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Breast Cancer Detection, Segmentation and Classification on Histopathology Images Analysis: A Systematic Review

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Abstract

Digital pathology represents a major evolution in modern medicine. Pathological examinations constitute the standard in medical protocols and the law, and call for specific action in the diagnostic process. Advances in digital pathology have made it possible for image analysis to take advantage of the information analysis from hematoxylin and eosin stained images. In spite of concern, it is recorded in the majority of breast cancer datasets, which makes research more difficult in prediction. The objective of our work is to evaluate the performance of the machine learning and deep learning techniques applied to predict breast cancer recurrence rates. This study starts with an overview of tissue preparation, analysis of stained images, and a prognosis for cancer patients. The high accuracy results recorded are compromised in terms of sensitivity and specificity. The missing loss function and class imbalance problems are rarely addressed, and most often the chosen performance measures are context-inappropriate. The challenge that presents itself is to analyse whole slide images for the content imaging required with diagnostic biomarkers, and prognosis support backed by digital pathology.

1 Introduction

Over the last decade, the growing worldwide demand for the early detection of breast cancer at screening sites and hospitals has opened up avenues for new research [96]. According to the World Health Organization (WHO), early cancer detection greatly increases the chances of making appropriate decisions for a successful treatment plan. Screening operations can be analyzed through computer-aided detection and prognosis systems like, CAD and CAP, that use medical images to improve clinical confidentiality in their analysis [14]. The evaluation of medical images by a clinician is naturally qualitative and varies from person to person. Much research has been directed to the field of medical image analysis, the focus being to assist in diagnosis and clinical studies[6].

In the last two decades, affordable digital cameras became available, allowing efficient capturing of still digital images at high resolution. Subsequently, digital slide scanners slowly made their way into pathology labs as a "digital age" alternative to the conventional microscope. Today's digital slide scanners are mostly table-top devices that take glass slides as input and produce whole-slide images as output, in a cost-effective and timely manner, often automating intermediate steps such as the localization of the tissue and focus plane selection[14]. The goal of whole-slide imaging (WSI), coupled with whole-slide image viewers, is to simulate slide viewing by a conventional microscope on a computer screen. Whole slide imaging (WSI) refers to producing a high resolution digital photomicrograph of an entire histology or cytology slide [15, 46]. A relatively large percentage of the samples that are analyzed in pathology labs are from breast cancer patients, since this disease is the most prevalent form of cancer among women [70, 89].

The hematoxylin eosin (H&E) stain has stood the test of time as the standard stain for histologic examination of human tissues [32]. This simple dye combination is capable of highlighting fine cell and tissue structures. Most cellular organelles and extracellular matrix are eosinophilic, while the nucleus, rough endoplasmic reticulum, and ribosomes are basophilic [57]. The early detection and prognosis of cancer have become a necessity in research, as it can facilitate the subsequent clinical management of patients. The importance of classifying cancer patients into high or low-risk groups has led biomedical

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and bioinformatics researchers to study the application of machine learning (ML) methods. These techniques have been applied to model the progression and treatment of cancerous conditions. Graphic processing units (GPUs) and deep learning techniques have had stupendous success in recent years in fields like image recognition, object detection, and speech recognition. For example, recent studies have shown that CNNs show promise in cancer detection and diagnosis [56, 58, 100, 107]. Computer aided diagnosis of cancer from histopathology images have various research prospect. They are:

- Examining tissue for the presence of cancer so as to diagnose disease;
- Cell/nuclei/lymphocytes detection and segmentation which accurately identifies and separates these regions from histopathology images;
- Classifying the histological subtypes of a particular type of cancer;
- Grading to quantify the severity of malignancy levels to provide insights for treatment planning and prognosis;
- Assessing the possibility of how quickly the cancer is likely to spread; and
- Highlight the contributions which solve or avoid these challenges.

CAD research using histopathology images has eventually resulted in the diagnosis of cancers of prostate, skin, breast, nerve tissue, lung, liver,lymph node, kidney, thyroid, brain, cervix, colon, oral, blood and ovaries. This survey reviews cancer diagnosis based on histopathology images. It explores the image processing approaches, deep learning algorithms, and machine learning methods employed for the computer-aided diagnosis of cancer from H&E stained histopathology images. Figures 1 and 2 shows the various methods and modality of breast cancer images.

This paper is organized in five sections. Sections 1 and 2 introduces the different image modalities in histopathology. In Sect. 3, highlighted the challenges in nuclei detection, segmentation,and classification. Section 4 illustrates the recent advances in nuclei detection, segmentation, and classification methods used in histopathologyand suggests ways to overcome them. We conclude with a discussion, pointing to future research directions and open problems related to nuclei detection, segmentation, and classification in Sect. 5.

2 Tissue Staining Analysis

Hematoxylin and eosin stain or haematoxylin and eosin stain (H&E stain or HE stains) is a key stain in histology, widely used in medical diagnosis. It is the most widely used stain in medical diagnosis. For example, when a pathologist looks at a
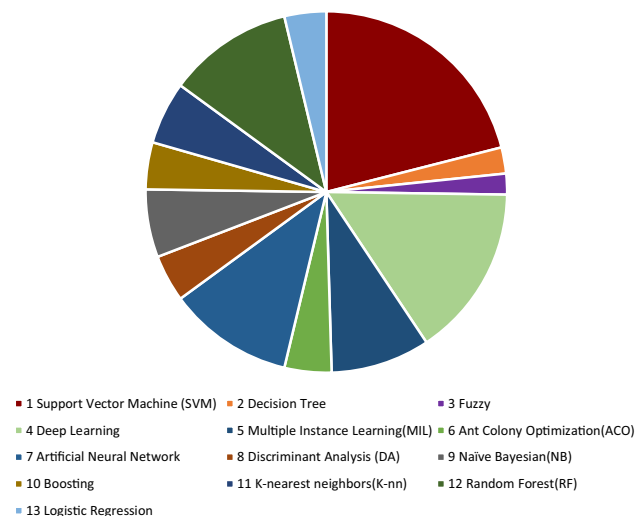

1 Support Vector Machine (SVM)　　**2** Decision Tree　　**3** Fuzzy
4 Deep Learning　　**5** Multiple Instance Learning(MIL)　　**6** Ant Colony Optimization(ACO)
7 Artificial Neural Network　　**8** Discriminant Analysis (DA)　　**9** Naïve Bayesian(NB)
10 Boosting　　**11** K-nearest neighbors(K-nn)　　**12** Random Forest(RF)
13 Logistic Regression

Fig. 1 Various method used in CAD for breast cancer

■ Detection　　■ Segmentation　　■ Feature Extraction　　■ Classification　　■ Registration
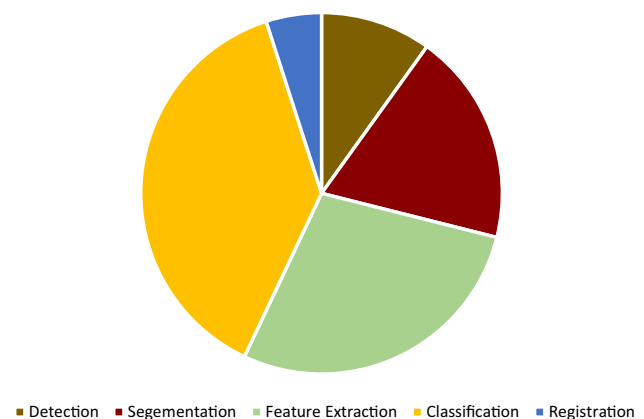
Fig. 2 Imaging modality

biopsy of a suspected cancer, the histological section is likely to be stained with H&E [32]. A combination of hematoxylin and eosin, it produces blues, violets and reds. Nuclei exhibit a wide variety of diagnostically significant patterns (related to the distribution of chromatin and the prominent nucleolus) [16, 24, 62, 94]. To reduce differences in illumination, most slide scanners provide standard packages that normalize and correct variations in spectral and spatial illumination. In addition, a long time is needed to design a digital images from collected biopsy samples, and high expertise is needed to distinguish between subtypes of breast cancer. There are marked variations in color because of the staining process, lab protocols, and scanner brightness in developing HP images, all of which complicate the process of training a multi-class CNN model efficiently, especially when using borderline cases. Figure 3 shows samples of H&E stain images and Fig. 4 explains different image processing techniques.To address problems associated with variations in non-standardized color, color
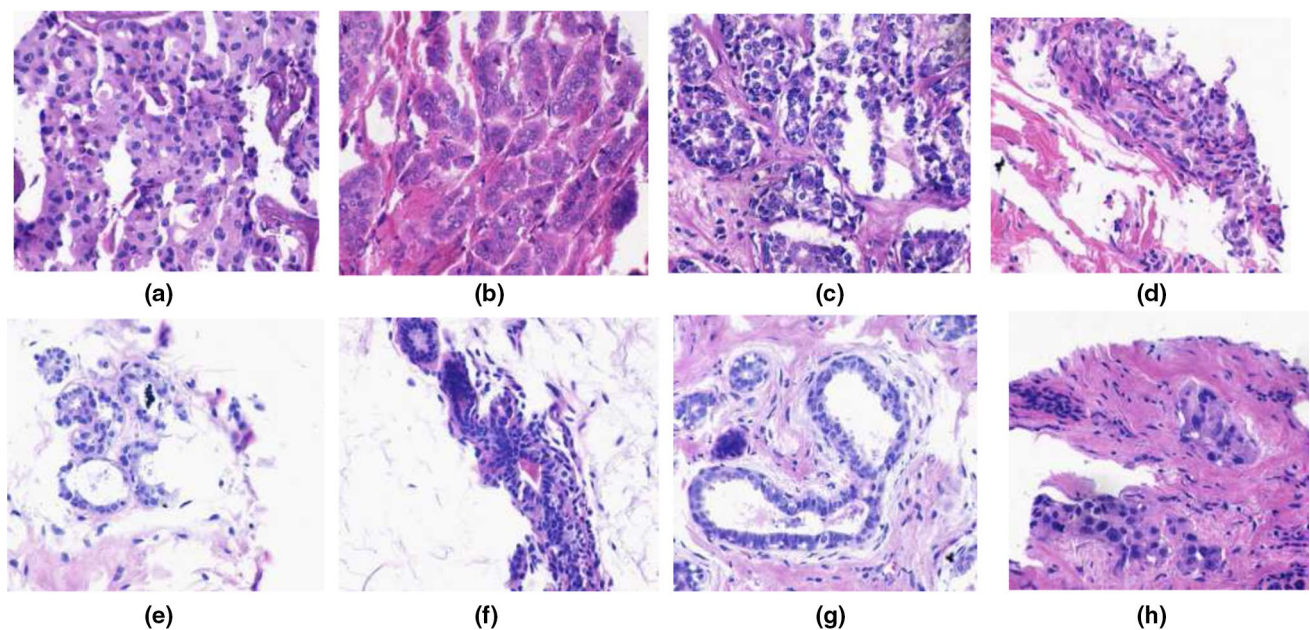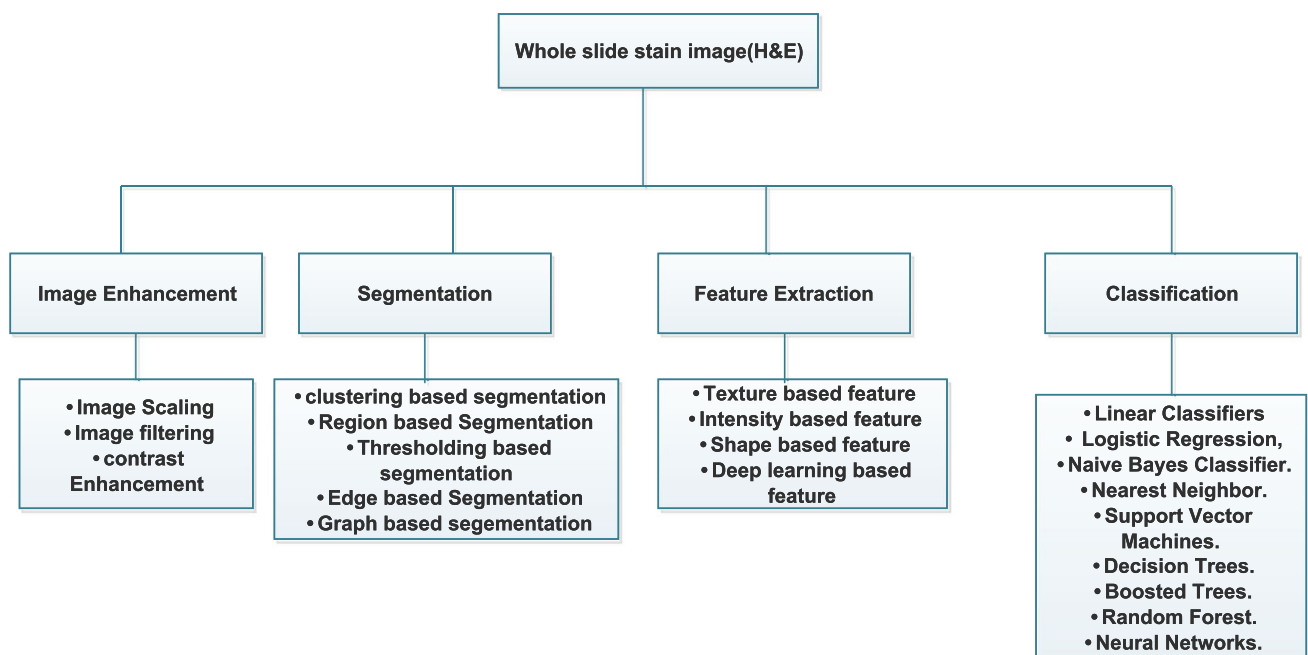
Fig. 3 Examples of H&E images

Fig. 4 Various image processing techniques

segmentation algorithms, as well as the spatial properties of salient objects, are discussed below.

3 Methodology

In this section, we have provided a review of various image descriptors in health care applications. Microscopic imaging is a major task in CAD and CAP, and is used to diagnose
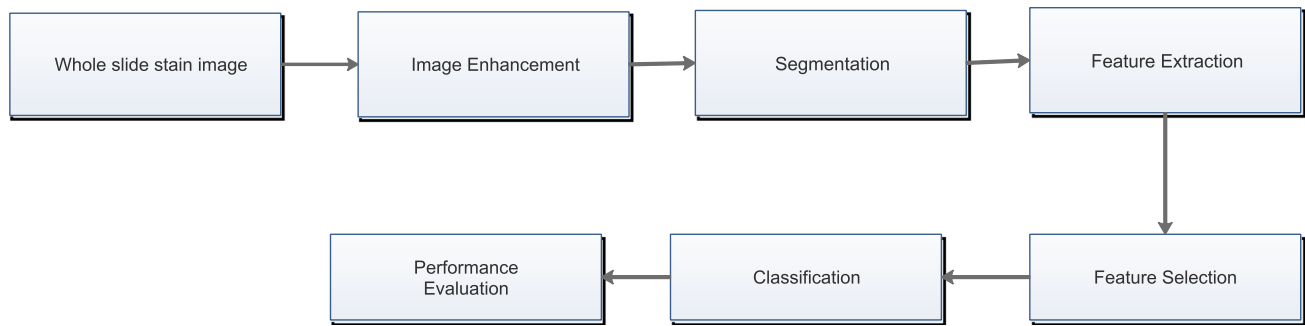
Fig. 5 Block diagram

cancer much more efficiently [4]. Fine needle aspiration biopsy/cytology (FNAB/FNAC) a very thin needle attached to a syringe is used to aspirate a sample of cells without using anesthesia. These cells are smeared onto a glass slide, then stained and examined under microscope by a pathologist to examine for abnormal cells. FNAC is generally used to diagnose metastatic carcinoma of head and neck, in the cervical region. It is hardly ever utilized as a first-line diagnostic tool. FNAC is not indicated in respectable GBC because the tumor has propensity for seeding the biopsy tracts and resection should be performed even if FNAC is negative. A histopathological image sample is analysed by expert pathologists, stored in the RGB format, and subjected to image enhancement. Figure 5 shows the basic steps of image processing.

3.1 Overview of Preprocessing Methods

Image enhancement and preprocessing are important stage since digital images contain noises and may not have adequate contrast. Image preprocessing may have dramatic positive effects on the quality of feature extraction and the results of image analysis. Preprocessing is analogous to the mathematical normalization of a data set, which is a common step in many feature descriptor methods. Preprocessing while adhering to grayscale conventions is necessary to eliminate problems brought on by color differences. Image enhancement is to improve the interpretability or perception of information in images for human viewers, or to provide "better" input for other automation. Image enhancement methods are of two kinds: spatial domain and frequency domain. The former operates directly on pixels and the latter on the Fourier transform of the image. Image enhancement improves the visual quality and overall appearance of an image in order to extract its spatial features. The preprocessing operation addresses the phases of reading and resizing the image, denoising, segmentation, and morphology (smoothing edges). The ROI has to do with processing a single subregion of an image, leaving other regions unchanged.

The ROI is defined by the given boundaries of an image of an object or a drawing. The ROI refers to the contours or surfaces defining a physical object [42, 64, 101]. A local adaptive thresholding technique, with an object perimeter gradient to detect nuclei cells, is combined with an active contour model The model features optimized initialization, and works within a restricted region to improve the convergence of nuclei segmentation. This approach, especially in cases where nuclei detection is processed, generates expensive training data and a deep learning model [25, 51].

3.2 Overview of Segmentation Methods

The segmentation of nuclei in cancer histopathology images can be considered a basic functional block in different applications. Other applications include extraction of prognostically relevant morphometric features (size, shape, chromatin texture), automatic nuclear pleomorphism grading as part of a computer-aided prognosis system, detection of lymphocytes infiltration, detection of malignancy and tubule formation in bottom-up manner [26, 40, 94, 98]. Similarly, a two-stage segmentation method to obtain cellular structures in high-dimensional histopathological images of renal cell carcinoma take place [2, 8, 47]. Generally active contour model or snake model based on the techniques of curve evolution will take place. A major limitation of active contours, however, (1) inability to resolve boundaries of intersecting objects, (2) handle occlusion. Multiple overlapping objects are typically segmented out as a single object [3]. In [95] color mixing and morphological operators, alongside marker-controlled watershed segmentation at multiple scales and with different markers, are applied. Post-processing is undertaken to reject false regions and merge results from multiple scales, with a mean estimated sensitivity of 0.875. A new approach for breast thermography image analysis involves the development of a fully automatic segmentation of the right and left breast for asymmetry analysis, using the shape features of the breast and polynomial curve fitting in [79]. Statistical tests show that particular features are

very significant in detecting breast cancer [66]. Semantic segmentation with the CNN renders complex mitosis images easily understandable, and provides the high-level information needed for classification.

3.3 Overview of Feature Extraction Methods

Feature extraction is one way of dimensionality reduction which efficiently represents compressed feature vector. The approach is useful when large image sizes are involved. The quantitative assessment of tissue and organ function relies on capturing proper features to characterize cellular and tissue structures. To measure the deviations at cell and tissue structures, morphological, texture, co-localization and spatially related features are used. Both local and global features include shape, size and color. Global features are used in image retrieval, object detection, classification, and local features for object recognition identification, and the detection of blobs, corners, and edge pixels.

3.3.1 Morphometric (Shape Based)

Morphometric analysis is a concept that envelop size and shape. It is commonly performed on organisms to analyse their fossil record. The impact of mutations on shape, developmental changes occurs, covariance between ecological factors, and shape as well for estimating quantitative feature of the particular shape [28, 55]. The following morphometric features, which is increased mean values and were statistically significant for the cell and for the nuclei: area, convex area and outline. Using this mean cell and nuclear outline, increases the grade progression as presented in [74]. The method based on FNAC (Fine needle aspiration cytology) included 55 benign breast diseases (BBD), 7 Atypical ductal hyperplasia (ADH), and 62 carcinoma cases. Nuclear morphometric parameters analyzed included 5 nuclear size, 2 shape, 4 texture, and 2 density parameters. The specificity was better (ranging from 98.29 to 100%) with a good sensitivity (ranging from 80 to 81%). The current standard of care is to perform complexion needle biopsies for diagnosis of palpable and image detected breast abnormalities. An overall accuracy of 87.9% is achieved on the test dataset was discussed in [65].

In [13], discussed a statistical Gamma-Gaussian Mixture Model (GGMM), which is employed in extraction of primary candidates for estimating the Probability Density Function (PDF) of mitosis and non-mitosis cells. In [82] have introduced breast thermography which is used in detection of breast cancer. This is based on the principle of chemical and blood vessel activity in both precancerous tissue and area surrounding the tissue in breast cancer is always higher than in the normal breast. In [17] discussed a method for color edges extraction based on statistical features and automatic threshold. This traditional edge detector based on

the first and second order neighborhood, which describes the relationship between current pixel and its neighbors, is extended to the statistical domain. Finally, it integrates to edge results over the three color components.

3.3.2 Color-Intensity Based Features

A framework for extracted intensity-based features by employing the RGB values of pixels in a tissue. For each color channel, here computed mean, standard deviation, skewness and kurtosis of the pixel values of an image and used them as the feature set of learning algorithm. They have also applied the hierarchical cell-graph approach to model and classify breast tissue samples which has a lobular/glandular architecture were discussed in [92].

3.3.3 Textural Features

Textural features for identifying objects in an image or regions of interest in an image. In texture analysis, statistical methods can be used to analyze the spatial distribution of gray values, by measuring local features at each point in the image and derive a set of statistics from the distributions of the local features [7, 36]. Generally discrete wavelet transform (DWT) are based on textural features and it classifies the cancerous cell images. Here have introduced a local binary pattern feature which is a powerful process used in computer vision and pattern recognition application, applied for texture recognition and classification. The patch is divided into blocks and for each pixel of the block, a binary string of the size of a predefined neighborhood will be produced. GLCM, wavelet and Law's texture features are extracted [12, 73]. Dominant Local Binary Patterns will be demonstrated that a minimum set of pattern labels that represents around 80% of the total pattern occurrences in an image can effectively capture the image textural information for classification task [11, 49, 60]. Grey Level Co-occurrence Matrix (GLCM) method is applied for extracting second order statistical texture features considering the spatial relationship of pixels. These features are entirely based on the grey-level differences[53]. Cellular texture features interpret the image in terms of cellular features. They define the following six different features: nucleus, membrane, halo, structured, border, float and background [61]. The GLCM features characterize the texture of an image by calculating how often pairs of pixel occur in an image with specific values and in a specified spatial relationship. This calculation is used to create GLCM, and then statistical measures are extracted from this matrix.

In GLCM the number of rows and columns is equal to the number of gray levels, G, in the image.

The matrix element P (i, j |Δx, Δy) is the relative frequency with which two pixels, separated by a pixel distance

(Δx, Δy), occur within a given neighborhood, one with intensity 'i' and the other with intensity 'j'.

The matrix element P (i, j|d, Δ) contains the second order statistical probability values for changes between gray levels 'i' and 'j' at a particular displacement distance d and at a particular angle (Δ). The class mark of ith intensity level is denoted by xi, frequency of ith level is denoted by fi and the relative frequency of the ith level is denoted by pi = fi/N.

GLCM features along with the extreme fuzzy Learning machines proves to be more efficient in terms of the training data, computational time, accuracy and the prediction ratio measurement. It outperforms other neural based classifiers by the higher peaks of difference and also needs more improvisation in terms of the prediction ratio measurement [80]. In [48] discussed about the overlapped nuclei in the cell. Since the form of distribution was known, parametric EM algorithm was applied to learn the GMM. In order to evaluate the optimal number of nuclei, cluster validation was performed based on the extracted regional maxima. A priori knowledge for the overlapped nuclei was incorporated to obtain separation line without jaggedness, as well as to reconstruct occluded contours in overlapped region.

3.3.4 Real Daubechies Wavelet Transform

Daubechies wavelet transform is a type of orthogonal wavelets, which is a discrete wavelet transform and represent by a maximal number of dissolve moments [74]. Approximate shift invariance property and extra information in imaginary plane for complex wavelet domain. Decomposition method is used for tissue images. Wavelet feature [F1] S-Parameter, Texture features (First order statistic), Mean, Standard Deviation, Entropy, Texture features (Second order statistic), Contrast, Correlation, Energy. These feature are extracted from the detection of cells were discussed in [64]. The complex wavelet transform is used to generate new images from which the statistical and co occurrence features are extracted, which is used to describe the nuclei texture variability. Debaucheries complex wavelet transform has given better result than other wavelet transform methods all these are discussed in [103].

3.3.5 Dual-Tree Complex Wavelet Transform

A dual-tree complex wavelet transform (DT-CWT) is performed to decompose the image patches into multi-scale forms, which provides near shift invariance and good directional selectivity compared to the standard wavelet transform. Here they applied mitotic cell image for feature extraction. Five different statistical features are extracted on each wavelet sub band. Further more the inter-scale dependencies between wavelet sub bands allow extraction of discriminative features of mitosis appearing at all resolution levels.

Mean, median, variance, energy, and entropy. The quantitative results suggested that the wavelet-based statistical features are able to capture important texture attributes related to mitosis development and differentiate mitotic from non-mitotic cells, which is presented in [29].

3.3.6 Fractal Texture Features

Fractal dimension(FD) is an expression of the image in material durability, and it can be used to describe the roughness of images surface [33, 71, 85]. In [72] have discussed a fractal analysis, which is commonly a mathematical tool for handling with a complex system. A method of estimating fractal dimension (FD) has been found to be useful for an analysis of various medical image applications. The Critical Exponent Analysis (CEA) has been established as an important tool for detecting the FD parameter of the self-affine series information from both horizontal and vertical landscape sequences indicate that a region of cells. This FD value higher than a region of cancer cells and a region of lymphocytes; in contrast, a region of lymphocytes has the FD value lower than other two regions. The main advantage of these approaches used in shade, prominence and time-domain fractal texture features.

3.3.7 Handcrafted Features

The handcrafted features are computed through the scattering transform which gives non-linear invariant texture features. The combination of handcrafted features with raw data produces sharp proximity maps and better detection results than the result of raw intensities with a similar kind of CNN architecture. In [51] presented a spatially constrained CNN (SC-CNN) by proposing features that capture texture characteristics and show that although CNN produces good results on automatically learned features.

3.4 Feature Selection

Generally feature selection played an important role in large scale data with high dimensional feature space, while it also had some potential pitfalls for small scale and sparse data in a high dimensional space. With high dimensional input, feature selection could be used for eliminating unnecessary information for training to reduce the overall training time while maintaining the original accuracy [23]. A feature selection method was discussed that is mainly based on the performance of different feature combinations, which means that each possible combination of features is to be evaluated to obtain the best combination in [18]. There are various strategies in feature selection methods namely, filter, wrapper, and embedded.

- Filter—various statistical tests to determine the subset of features with the highest predictive analysis;
- Wrapper—selection of a set of features as a search problem, where different combinations are evaluated and compared to other combinations;
- Embedded—learn which features best contribute to the accuracy of the model while the model is being created;

Some examples of filter methods include the Chi squared test, information gain and correlation coefficient scores. A predictive model used to evaluate a combination of features and assign a score based on model accuracy, an example for wrapper method is the recursive feature elimination algorithm [102]. A chain-like agent genetic algorithm (CAGA) proposed was applied to obtain the optimal subset of features for SVM classifier, and obtained satisfactory classification accuracy [104]. Multi-population co-genetic algorithm with double chain-like agents structure (MPATCGA). The feature selection experimental results show that MPATCGA has higher optimization precision than some well known GAs averagely, is not affected by different classifiers, and can be used for parallel feature selection than some other optimization algorithms. It means that MPATCGA is very suitable for complex optimization problems such as global numerical optimization, feature selection, and so on, with satisfying optimization precision and speed. 3D deep supervision mechanism by connecting hidden layer features to auxiliary classifiers. This strategy can not only address the optimization challenges when training deep 3D networks, but also improve the discriminative capability of networks [27, 59].

Regularization methods are also called penalization methods that introduce additional constraints into the optimization of a predictive algorithm, that bias the model toward lower complexity (fewer coefficients). Examples of regularization algorithms are the LASSO, Elastic Net and Ridge Regression. Here it is applied in "gradient feature testing" this feature selection process is not separated. Within the grafting framework, a loss function shows preference for classifiers with larger margins. They have also applied a linear classifier in the data set[83].

3.5 Classification

Classifiers are a class of algorithms which can be trained by examples in order to learn and classifies objects based on a set of features. Generally the classification can be based on data, such as supervised, unsupervised and semi supervised data. Theories underlying state-of-the-art classifiers determine the approaches used. Transfer learning for large scale dataset is very beneficial in medical domain mainly for detection part. Classification systems aimed at supporting clinical decisions. As such, classifiers play an important role in the performance of system for validation. Therefore,

primarily interested in large-scale of data used in clinical managements. Using this analysis we have found that deep learning classification techniques will give more accurate and faster results in the large scale of data as explained in [9, 38, 52, 86, 98]. The objective of the multi-scale constitutional network (MSCN) is to extract multi-scale feature vectors for nucleus region detection. The modified Ada Boost enables inclusion of the computational cost of each feature during selection, thereby improved the computational efficiency of the resulting detectors. The outputs of two detectors are merged by a globally optimal active contour algorithm to refine the border of the detected nuclei with a detection rate of 95% [48, 99]. An unsupervised Bayesian classification scheme is used for separating overlapped nuclei for tumor cells. The topographic surface generated by distance transform is viewed as a mixture of Gaussians algorithm. In order to learn the distribution of the topographic surface, the parametric expectation-maximization (EM) algorithm is employed. Cluster validation is performed to determine how many nuclei are overlapped [37, 50].

In [5] developed a Convolutional Neural Network (CNNs) method to classify images in to four classes, normal tissue, benign lesion, in situ carcinoma, invasive carcinoma, and further into two classes, carcinoma, and non-carcinoma. The features are extracted using CNN model and also used for training a Support Vector Machine classifier. Accuracy of 77.8% for four class and 83.3% for carcinoma/non-carcinoma are achieved. The sensitivity of our method for cancer cases is 95.6%. A novel deep learning framework for the detection and classification of breast cancer using the concept of transfer learning is applied. Features are extracting from breast cytology images using three different CNN architectures (Google Net, VGG Net, and Res Net) which are combined using the concept of transfer learning for improving the accuracy of classification [54]. In [56] have developed a variant of Deep Cut method and it compares those to a naive approach to CNN training under weak supervision. Tested for its applicability to resolve brain and lung segmentation problems on a challenging fetal magnetic resonance dataset and encouraging results in terms of accuracy.

3.5.1 Stacked Sparse Auto Encoder (SSAE)

The stacked autoencoder is a neural network consisting of multiple layers of basic SAE in which the outputs of each layer are wired to the inputs of each successive layer. Here considered the two layer SAE, which consists of two hidden layers, and the Stacked Sparse Autoencoder (SSAE) to represent the two layer SAE , which is represented as latent feature of images [30, 90, 108].

3.5.2 Genetically Optimized Neural Network (GONN)

Genetically Optimized Neural Network (GONN) algorithm, helps solving classification problems. It evolves a neural network genetically to optimize its architecture (structure and weight) for classification. It introduces new crossover, and mutation operators which differ from standard cross over, and mutation operators to reduce the destructive nature of these operators. This algorithm helps classify breast cancer tumors as benign or malignant. The enhanced Genetically Optimized Neural Network (GONN) algorithm, helps to solve multi-class classification problems. Used as a multi-tree GONN representation that integrates multiple GONN trees, each individual is a single GONN classifier. This classifier is an integrated version of individual GONN classifiers for all classes. The integrated version of classifiers is genetically evolved to optimize its architecture for multi-class classification [9, 10].

3.5.3 Convolution Neural Network]

To provide an accurate and reliable solution for breast cancer multi-classification they have developed class structure-based deep convolutional neural network (CSDCNN). The CSDCNN has broken through the above mentioned barriers by leveraging hierarchical feature representation, which plays a key role for accurate breast cancer multi-classification. The CSDCNN is a non-linear representation learning to model that abandons feature extractions, it also bypasses feature engineering that requires a hand-designed manner. CSDCNN adopts the end-to-end training manner that can automatically learn semantic and discriminative hierarchical features from low-level to high-level.

CSDCNN is carefully designed to fully take into account the relation of feature space among intra-class and inter-class for overcoming the obstacles from various histopathological images. Particularly, the distance of feature space is a standard for measuring the similarities of images; however, the feature space distance of samples from the same class may be larger than the samples from different classes [35, 48].

In [75] a region proposal network (RPN) was introduced that shares full-image convolutional features with the detection network, thus enabling nearly cost-free region proposals. The RPN is a fully convolutional network that simultaneously predicts object bounds and object scores at each position. The RPN is trained end-to-end to generate high-quality region proposals, which are used by fast R-CNN for detection. Fast R-CNN have reduced the running time of these detection networks, exposing region proposal computation as a bottleneck. Fast R-CNN into a single network by sharing their convolution features using the recently popular terminology of neural networks with 'attention' mechanisms, the RPN component tells the unified network where to look. CNN trained from scratch with (DeCAF) features repurposed from another CNN trained on natural images, which often is not possible with medical image datasets since they are too small. From the results observed that these features are a viable alternative for a fast creation of image recognition systems using deep learning, and this system can perform better than systems using visual feature descriptors [88, 31]. Pan et al. [69] introduced a novel multi-scale fully convolutional neural networks approach for regression of a density map to robustly detect the nuclei of pathology and microscopy images.
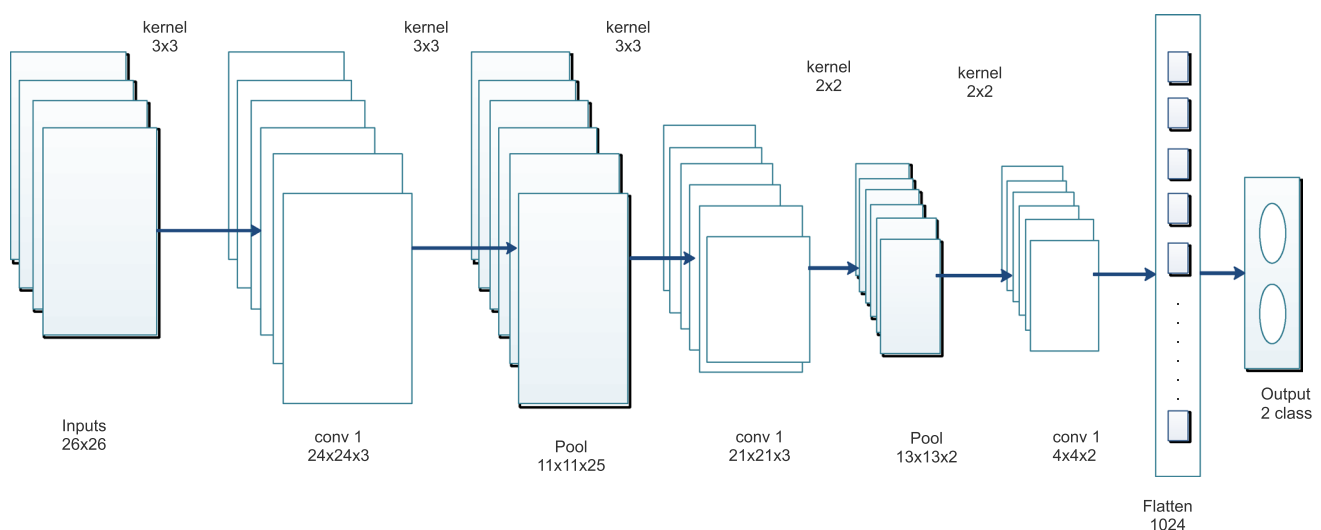

Fig. 6 Block diagram of CNN

Table 1 Summary of nucleus detection, segmentation, classification methods

References	Topic	Staining	Method
Song et al. [86]	Segmentation of cytoplasm and nuclei	H&E	Multi-scale CNN and graph-partitioning-based method
Janowczyk et al. [43]	Nucleus segmentation	H&E	Resolution adaptive deep hierarchical learning scheme
Kashif et al. [51]	Nucleus detection	H&E	Combination of CNN and hand-crafted features
Romo et al. [76]	Tubule nucleus detection	H&E	CNN-based classification of pre-selected candidate nuclei
Sirinukunwattana et al. [84]	Nucleus detection and classification	H&E	CNN with spatially constrained regression
Song et al. [87]	Cell segmentation	H&E	Multi-scale CNN
Sethi et al. [81]	Comparison of normalization algorithms	H&E	Presents effectiveness of stain normalization for application of CNNs
Janowczyk et al. [44]	Stain normalization	H&E	Used SAE for classifying tissue and subsequent histogram matching
Khan et al. [54]	Nuclei detection and classification	H&E	Transfer Learning
Duc my Vo et al. [99]	Classification	H&E	Incremental boosting convolution networks
Abdulkadir et al. [2]	Cell segmentation	H&E	SLIC superpixel algorithm
Xipeng Pan et al. [69]	Cell detection	H&E	Multi-scale fully convolutional neural networks
Kolarevic et al. [55]	Cell detection	H&E	Bootstrap
Song et al. [86]	Cytoplasm segmentation	H&E	Multi scale Convolutional Network
Xie et al. [105]	Cell counting and detection	H&E	Fully convolutional regression networks
Change et al. [19]	Tissue classification	H&E	Transfer Learning using convolution Sparse coding ensemble Of CNNs
Veta et al. [97]	Nuclear area measurement	H&E	CNN directly measure nucleus area
Xing et al. [106]	Nuclear detection & cell counting	H&E	Cell counting using fully connected CNN
Wang et al. [67]	Nuclear detection	H&E	Tumor Proliferation& Score Prediction
Hamad et al. [34]	Nuclei classification	H&E	Fully Convolutional Regression Network and Convolutional Neural Network
Saha et al. [78]	Hotspot detection	Ki-67	Gamma mixture model (GMM) with Expectation-Maximization for seed point detection
Kemeng et al. [21]	Cell nuclei detection and segmentation	H&E	Deep learning U-Net
Hou et al. [39]	Nuclei detection	H&E	Sparse Convolutional Autoencoder
Wang et al. [101]	Nuclei segmentation and detection	H&E	Multi-Path Dilated Residual Network
Chao hui et al. [41]	Nucleus detection and classification	H&E	eXclusive autoencoder (XAE)
Mahmoud et al. [1]	Nuclei segmentation	H&E	Multilevel thresholding and the watershed algorithm to separate clustered nuclei

Overview of papers using deep learning for digital pathology images. The staining and imaging modality abbreviations used in the table are as above: H&E: hematoxylin and eosin staining, Ki-67

Janowczyk et al. [45] developed a resolution adaptive deep hierarchical (RADHicaL) learning to scheme where DL networks at lower resolutions are leveraged to determine if higher levels of magnification, and computation are necessary to provide precise results. In [77] a patch-based classifier(PBC)using convolutional neural network(CNN)for automated breast histology image classification is applied. Convolution recurrent neural network is the combination of two of the most prominent neural networks. The CRNN (convolutional recurrent neural network) involves CNN(convolutional neural network) followed by the RNN(Recurrent neural networks). This network is similar to the CRNN but generates better or optimal results. Figure 6 explains basic block diagram of CNN architecture.

4 Discussion

A comprehensive review will focus on medical images (tissue images) used for detection and validation for different diseases. We have narrowed down our choice to these image exams, relevance of works based on the use of image labels. It mainly focuses on the feature extraction, selection, and classification of the image labels to diagnosis a problem. Various methods and their performances are explained in Tables 1 and 2. From this review, it is evident that deep learning has extended every aspect of medical image analysis. A large diversity of deep learning architectures are covered. The earliest excogitate used pretrained CNNs as feature

Table 2 Performance of difference techniques for detection and classification of breast cancer using histopathological images

References	Accuracy (%)	Specificity	Sensitivity	f1-score
Niwas et al. [65]	87.8	0.982	0.80	0.8
Araujo et al. [5]	77.8	0.874	95.6	Nil
Bhardwaj et al. [9]	98.24	0.987	1	8.89
Tang et al. [93]	88	0.78	0.80	0.77
Pan et al. [68]	92.2	0.9	0.87	0.83
Naylor et al. [63]	95.4	0.76	0.86	0.80
Chen et al. [20]	89.7	0.85	0.84	0.77
Janowcyk et al. [45]	82.2	0.88	0.89	0.80
Roy et al. [77]	87.4	0.86	0.83	Nil
Feng et al. [31]	98.25	0.97	0.91	0.97
Vo et al. [99]	96.4	0.5	0.96	0.97
Sudharshan et al. [91]	92.3	0.91	0.87	0.89
Das et al. [22]	Nil	0.96	0.95	0.84
khan et al. [54]	97.52	0.95	0.97	0.98
Ozturk et al. [66]	Nil	0.91	0.92	0.93
Han et al. [35]	93.4	0.89	0.87	0.89

extractors only. The fact that these pretrained networks could simply be downloaded and directly applied to any medical image facilitated their use. After reviewing so many papers one would expect to be able to express the perfect deep learning method and architecture for each individual task and various application. Although convolutional neural networks are now clearly the top performers in most medical image analysis competitions.

Applying deep learning algorithms for classification often differentiate themselves in aspects outside of the deep neural network, like novel augmentation techniques. The last aspect we want to touch on is model hyper parameter optimization which can help squeeze out extra performance from own network. Thus deep learning has great impact in medical image processing applications.

5 Conclusion

In this paper have highlighted the various methodologies, algorithms, concepts of feature extraction, selection techniques and classification used in histopathology image. Different merits and demerits are evaluated with various method used. Using validation techniques, many issues pertaining to accuracy, specificity, sensitivity have been addressed. This review can be helpful to know the various feature extraction and selection algorithms used for training the data in cell images. Furthermore, we will incorporate appropriate feature extraction techniques and classification in big data

analytics. We can evaluate framework in various applications of histopathology analysis.

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