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Original Article

A Systematic Review on Deep Convolutional Neural Network-based Breast Cancer Classification on Histopathological Images

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Abstract - *Breast cancer (BC) is an increasingly prevalent malignant disease in females globally. Lately, early diagnoses and the best adjuvant therapy have considerably enhanced patient outcomes. However, new challenges have occurred as our growing understanding of tumors has exposed their complex nature, and diagnoses by histopathology have proved to be helpful in guiding BC treatment. We faced an absolute necessity for accurate histopathologic BC diagnoses to make better therapy decisions as patient demand for personalized BC therapy increases. Furthermore, current development in memory capacity and computational power resulted in the applications of medical image processing and Deep Learning (DL) techniques to analyze and process histopathological images (HIs) of BC. Therefore, this study performs a Systematic Review of Deep Convolutional Neural Network based BC Classification on HIs. This survey aims to review the conventional and recently developed DL techniques for BC diagnosis using HIs. Firstly, the role of machine learning (ML) and DL algorithms for HI classification for BC detection is elaborated briefly. Next, the recently developed DL-based HI classification models for BC are reviewed in detail. Moreover, a comparison stud of the reviewed models with result analysis is performed. Furthermore, an elaborate description of the challenging issues with possible future directions is identified at the end of the survey.*

Keywords - *Computer-aided diagnosis, Histopathological images, Deep learning, Breast cancer, Machine learning.*

1. Introduction

BC has advanced mortality and sickness among women, as per the World health organization report, and this kind of cancer causes a few hundred thousand deaths annually around the world [1, 2]. The earlier diagnoses and treatment could considerably decrease the mortality rate. The histopathological diagnoses based on light microscopy are a golden standard for BC detection [4, 5]. Histopathological inspection needs pathologists having rich experience and strong professional backgrounds, and primary-level clinics and hospitals suffer from the lack of expert pathologists [7]. In addition, traditional manual diagnoses require an enormous amount of work, and diagnostic errors can be prone to occur with the protracted work of pathologists. One potential solution to resolve these challenges is proposing intelligent diagnostic techniques [8]. It learns from the senior pathologists and later inherits the experience used for training the younger pathologists.

Moreover, using the robust computing capability of hardware [9], namely GPU, the automated technique could reduce the error rate and speed up the manual diagnosing process. Histopathological image (HIs) analysis is a time-consuming and difficult task requiring professional knowledge [10,12,13]. The diverse kinds of breast diseases in HIs are illustrated in Fig. 1.

Computer-assisted analysis of HI's plays a critical role in its prognosis and the diagnosis of BC [14]. But the succeeding challenges impede the process of designing tools to perform these analyses. Firstly, HIs of BC are a fine-grained, high-resolution image that depicts complex textures and rich geometric structures [15, 17]. The consistency between classes and the variability within a class could make classification tremendously challenging, particularly while handling multiple classes [18]. The next is the limitation of the feature extraction method for HIs of BC. The deep learning (DL) technique can automatically retrieve data from information, learn advanced abstract representations of information, and automatically extract features. They could resolve the feature extraction problem and are effectively used in biomedical science, computer vision (CV), etc. [19,21,22]. Because of the robust feature extraction benefits of DL and the threats in HIs of BC, this study analyzed HIs of BC using the DL technique.

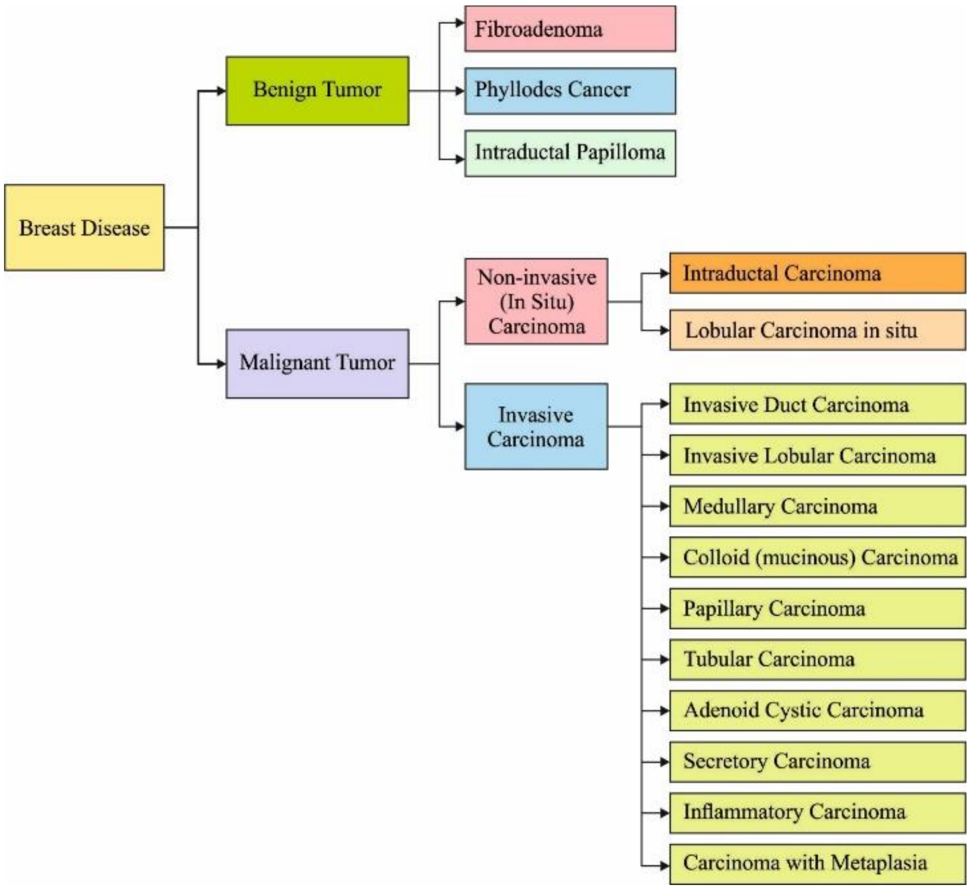

Fig. 1 Different types of breast diseases

This study performs a Systematic Analysis of Deep Convolutional Neural Network based Breast Cancer Classification on Histopathological Imaging. This survey aims to review the conventional and recently developed DL techniques for BC diagnosis using HIs. Firstly, the role of machine learning (ML) and DL algorithms for HI classification for BC detection is elaborated briefly. Next, the recently developed DL-based HI classification models for BC are reviewed in detail. Moreover, a comparison stud of the reviewed models with result analysis is performed. Furthermore, an elaborate description of the challenging issues with possible future directions is identified at the end of the survey.

2. Role of ML and DL Models in Histopathology Image Analysis

Latest advancements in promising AI dramatically change the way BC is detected and treated [23]. The distinction between deep learning, AI, and machine learning is not often noticeable to non-experts. AI incorporates the technique for the machine to go beyond or mimic human intelligence, primarily in cognitive abilities. AI involves different subfields, namely rule-based systems, a traditional technique of AI where the computer programmer explicitly encodes the knowledge given by the expert [25, 26]. On the other hand, ML is a subdomain of AI which employs statistical approaches for learning to identify patterns from the sequence of data without any human intervention. DL is a new ML technique which exploits bio-inspired networks to characterize data via modest and non-linear methods that convert the preceding representation into a greater abstract representation [28, 29]. The complicated nature of the framework enables DNNs to form nonlinear and extremely complicated representations that offer unprecedented discriminative power [30].

The deep network has generated revolutionary outcomes in various challenges involving speech recognition and image classification [32-34]. Computerized diagnosis systems in medicine and technology usually have conventionally been rule-based. But over the last few decades, we have seen fundamental improvement in numerous features; the ever-growing digitization of medical information, the emergence of robust ML approaches, and the progression of graphics computation resources. This development led to the explosion of interest in ML since this system progressively replaced classical image analysis for automated medical diagnoses [35]. Fig. 2 shows the working of CAD methods for classifying BC.

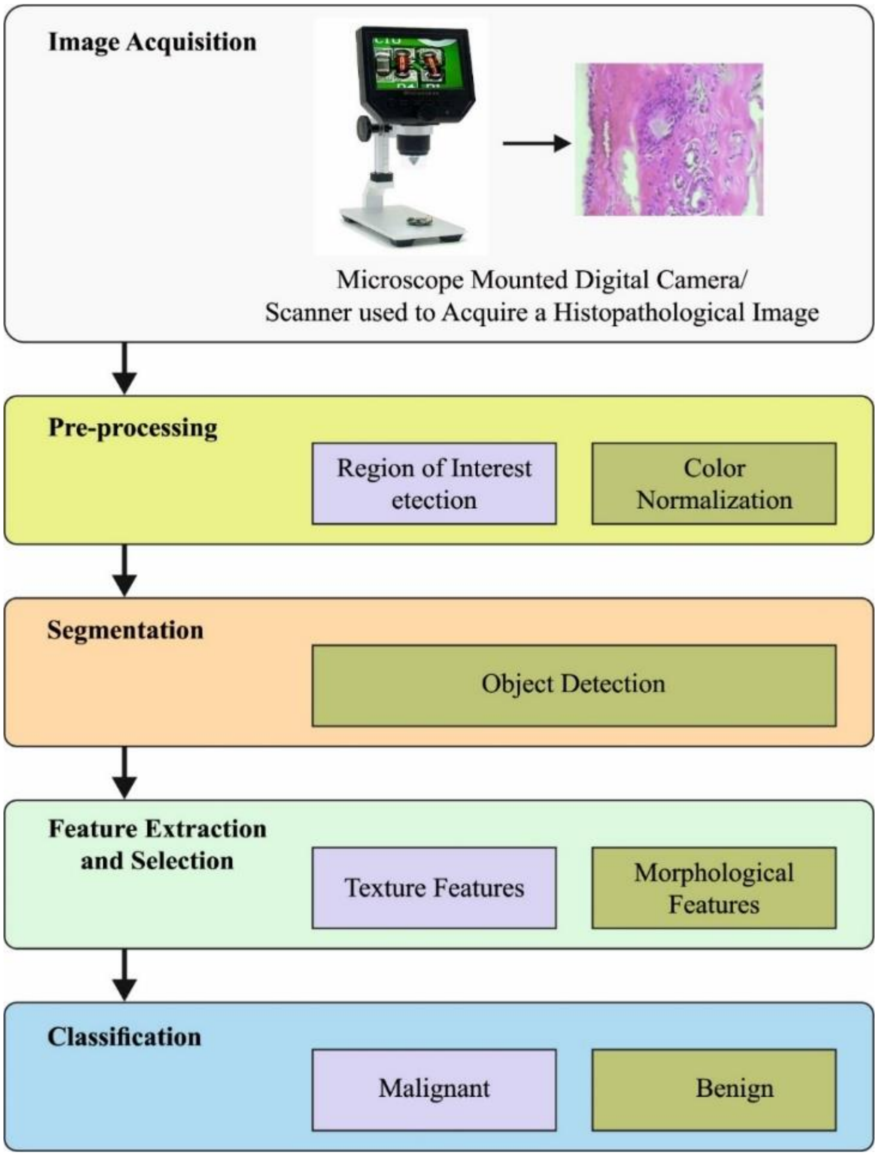

Fig. 2 Pipeline of CAD model for BT classification

The objective of the ML technique is to utilize the task-related training dataset for learning the task, which generally includes the input dataset and processes them to generate an accurate output. The training dataset comprises various instances. Also, it includes examples of the accurate output that is popularly known as labels. Once the input dataset includes the respective label for every example, supervised learning scenarios are named [36].

Currently, supervised learning is a popular technique in digital histopathology. The given labelling for the visual input dataset corresponds to a window within the image, the whole image, or at the pixel level. Due to the emergence of the DL method that powerfully benefitted from pixel-level annotation, the second is the major kind of issue that has been researched currently [37]. DL method is used for end-to-end learning, and differently from other learning techniques, DL needs the least processing on the output or input values. End-to-end models take in the raw dataset and directly produce the desired outcome without the designed experts' feature extraction phase needed by other learning techniques [38]. DL includes modelling through multiple layers of non-linear transformation.

3. Review of CAD Models for BC Classification

Bruno et al. [39] presented a technique related to the association amongst CT, LBP, and FS by distinct classification and statistical analysis approaches to assist the expansion of the CAD system. The comparable feature was detached through the statistical analysis of variance

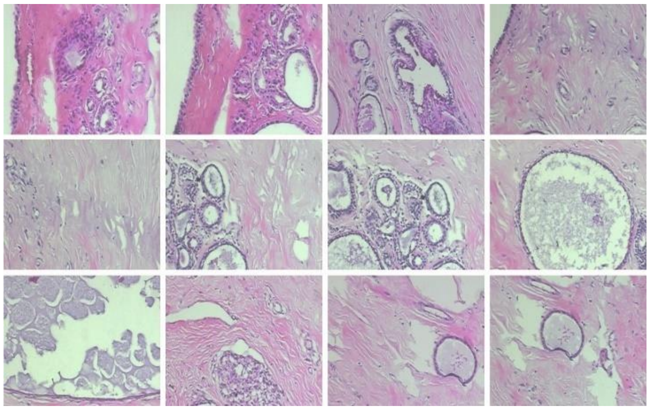

Fig. 3 Sample his

(ANOVA). The feature understanding was assessed through the DT, RF, SVM and polynomial (PL) classifications, which consider the area under the ROC curve (AUC) and metrics accuracy (AC). Reis et al. [40] remodelling of collagen fibre provide intensification to notice patternings in Hematoxylin and Eosin (H&E) stained sliding's from medical invasive breast carcinoma cases that the pathologists could be labelled as immature or mature stroma. The objective is to classify and categorize stromal regions based on maturity automatically. It shows that the classification agreed with the expert observer, thereby offering a quantitative and repeatable measure for analytical research. A few samples of HIs are shown in Fig. 3.

Zhang et al. [41] presented a novel automated BC classification scheme related to histological images. The image feature was extracted through the Completed LBP (CLBP), CT, and statistics of GLCM correspondingly. The three distinct features are integrated and exploited for the classifier. A classifier ensemble technique named Random Subspace Ensemble (RSE) is utilized for selecting and aggregating a sequence of base neural network classifiers. In [42], an enhanced hybrid active contour method-based classification technique was exploited for segmenting nuclei from the image. The semantic level feature was extracted through the CNN technique, describing the proportion of nuclei belonging to the various grades. Besides object-level (architecture) and pixel-level (texture) features, for creating the incorporated set of image attributes that could be outperformed a subset of features. Then, a cascaded method is utilized for training multiple SVM classifiers with the combination of feature subtypes to enable the probability of performance to maximize through leveraging distinct feature sets extracted from various levels.

The authors in [43] Developed a technique for classifying H&E-stained breast biopsy imaging through CNN. The image was categorized into four classes, benign lesion, normal tissues, invasive and non-invasive carcinoma, and two types, non-carcinoma and carcinoma. The study intends to retrieve data at distinct scales involving overall tissue organization and nuclei. This presented method enables the addition of the presented technique for complete slide histology imaging. Also, the feature extracted by the CNN is utilized to train an SVM classifier. Roy et al. [44] established patch-based classifiers (PBC) with CNN for the automated classification of HIs. The incidence of restricted images required the extraction of patches and an increase in the training sample count. Therefore, patches of appropriate size carrying essential diagnosis data were extracted from the original image. The presented classifying technique functions in 2 dissimilar manners: All Patches in One Decision (APOD) and One Patch in One Decision (OPOD).

Baker et al. [45] introduce an architecture for auto-classification and detection of BC from microscopic histological images. The image was categorized into malignant or benign. The presented technique includes various stages that involve image classification, image enhancement, image segmentation, and feature extraction. The presented technique makes use of novel integration of K-means watershed and clustering techniques in the segmenting phase. Then, applied K-means clustering to generate initial segmented images and later employed the watershed segmentation technique. In [46], the multiclass BC classification is implemented through DCNN based TL technique. A pre-trained DCNN mechanism is inherited to examine the possibility of TL in breast histology, and at the same time, a multiscale feature concatenation technique is applied. Furthermore, it integrates channel colour modification and stain normalization techniques.

Beevi et al. [47] discovered the possibility of TL for mitosis identification. A pre-trained CNN is converted by pairing RF classifiers with the primary FC layer to extract discriminative factors from nuclei patching and precisely predict the class labellings of cell nuclei. The adapted CNN exactly categorize the cell nuclei with restricted training data. The proposed method achieves the greatest achievement of the classification by pre-processing the extracted factors and fine-tuning the pre-trained module. Vo et al. [48] developed a DL technique with a convolutional layer to extract visual features for the classification of BC. It is demonstrated that the DL technique extracts more features than that hand-crafted feature extraction techniques. Also, it proposed a boosting technique for achieving the primary objective, where the method is proficiently augmented by gradually merging the DL model (weak classifier) with the strong classifiers.

In [49], a fusion-level set-based segmenting technique for segmenting nuclei from the image. A quantile normalization technique has been exploited to improve the colour images' consistency. The semantic level feature was extracted through the CNN method, which defines the proportion of nuclei that belong to the dissimilar gradings, besides object-level (structure) and pixel-level (texture) factors, to form the incorporated set of features. An SVM classifier has been trained to discriminate the BC between lower, intermediate, and higher grades. Khan et al. [50] projected a DL architecture for recognizing and classifying BC in breast cytology imaging with the TL concept. In the presented technique, the feature from the image was extracted through pre-trained CNN structures like ResNet, GoogLeNet, and VGGNet that are fed into an FC layer for benign and malignant cell classification with the average pooling classification.

Gupta and Chawla [51] focus on leveraging pretrained (CNN) activation features on conventional classifiers to implement automated classification of BC imaging. For these purposes, a two-stage method was introduced for automated classification based on magnification, consequently categorizing the sample as benign and malignant. In [52], a Nucleus-Guided Transfer Learning (NucTraL) method is projected as an affordable and modest BT segmentation technique. The image features are characterized using a combination of local nuclei features extracted through the CNN model pretrained on ImageNet databases. The nucleus patch extraction approach is applied to avoid fine classification of nuclei boundary; however, it gives features with a better discriminatory classification ability. Classification of the combined feature into malignant and benign classes can be implemented through SVM classifiers.

Wang et al. [53] established an effectual technique for classifying H&E-stained histological BC imaging. To enhance the robustness and accuracy of the classifiers, the extracted imaging factors of the multiple networks were through four pre-trained DCNN techniques. Furthermore, an FS technique of the DOLL method improves the outcomes by decreasing the feature dimension to mitigate over-fitting. Furthermore, the E-SVM classifiers were trained through the merged feature and voting strategies to enhance the performance of the classification. In [54], the DL model with HI implements an automatic IDC recognition. DenseNet and ResNet techniques are exploited for automatic IDC recognition. The 50 × 50 image patches belong to the WSI of the subject. In [55], a patch dependedDL technique by name Pa-DBN-BC is developed to classify and detect BC on HIs with the DBN. The feature was put under extraction by the supervised fine-tuning and unsupervised pre-training levels. Then extracts feature from the image patch. LR is exploited for categorizing the patch from HI's.

Boumaraf et al. [56] proposed a novel DL model for automated BC recognition on HIs, comprising magnification-dependent (MD) and magnification-independent (MI) classification. The presented DL approach relies on the block-based fine-tuning process where the final two residual blocks of the DL technique are high domain oriented to the target. Besides, the suitability of the presented method can be enhanced via GCN, which depends upon the target data value and 3-fold data augmentation on the training dataset. Chattopadhyay et al. [57] developed a dual shuffle attention-guided DL model based on the bottleneck unit. It improves the capability of the model to learn complicated image patterns.

Alqudah and Alqudah [58] presented a novel sliding window (SW) approach to produce feature vectors exploiting the LBP features. Each image results in a set of 25 SWs, and the features are generated from every SW. The BC classification procedure is executed using the SVM classification model, which recognizes benign as well as malignant images. In [59], handcrafted feature extractors and DNN models can be applied to classify BC on the BreakHis database. The produced features using hand engineering models can be utilized for training the DNN models with 4 dense and 1 softmax layer. Finally, the data can be augmented to resolve the overfitting problem. A summarization of the reviewed technique is demonstrated in Table 1.

4. Discussion

This section gives a short comparative study of the different existing BC classifications. Table 2 and Fig. 4 exhibit a comparative $\boldsymbol{accu_y}$ inspection of various classification models. The results indicated that the LBP+RDT, DBN+LR, and CNN+FCN models have accomplished reduced $\boldsymbol{accu_y}$ of 84%, 86%, and 87% respectively. Meanwhile, the CNN+SVM model has provided $\boldsymbol{anaccu_y}$ of 90%. Next to that, the VGGNet+RF, VGG16+LR, and DenseNet-161+FCN models have highlighted identical $\boldsymbol{accu_y}$ of 91%, whereas the Inception+GBT model has reached $\boldsymbol{accu_y}$ of 92%. Contrastingly, the VGG16+FCN and AlexNet+SVM models have reported reasonably closer $\boldsymbol{accu_y}$ values of 95% and 96%, respectively. Finally, the GoogleNet+FCN and ResNet-50+E-SVM model has shown higher $\boldsymbol{accu_y}$of 97% and 97%, respectively.

5. Challenging Issues and Future Scope

Earlier conventional techniques that involve the pipeline method have gained considerable attention in processing BCHI. This method includes dissimilar stages, classification, pre-processing, segmentation, and feature extraction [60]. But the performance of this system relies on the feature extraction and segmentation method from the recognized region. The handcrafted feature was used for determining the ROI. But the handcrafted feature might not capture each variation in the pattern of the dataset and thereby decreasing the model performance. Developing this system also requires wide domain knowledge in HIs and image processing.

Table 1. Summary of reviewed approaches

References	Pre-processing	Segmentation	Feature Extraction	Classification	Evaluation Metrix
Bruno et al. [39]	-	-	Curvelets and LBP	DT, SVM, RF	$Accu_y = 91\%$
Reis et al. [40]	Colour deconvolution	-	LBP	Random Decision Tree	$Accu_y = 84\%$
Zhang et al. [41]	Macenko, Non-linear conversion	Thresholding	Colour/texture/shape	SVM	$F_{score} = 88\%$
Wan et al. [42]	Non-linear mapping	Hybrid active counter	Pixels, Objects, semantic levels	SVM	$Accu_y = 92\%$
Araújo et al. [43]	Macenko	-	Colour, shape, Nuclear density	CNN, SVM	$Sens_y = 95\%$
Roy et al. [44]	Macenko	-	CNN	FCN	$Accu_y = 87\%$
Baker et al. [45]	Gaussian Blur Filters	K-means, Watershed	Morphological and geometrical features	Rule-based, Decision Tree	$Accu_y = 70\% \; to \; 86\%$
Kausar et al. [46]	Macenko	-	VGG-16	FCN	$Accu_y = 94\% \; to \; 97\%$
Beevi et al. [47]	Colour deconvolution	-	VGG-Net	Random forest, FCN	$F\_score = 88\%$
Vo et al. [48]	Macenko	-	Inception network	Gradient Boosting Tree	$Accu_y = 91\% \; to \; 95\%$
Cao et al. [49]	Quantile normalization	Hybrid level set	CNN	SVM	$Accu_y = 90\%$
Khan et al. [50]	Macenko	-	Google Net, VGG-Net, ResNet	FCN	$Accu_y = 97\%$
Gupta and Chawla [51]	Image rescaling	-	VGG-16, VGG-19, Xception, ResNet-50	SVM, Logistic regression	$Accu_y = 83\% \; to \; 93\%$
George et al. [52]	Macenko	Laplacian of Gaussian	AlexNet, ResNet-18, ResNet-50, ResNet-101, GoogleNet	SVM	$Accu_y = 96\%$
Wang et al. [53]	Colour enhancement	-	ResNet50, DenseNet121, Inception-V3, VGG-16	E-SVM	$Accu_y = 97\%$
Celik et al. [54]	-	-	ResNet-50, DenseNet-161	FCN	$Accu_y = 91\%$
Hirra et al. [55]	Threshold window, Gaussian filter	-	DBN	LR	$Accu_y = 91\%$
Boumaraf et al. [56]	-	-	ResNet 18	GCN	$Accu_y = 92.03\%$
Chattopadhyay et al. [57]	-	-	Dual Shuffle	Residual Dual-Shuffle Attention Block	$Accu_y = 97.43\%$
Alqudah and Alqudah [58]	-	-	LBP	SVM	$Accu_y = 91.12\%$
Joseph et al. [59]	-	-	Handcrafted	DNN	$Accu_y = 97.87\%$

Table 2. Comparative analysis of distinct existing bc classification

Methods	Accuracy (%)
LBP+Random Decision Tree	84.00
CNN+FCN	87.00
VGG16+FCN	95.00
VGGNet+Random Forest	91.00
Inception+Gradient Boosting Tree	92.00
CNN+SVM	90.00
GoogleNet+FCN	97.00
VGG16+Logistic Regression	91.00
AlexNet+SVM	96.00
ResNet-50+E-SVM	97.00
DenseNet-161+FCN	91.00
DBN+LR	86.00

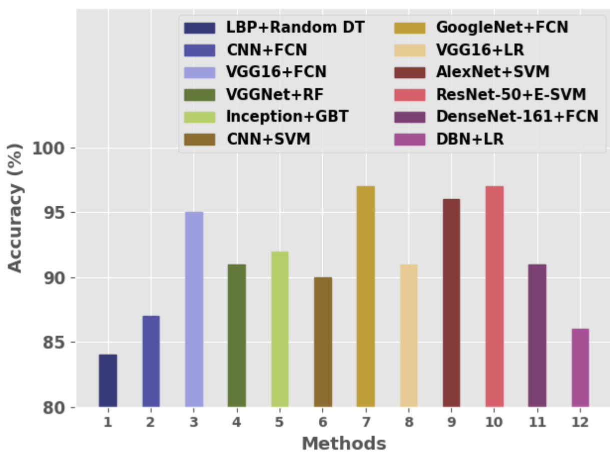

Fig. 4 Accuracy analysis of distinct existing BC classification

DL has become popular over the past decades for HIs processing because of its capability to model convolutional patterning and raise computation power. CNN is a prevalent option for feature extraction since the process learned for extracting the most applicable feature depends on the BP technique. But researcher should examine each layer's outcomes to justify the performance of the presented method for the BCHI analysis. The advancement of the CNN model for the HIs analysis also needs experts in DL. However, the DL-based algorithm requires a largescale data with annotation for model training. The shortage of a typical annotation dataset makes it hard to design a DL-based model for HIs processing. Furthermore, feature analysis and visualization are essential for understanding the system's behaviour.

There exist a large number of studies on the applications of medicinal image processing methods for processing BCHI. But there are some difficulties which are shown in the following.

- Creating annotation for the nuclei classification is time-consuming, challenging and dreary.
- The lack of a typical dataset makes them hard to compare and evaluate different techniques. A typical dataset provides different researcher workers with a common platform which facilitates proper comparison.
- There exist no standardized metrics to assess the accuracy of the colour normalizing method.
- Nuclei segmentation from 400x magnification remained problematic because of clustered nuclei and overlapping. Furthermore, nuclei segmentation at 100x is complicated because of the random distribution, smaller size, and varying structure of nuclei.
- The malignant sample's heterogeneous features make it hard to model the pattern to distinguish them from the benign sample.
- The CNN-based method for classifying HI extracts the feature from the whole image. It might not emphasise the ROIs like glands, mitotic cells and nuclei that largely contributed toward the decision of categorizing the image into benign and malignant. Therefore, there is a possibility for integrating the attention module in CNN to enable the algorithm to emphasise the ROI.
- There is a possibility for designing a unified method to classify HIs and nuclei segmentation.

Future research might need strong cohorts with multi-omics datasets. But the challenge for ML is not to recognize metastasis or tumours in an image because an expert pathologist could complete these tasks faster. DL is used for predicting the prognostic of the tumours and therapy response and complementing or integrating with transcriptomics and genomics for patient stratification. Collaborations between research pathologists, computer scientists, and bioinformaticians are of the greatest significance for the progress of computer-aided prognosis and relevant algorithms. In the future, we envision a DL model combined with multi-omics data for progressive accuracy in medicine.

6. Conclusion

This paper provided a comprehensive survey of DL-based BC classification models on HIs. This survey elaborated on the conventional and recently developed DL approaches for BC detection using HIs. Firstly, the role of ML and DL techniques for HI classification for BC detection is elaborated briefly. Next, the recently developed DL-based HI classification algorithms for BC are reviewed in detail.

Moreover, a comparison stud of the reviewed models with result analysis is performed.

Furthermore, an elaborate description of the challenging issues with possible future directions is identified at the end of the survey. Finally, we have pointed out the general process involved in the BC classification model with different challenging issues and possible solutions. It paves the way for the readers to work on designing automated CAD models for BC classification.

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