An input considered for performing classification of colon cancer is implied by N_g .

3.4.1. CNN

CNN (Gessert et al., 2019b) is utilized for classification chores, whereas an image is directly passed to CNN that learns for extracting related features and performs classification in output. The features that are computed inside convolutional layers are reutilized in following layers. In this manner, architecture of CNN is highly effective regarding count of learnable parameters as the features are reutilized heavily. In the standard convolution, an overall feature is implicitly learned by means of summation. It comprises of series of layers for transforming input layer to an output layer. Various generally utilized layers are activation layer, convolutional layer, fully connected layer, and pooling layer (Huang et al., 2019).

(a) Convolutional layer: In this layer, the neurons share similar biases and weights that are frequently known as filter or kernel. Correspondingly, an output for $(x, y)^{th}$ neuron is given by,

$$O_{x,y} = \sum_{\alpha=0}^{\eta-1} \sum_{\mu=0}^{\eta-1} W_{\alpha,\mu} u_{x+1,y+\mu} + B \quad (3)$$

(b) Pooling layer: The purpose of pooling layer is to partition neurons of prior layer into group of non-overlapping rectangles and executes down-sampling function on each of the sub-region for obtaining a value of single neuron in present layer.

(c) Activation layer: This layer applies element-wise nonlinearity and is generally utilized instantly after fully connected or convolutional layers.

(d) Fully connected layers: Each of the neuron in this layer is associated with each neuron of prior layer. An output of x^{th} neuron in fully connected layer is represented by,

$$O_x = \sum_y W_{xy} u_y + B_x \quad (4)$$

Here, W_{xy} represents a weight among y^{th} neuron of prior layer and x^{th} neuron of present layer, whereas B_x indicates bias of x^{th} neuron of present layer. The output predicted by CNN is V_g .

3.4.2. RNN

RNN (Mou et al., 2017) is a category of artificial neural network, which extends conventional feed-forward neural network with the loops in links. Unlike feed-forward neural network, RNN is capable for processing series inputs with recurrent hidden criteria where in activation at each of the step depends upon prior phase.

For a given series of data $a = (a_1, a_2, \dots, a_z)$, if a_t represents data at t^{th} time phase, then RNN updates the recurrent hidden state r_z as given below.

$$r_z = \begin{cases} 0, & \text{if } z = 0 \\ \phi(r_{z-1}, a_z), & \text{otherwise} \end{cases} \quad (5)$$

Here, ϕ denotes non-linear function. Optionally, RNN can have the output $k = (k_1, k_2, \dots, k_z)$. For few chores like classification of hyper spectral image, single output is needed that is given by k_z .

In classical RNN techniques, an updated rule of recurrent hidden criteria in Eq. (5) is generally executed as follows:

$$r_z = \phi(R_{a_z} + S r_{z-1}) \quad (6)$$

Here, R and S represent coefficient matrices for an input at current phase and recurrent hidden unit activation at prior phase,

respectively. An output for colon cancer classification by RNN is signified by K_g .

3.4.3. Transfer learning

CNN generally performs in large datasets than small datasets, whereas transfer learning is helpful in the applications of CNN, where datasets are not larger. The trained model from larger datasets like ImageNet is utilized for the applications with comparably small datasets.

Presently, transfer learning is utilized in several application fields like medical, screening of baggage, and manufacturing. It eliminates the necessity of having larger datasets and also decreases longer training time, which is needed by deep learning techniques generated from scratch (Rahman et al., 2020).

Transferable knowledge in the formation of expression features is extracted from a source area by feature learning techniques (Pal et al., 2021). The source area data are indicated by

$$T_Y = \left\{ (i_{Y1}; j_{Y1}), (i_{Ym}; j_{Ym}) \right\} \quad (7)$$

Here, $i_{Yb} \in I_Y$ denotes a data instance, whereas consequent class label is given by $j_{Yb} \in J_Y$. Similarly, target area data are represented by

$$T_X = \left\{ (i_{X1}; j_{X1}), (i_{Xm}; j_{Xm}) \right\} \quad (8)$$

Here, input is $i_{Xb} \in I_X$, whereas related output is $j_{Xb} \in J_X$; in most of the cases $0 < m_X \ll m_Y$. For a given learning chore X_Y from a source area T_Y and the learning chore X_X at target area T_X , transfer learning intends for developing a learning of objective predictive function $p_X(\cdot)$ in T_X utilizing knowledge in T_Y and X_Y , where $T_Y \neq T_X$ or $X_Y \neq X_X$. The predicted output from transfer learning is denoted by D_g .

3.4.4. AlexNet

The architecture of AlexNet (Chen et al., 2022) for all databases up to flattening layer creates similar count of inputs as well as outputs. An output of flatten layer is utilized for dense layer input. The neurons in an initial hidden layer are 64 units; neurons in second hidden layer are 128 units whereas neurons in the third hidden layer are 256 units. It utilized data segmentation as well as dropout for reducing over fittings on an image data. An activation function utilized in hidden layer is ReLU, which can be given by,

$$f(h) = \max(0, h) \quad (9)$$

The single output with hidden layer is to the extent that counts of traditional classes like 10 units with the softmax activation function. The softmax provides distribution of learning outcomes or else predictions from prior layers ranging among 0 and 1, with an outcome of elements overall value being as 1. The higher value developed by softmax is a predicted class by CNN. The formulation of softmax operation is illustrated below.

$$\delta(s)_l = \frac{e^{s_l}}{\sum_{q=1}^M e^{s_q}}, \quad l = \{1, 2, \dots, M\} \quad (10)$$

Here, an index of the each element s is represented by l whereas M denotes an overall count s of every elements. The classified output from AlexNet is symbolized by L_g .

3.4.5. GoogLeNet

It is a deep CNN architecture, which enhanced accuracy when keeping computation load at constant by increasing depth as well as width of networks. The most general way to improve performance of deep neural network is by increasing the network size. It includes count of layer, which is considered as depth and count of units in the each layer, which is considered as width. But increasing the network size has few limitations. It should increase the count of parameters for training and consequences; it needs more computation resources. These troubles can be resolved by moving from the fully connected layers toward sparsely linked architectures, even within convolutions.

GoogLeNet resolves it by utilizing inception model. An inception model utilizes parallel integration of 1×1 , 3×3 and 5×5 . The 1×1 convolutions are utilized for computing reductions before an expensive 3×3 and 5×5 convolutions. The architecture of GoogLeNet utilizes nine inception modules consisting of 22 layers deep while numbering only layers having parameters. Besides 22 layers deep network, if only layers having parameters are counted, there are five pooling layers also. It includes four max-pooling layers and one average-pooling layers. An average-pooling layer having 5×5 filter dimension and stride 3 is utilized before classifier. GoogLeNet utilizes dropout layer having 70% ratio of the dropped outputs. ReLU is utilized in all the convolutional layers wherein with inception models are also included. Due to fast computation and best performance achievement for colon cancer image classification, GoogLeNet is specified as better classifier for classification of colon cancer and an output attained is represented by G_g .

4. Results and Discussion

The results obtained by comparative assessment of various deep learning approaches are elucidated in this segment.

4.1. Experimental setup

The execution of this work is carried out for colon cancer classification in python tool on PC with Intel Core-i3 processor, 4 GB RAM, and 10 OS.

4.2. Dataset description

The CT colonography dataset (Kirby, 2023) comprises of 825 cases with XLS sheets, which provides polyp description and location inside colon segments. The number of series in this dataset is 3451 and number of images is 941,771, whereas image size is 462.6 GB.

- No. of images used for training phase 700
- No. of images used for testing phase 300
- No. of cases with 6 to 9 mm polyps 69
- No. of cases with at least one > 10 mm polyp 35
- No. of negative cases 243
- Total no. of images 1000

4.3. Performance measures

An assessment of several deep learning techniques for colon cancer classification is investigated for the performance considering performance measures like specificity, accuracy, and sensitivity.

4.3.1. Accuracy

Accuracy is referred to a metric utilized for classification problems to specify the percentages of accurate prediction. It can be illustrated by

$$A = \frac{T_N + T_P}{T_P + \mathfrak{S}_P + T_N + \mathfrak{S}_N} \tag{11}$$

Here, T_N and T_P are true negative and true positive results, whereas \mathfrak{S}_P and \mathfrak{S}_N are false positive and false negative results.

4.3.2. Specificity

Specificity is defined as the metric that estimates the true negative predictions in each of the category. It is formulated by

$$\gamma = \frac{T_N}{T_N + \mathfrak{S}_P} \tag{12}$$

4.3.3. Sensitivity

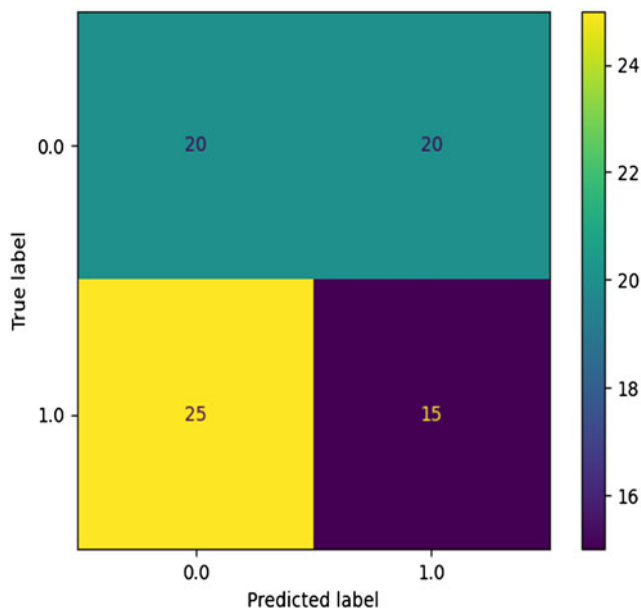
It is a metric, which assess the true positive predictions in each of the category and given by,

$$E = \frac{T_P}{T_P + \mathfrak{S}_N} \tag{13}$$

4.4. Analysis with confusion matrix

The confusion matrix for classification of colon cancer with positive and negative cases is elucidated in Figure 2. From the figure, it can be observed that from 45% of true cases of positive column, 20% is predicted as positive with colon cancer and 25% is predicted as negative with colon cancer. Similarly, from 35% of true cases of negative column, 15% is predicted as negative with colon cancer and 20% is predicted as positive with colon cancer.

Figure 2
Confusion matrix for classification of colon cancer with positive and negative cases



4.5. Comparative techniques

The comparison assessment is carried out among several deep learning techniques like CNN (Gessert et al., 2019b), RNN (Mou et al., 2017), transfer learning (Gessert et al., 2019a), AlexNet (Chen et al., 2022), and GoogLeNet (Sustika et al., 2018) with regard to metrics for evaluation.

4.6. Comparative analysis

The assessment is conducted for various deep learning approaches by varying percentages of training data and values of k -fold in terms of performance metrics.

4.6.1. Analysis based upon training data

Figure 3 demonstrates a comparative assessment of various deep learning techniques regarding evaluation metrics by varying percentages of training data from 60% to 100%. An evaluation of deep learning techniques on basis of accuracy is shown in Figure 3(a). Accuracy attained by techniques like CNN, RNN, transfer learning, AlexNet, and GoogLeNet is 71.599, 76.599, 88.679, 90.678, and 94.759 when percentage of data = 60%. Figure 3(b) delineates an analysis of several deep learning methods with respect to sensitivity. For 60% of data, sensitivity acquired by CNN is 71.685, RNN is 74.165, transfer learning is 82.365, AlexNet is 97.270, and GoogLeNet is 97.463. An estimation of specificity is illustrated in Figure 3(c). Specificity attained by deep learning approaches like CNN, RNN, transfer learning, AlexNet, and GoogLeNet is 69.265, 74.322, 78.652, 83.979, and 84.688, while data are considered as 60%. Moreover, GoogLeNet is proven as an effective classifier for colon cancer classification in terms of performance measures.

4.6.2. Analysis based upon k -fold value

An assessment of various deep learning techniques for colon cancer classification with regard to evaluation measures by varying k -fold values from 5 to 9 is represented in Figure 4. Figure 4(a) interprets an evaluation of various deep learning methods with regard to accuracy. For k -fold value = 5, accuracy achieved by CNN is 76.786, RNN is 79.674, transfer learning is 83.685, AlexNet is 93.856, and GoogLeNet is 94.165. An estimation of deep learning techniques in terms of sensitivity is elucidated in Figure 4 (b). Sensitivity achieved by methods like CNN, RNN, transfer learning, AlexNet and GoogLeNet are 73.499, 77.599, 84.547, 97.269 and 97.589, when k -fold value = 5. Figure 4 (c) explains an estimation of deep learning methods with respect to specificity. While k -fold value is considered as 5, specificity attained by CNN is 66.157, RNN is 71.499, transfer learning is 79.896, AlexNet is 84.269, and GoogLeNet is 87.359. Therefore, GoogLeNet is confirmed as an effectual classifier while k -fold value is 5 based on performance measures.

4.7. Comparative discussion

The comparative assessment discussion for several deep learning techniques to classify colon cancer is explicated in Table 1. Table 1 recognizes GoogLeNet is the best classifier for colon cancer classification, which achieved maximum accuracy, sensitivity, and specificity of 94.165, 97.589, and 87.359 by considering k -fold value = 5. The phase for discussion includes the classification of colon cancer using the combined techniques like transfer learning with AlexNet, GoogleNet, and VGGNet.

Figure 3

Assessment based on training data (a) accuracy, (b) sensitivity, and (c) specificity

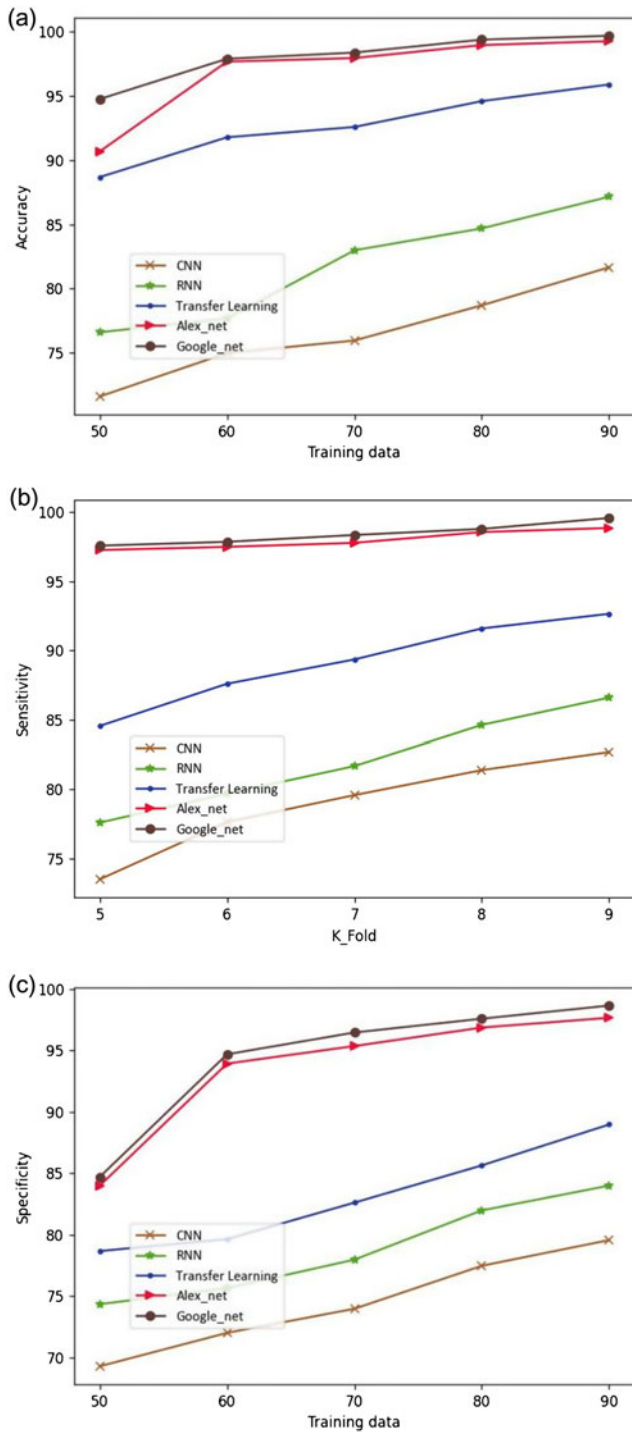


Figure 4

Assessment based on k-fold value (a) accuracy, (b) sensitivity, and (c) specificity

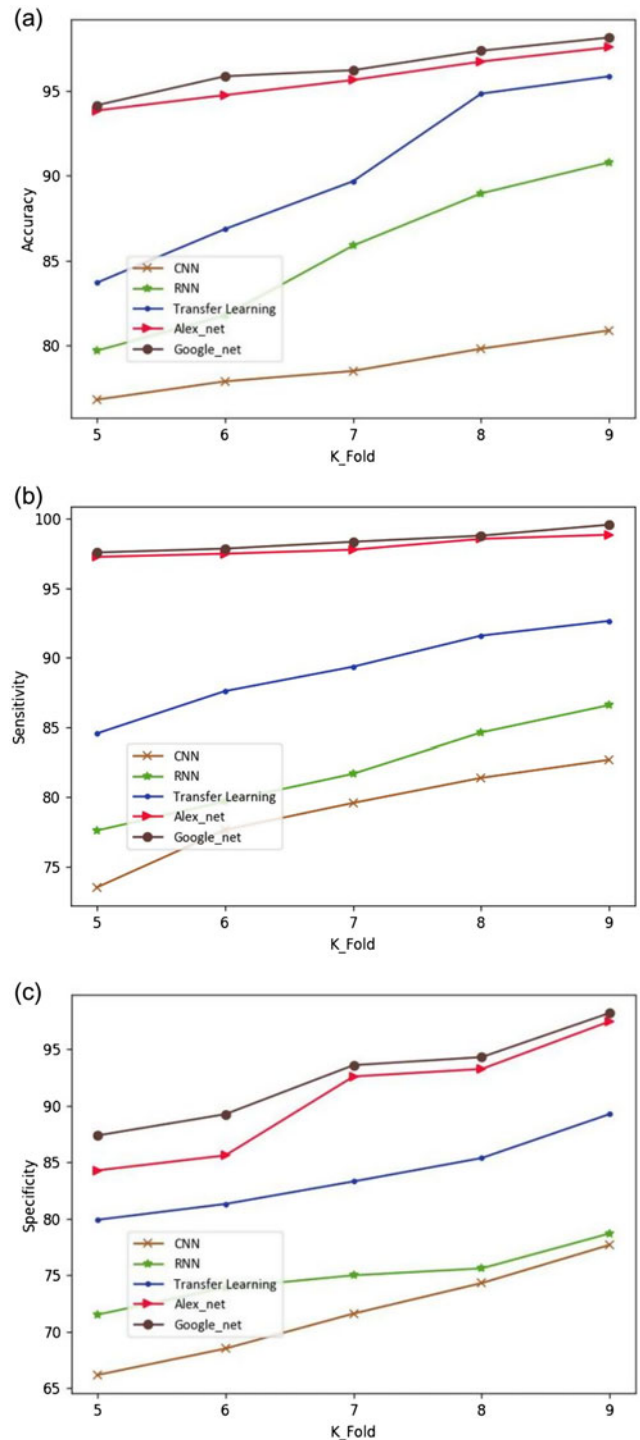


Table 1
Comparative discussion

Analysis based on	Metrics/Methods	CNN	RNN	Transfer learning	AlexNet	GoogLeNet
Training data = 60%	Accuracy	71.599	76.599	88.679	90.678	94.759
	Sensitivity	71.685	74.165	82.365	97.270	97.463
	Specificity	69.265	74.322	78.652	83.979	84.688
K-fold value = 5	Accuracy	76.786	79.674	83.685	93.856	94.165
	Sensitivity	73.499	77.599	84.547	97.269	97.589
	Specificity	66.157	71.499	79.896	84.269	87.359

The authors calculated the K Fold Values and highlighted represents the final output.

5. Conclusion

Colon cancer is referred as serious type of cancer having higher incidences as well as mortality rate in the developed regions. It occurs in both male and female, where these types of cancers are grouped together as they have several ordinary features. There are several deep learning techniques, which are utilized for colon cancer classification. Hence, this research focuses on comparative assessment of various deep learning techniques to find out the best classifier. The methodology phases involved for colon cancer classification are pre-processing, segmentation and, finally, colon cancer classification. Initially, an input colon cancer is considered and given to pre-processing stage. The pre-processing is carried out utilizing median filter to remove noises in an input image. In segmentation phase, infected areas in filtered image are segmented using SegNet. Thereafter, colon cancer classification is done employing several deep learning approaches like CNN, RNN, transfer learning, AlexNet, and GoogLeNet. These techniques are compared to identify effective classifier for colon cancer classification. Therefore, an assessment showed GoogLeNet is the best classifier for colon cancer classification with maximal accuracy of 94.165, sensitivity of 97.589, and specificity of 87.359. As a future task, the best classifier will be assessed considering other performance measures and compares with existing techniques to prove its efficacy for colon cancer classification. The limitations of the model are that they are used to classify the cancer and in order to achieve the more accuracy for detecting the colon cancer GoogleNet and AlexNet are combined with any hybrid optimization algorithm.

Conflicts of Interest

The authors declare that they have no conflicts of interest to this work.

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