A comprehensive review of computer-aided whole-slide image analysis: from datasets to feature extraction, segmentation, classification and detection approaches

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Published online: 31 January 2022
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Abstract
With the development of Computer-aided Diagnosis (CAD) and image scanning techniques, Whole-slide Image (WSI) scanners are widely used in the field of pathological diagnosis. Therefore, WSI analysis has become the key to modern digital histopathology. Since 2004, WSI has been used widely in CAD. Since machine vision methods are usually based on semi-automatic or fully automatic computer algorithms, they are highly efficient and labor-saving. The combination of WSI and CAD technologies for segmentation, classification, and detection helps histopathologists to obtain more stable and quantitative results with minimum labor costs and improved diagnosis objectivity. This paper reviews the methods of WSI analysis based on machine learning. Firstly, the development status of WSI and CAD methods are introduced. Secondly, we discuss publicly available WSI datasets and evaluation metrics for segmentation, classification, and detection tasks. Then, the latest development of machine learning techniques in WSI segmentation, classification, and detection are reviewed. Finally, the existing methods are studied, and the application prospects of the methods in this field are forecasted.

Keywords Whole-slide image analysis · Computer-aided diagnosis · Feature extraction · Image segmentation · Image classification · Object detection

Abbreviations
AUC Area under ROC curve
BOF Bag-of-features
CAD Computer-aided diagnosis

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| Abbreviation | Description                                      |
|-------------|--------------------------------------------------|
| CAE         | Convolutional automatic encoder                  |
| CBMIA       | Content-based microscopic image analysis         |
| CCD         | Charged coupled device                           |
| CCV         | Color coherence vectors                          |
| CDSA        | Cancer digital slide archive                     |
| CM          | Co-occurrence Matrix                             |
| CNN         | Convolutional neural network                     |
| CRF         | Conditional random field                         |
| CT          | Computed tomography                              |
| DCIS        | Ductal carcinoma In-situ                         |
| DCN         | Deep convolutional networks                      |
| DNN         | Deep neural network                              |
| DT          | Decision tree                                    |
| FCN         | Fully convolutional network                      |
| FESI        | Traditional foreground extraction                |
| FN          | False negatives                                  |
| FP          | False positives                                  |
| FRBS        | Fuzzy rule-based model                           |
| FROC        | Free receiver operating characteristic curve     |
| GAN         | Generative adversarial network                   |
| GBM         | Glioblastoma multiforme                          |
| GLCM        | Gray-level co-occurrence matrix                  |
| H&E         | Hematoxylin and eosin                            |
| HOG         | Histogram of Oriented Gradient                   |
| ICIAR       | International conference on image analysis and recognition |
| IDC         | Invasive ductal carcinoma                        |
| IHC         | Immunohistochemistry                             |
| ISBI        | International symposium on biomedical imaging    |
| k-NN        | k-nearest neighbor                                |
| LBP         | Local binary pattern                             |
| LSTM        | Long short term                                  |
| LYNA        | Lymph node assistant                             |
| MFEM        | Multi-scale feature extraction module            |
| MICCAI      | Medical image computing and computer assisted intervention society |
| MIL         | Multiple instance learning                       |
| MIML        | Multi-instance multi-label                       |
| MRI         | Magnetic resonance imaging                       |
| MSER        | Maximally stable external regions                |
| M-WRSF      | Multi-channel weighted region scalable fitting   |
| OOF         | Out-of-focus                                     |
| PPV         | Positive predictive value                        |
| PSO         | Particle swarm optimization                      |
| RAZN        | Reinforced auto-zoom net                         |
| RBF         | Radial basis function                            |
| ResNet      | Residual network                                 |
| RF          | Random forest                                    |
| RMDL        | Recalibrated multi-instance deep learning        |
| ROC         | Receiver operating characteristic               |
| ROI         | Region of interest                               |

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1 Introduction

1.1 Whole-slide imaging technique

*Whole-slide Image* (WSI), also known as “virtual microscopy”, aims to imitate typical light microscopy in a computer-generated model (Farahani et al. 2015). People usually think of whole-slide imaging as an image acquisition method. It is possible to transform the whole glass slide into a digital form (Al-Janabi et al. 2012a). In addition, the “digital slides” are used for human observation or performing them to automated image analysis (Aeffner et al. 2019).

The processing of whole-slide imaging is performed by the WSI system. A WSI system has a scanner, networked computer (s), and possibly a server or cloud solution for storage, display (e.g. tablet, etc.), and compatible software for image creation, management, and analysis (El-Gabry et al. 2014; Saco et al. 2016; Pantanowitz et al. 2013). The first part applies technical hardware (scanner) to digitize glass slides, generates a sizable classical digital image (so-called “digital slide”) accordingly. The second part exploits technical software (ie, virtual slide viewer) to view and/or analyze these huge digital images (Weinstein et al. 2009). WSI devices have different looks and performances, but overall, the WSI scanner includes the following parts: an optical microscope system with a camera, an acquisition system, computer hardware/software, scanning software, and a digital slide viewer. Supplemental components include the feeder or image processing systems (Farahani et al. 2015).

As shown in Fig. 1, the optical microscope system is an essential part of the WSI scanner, especially the lens optics and the camera, because it can determine the quality of the images. The charged coupled device (CCD) sensors on cameras can convert analog signals into digital signals. There are two effective methods of slide acquisition. One is area scanning, and another is line scanning. The main difference between area scanners and line scanners is that the former mainly uses a CCD camera with a square sensor. While scanning a slide, the CCD camera stops after scanning every block to record an image. Then the CCD camera moves to the next block and repeats the operation immediately until the scanning process is complete (Watanabe et al. 2013). In contrast, the line scanner mainly uses a linear array to scan. The linear arrays include ordinary linear arrays and time delay and integration (TDI) CCD linear arrays. The ordinary linear array uses three sensors to...
capture red, green, and blue lines respectively and integrates them, while the TDI CCD linear array integrates the signal 64 times (Bodenstorfer et al. 2007; Higgins 2015). Due to the different working principles of area scanners and line scanners, each has its advantages and disadvantages. The main advantages of area scanners are high resolution and high accuracy. However, because of its stop-and-go work, work efficiency is low. Although the line scanner works fast and moves continuously, its lower accuracy can easily cause problems with image focusing. In the working process of generating WSI, the scanning method can be selected according to the working accuracy and the required time. After choosing a region of interest (ROI) on a slide, adjust focus, and scan the slide (Amin et al. 2008). If WSI scanners have a Z-stacking facility (scan slides at different focal planes along the vertical Z-axis and stack images on top of each other to produce composite multi-planar images (Farahani et al. 2015)), they can better center on particular ROI (El-Gabry et al. 2014). Owing to the images generated by the WSI systems are large, the visual field of a computer should be bigger than the visual field of a traditional microscope over four times (Rojo et al. 2006).

With the accelerating development of science and technique, the WSI system has progressed rapidly. WSI offers higher quality and resolution images with annotation (Aeffner et al. 2019). The scanner with fast scanning speed has improved image quality and reduced storage costs (Al-Janabi et al. 2012a). The digital approach also can reduce the time of transporting glass slides and the risk of breakage and fading (Ghaznavi et al. 2013; Camparo et al. 2012; Webster and Dunstan 2014). Moreover, the digital slides do not deteriorate over time (Saco et al. 2016).

Fig. 1 The workflow of whole-slide imaging. a Histopathological tissues from biopsy. b Whole mount glass slides. c Whole slide imaging scanner. d The final WSI
WSI infuses many fields such as E-education, virtual workshops, and histopathology aspect. Now, there is a growing need for pathology to improve quality, patient safety, and diagnostic accuracy. These causes and economic pressures lead to consolidation and centralized diagnostic services (Ghaznavi et al. 2013). Moreover, WSI can boost distinct pathology practices, generally used in pathology (Cornish et al. 2012). Digital pathology networks based on WSI systems can solve some complex problems with pathology. For example, WSI can be explored by several observers from different areas at the same time. Discussions using WSI can save the time needed for transferring glass slides to distant places for attaining second minds and teleconsultation (Al-Janabi et al. 2012a; Webster and Dunstan 2014; Al-Janabi et al. 2012b). WSI equivalently broadens the scope of cytopathology where virtual slides are used for numerous intents like Tele-cytology, quality activities (e.g. archiving and proficiency testing) and education (El-Gabry et al. 2014). It also helps pathologists become more efficient, precise, and creative at quantifying prognostic biomarkers like HER2/neu (c-erbB-2). Nowadays, the WSI analysis techniques are advanced in clinical, nonclinical, and research image-related applications (Farahani et al. 2015).

1.2 The development of WSI analysis

The traditional histopathological section analysis method requires specially trained pathologists to look for ROI under the microscope one by one and then analyze them based on professional knowledge. Traditional manual analysis of histopathological images has many drawbacks and problems. There are no quantitative indicators, so the qualitative analysis results cannot be reproduced (Singh et al. 2010). Moreover, most doctors have tight working conditions, heavy workloads, and time pressure. In this case, the human cognitive process is easily disturbed, leading to incomplete diagnosis and misdiagnosis (Goggin et al. 2007). Although traditional slide analysis is accurate, it can be deeply personal. It is available for the same person to evaluate a slide one day and get different conclusions the following week. Besides, the procedure is a challenging and time-consuming task (Higgins 2015). Therefore, computer-aided diagnosis (CAD) is a more efficient, accurate and intuitive method.

The computer-aided reading slide can improve diagnosis accuracy and detection rate and reduce the overall misdiagnosis rate. Moreover, the computer is not affected by fatigue and human error and provides better assistance to doctors (Niazi et al. 2019; Parwani 2019). It is also a valuable tool to reduce the workload of clinicians (Hanna et al. 2020). While reducing pathologists’ workload and improving efficiency, it can also perform intuitive quantitative analysis of histopathological conditions. These are better than manual reading slides. Computer-aided viewing of WSI is now rapidly developing. WSI improves the pathology field’s unique clinical, nonclinical and analysis of image-related applications (Farahani et al. 2015).

In recent years, the histopathological WSI analysis performed by CAD doctors has been widely used in different cancer fields (i.e., breast cancer, prostate cancer, gastric cancer, neuroblastoma). The scope of applications focuses on disease classification, early screening, tissue localization, and benign and malignant diagnosis. Common tasks with CAD include classification, segmentation, and detection. Image classification is based on each image as a unit and distinguishes it from other images. Image segmentation is based on pixel points, dividing the image into several specific areas with unique properties, including segmentation of the image with the precise boundary of the existing target. Image detection refers to retrieving a given sub-image from a known image and the difference
with classification is that multiple objects in an image may be retrieved (Gonzalez and Woods 2007; Rawat and Wang 2017; Karpathy and Fei-Fei 2015; Zhao et al. 2019; Vedaldi et al. 2009).

For example, in the work of Huang and Racoceanu (2017), automatic detection and sequencing system based on Gleason pattern recognition is proposed for the automatic detection of high-grade prostate cancer. In the field of breast cancer, the work of Mehta et al. (2018) makes the segmentation of WSIs of breast biopsy with biologically significant tissue markers. The study of Korbar et al. (2017a) trains a modified version of the residual network (ResNet) to classify different types of colorectal polyps on WSIs. At present, the development trend of computer-aided viewing of WSIs is shown in Fig. 2.

As shown in Fig. 2, the CAD techniques continue to advance with time. The number of cases in the three main applications of classification, segmentation, and detection has increased significantly. The number of cases in other applications is also growing, such as retrieval (Ma et al. 2016), localization (Alomari et al. 2009). Since 2014, there has been an increasing trend in the number of CAD with WSI. Gradually by 2020, the growth rate of CAD has increased, reflecting the vigorous development of this technique.

Besides, to explain and clarify CAD in viewing WSI, an organization chart is shown in Fig. 3. The figure shows the general process of CAD and processing WSI. It shows seven important steps in the histopathology image analysis system, including data acquisition, image presentation, image preprocessing, feature extraction, data post-processing, classifier design, and system evaluation.

In Fig. 3, the first histopathological data is obtained from the medical field, and then the following steps are performed: first, two-dimensional or three-dimensional digital microscope images are captured by various imaging devices (such as optical microscopes); second, the images extracted in the first step are saved in a specific color space (such as red,
green, and blue (RGB)); third, the saved images are preprocessed, and the attributes of the images are improved by dataset enhancement, segmentation, and other methods. These steps are all preliminary work for the input of feature extraction. Next, feature extraction is performed. The images can be expressed as attributes (shape, texture, and color features), layout features (global and local features), or extraction style (manual or automatic). These feature extraction categories are not independent, they can be converted to each other or into other categories through some other methods. After that, the post-processing step enhances the extracted features, where filter, morphological processing, and normalization are used. Also, the classifier can be classified as shallow or deep according to its learning structure. Finally, various numerical and intuitive methods are used to evaluate the classification system, such as accuracy, error rate, sensitivity, and specificity. Besides, each step is not independent and is connected with other steps through information feedback. Therefore, the entire CAD viewing WSI system is an organic whole (Li 2016). It should be noted that the data used in the papers discussed in this review are all WSIs, but due to equipment and method problems, there are many situations when analyzing the WSIs in detail. Sometimes the WSI is analyzed directly (as shown in Fig. 11), and sometimes it is necessary to perform cropping preprocess and other operations on these WSIs (as shown in Fig. 17).

1.3 Motivation of this review

The WSI analysis technique has various applications. For example, to perform preliminary diagnosis of surgical pathology, and perform intraoperative frozen section diagnosis through remote consultation (Huang et al. 2018; Boyce 2017), and seek expert advice without incurring international transportation costs or delays (Boroujeni et al. 2016). WSI also provides advantages in tumor diagnosis, prognosis, and targeted therapy. It can also
facilitate teachers and students in teaching (Ghaznavi et al. 2013). Therefore, the research field of WSI analysis through CAD systems is significant.

To the best of our knowledge, there exist some survey papers that summarize WSI analysis (e.g., the reviews in (Gurcan et al. 2009; Pantanowitz et al. 2011; Kothari et al. 2013a; Veta et al. 2014; Sharma et al. 2015b; Li et al. 2018; Komura and Ishikawa 2018; Chang et al. 2019; Nichols et al. 2019; Wang et al. 2019a; Dimitriou et al. 2019; Kumar et al. 2020)). In the following part, the summary of survey papers related to the WSI analysis is presented.

In this work, we have found 12 review papers related to WSI analysis. Among them, the work of (Gurcan et al. 2009; Pantanowitz et al. 2011; Kothari et al. 2013a; Veta et al. 2014) introduces some research status of WSI in histopathology. The survey of Pantanowitz et al. (2011) focuses on the routine histopathological diagnosis, the survey of Gurcan et al. (2009) focuses on WSI analysis procedures, the survey of Kothari et al. (2013a) focuses on WSI informatics methods and future development prospects. The survey of Veta et al. (2014) summarizes the preparation process of WSI and extends to the prognosis of CAD and breast cancer patients. Although Li et al. (2018); Komura and Ishikawa (2018); Chang et al. (2019); Nichols et al. (2019), these four review papers also involve WSI, they only use WSI-type databases when discussing datasets, but do not introduce relevant CAD techniques. In Wang et al. (2019a); Dimitriou et al. (2019), deep learning algorithms are introduced into WSI analysis, but the number of articles analyzed and investigated is very less. In the survey of Kumar et al. (2020), although the full text is all about the applications and prospects of WSI, it does not involve specific technologies. Based on the review papers mentioned above, we summarize a histogram chart in Fig. 4 to compare the contribution of each review to the field. Therefore, we present this review paper to analyze related works using CAD combined with WSI in the past few decades.

This survey summarizes more than 220 related works from 2004 to 2020. At the beginning of the preparation of this review, we first search for possible related papers by keywords. Next, some duplicate, irrelevant, and incomplete papers are removed. Finally, we choose the papers we need to use. The paper screening process is shown in Fig. 5. The

![Fig. 4 A comparison of the number of relevant WSI papers using CAD technologies](image-url)
audience for this review is related researchers in the field of medical imaging and medical professionals.

2 Datasets and evaluation methods

In this section, we have discussed some commonly used datasets and evaluation metrics for the classification, segmentation, and detection tasks.

2.1 Publicly available datasets about WSI

To better realize the purpose of applying the WSI technique to CAD and analyzing it, we summarize some datasets commonly used in WSI research. The four most commonly used WSI datasets are The Cancer Genome Atlas (TCGA) (Atlas 2006), Camelyon datasets (Litjens et al. 2018), TUPAC16 (Veta et al. 2019), and Kimia Path24 (Babaie et al. 2017). The basic attributes of these datasets are shown in Table 1.

2.1.1 TCGA database

TCGA is a cancer research project jointly established by the National Cancer Institute and the National Human Genome Research Institute in 2006 (Atlas 2006). By collecting and sorting out various omics data related to cancer, it provides a large, all-around cancer research reference database (Tomczak et al. 2015). The database is open, free, and has collected more than 2 Petabytes of data, including RNA sequencing, MicroRNA sequencing,
DNA sequencing, Array-based DNA methylation sequencing, and Reverse-phase array data. It is a very important data source for cancer researchers. Although the main work of this database is focused on genomics, it has accumulated a lot of WSIs data for relevant researchers to use.

Due to the large pixels of WSIs data, it is difficult to perform tasks such as management, visualization, sharing, and quantitative analysis. To facilitate research, David et al. (Gutman et al. 2013) propose an open-source software digital pathology platform called Cancer Digital Slide Archive (CDSA) to observe WSI. Figure 6 is an example of WSIs in adrenocortical carcinoma in the TCGA database.

### 2.1.2 Camelyon database

The Camelyon Challenge is an academic conference in the field of medical image analysis organized by International Symposium on Biomedical Imaging(ISBI) (Litjens et al. 2016). Table 1 shows the basic information of the publicly available used datasets.

| Databases   | Year | Field            | Number of images       | Number of actual cases |
|-------------|------|------------------|------------------------|------------------------|
| TCGA        | 2006 | Cancer related   | \                      | \                      |
| NLST        | 2009 | Lung             | 1250 H&E slides        | 450 patients           |
| BreakHis    | 2015 | Breast cancer    | 9109 microscopic images| 82 patients            |
| TUPAC16     | 2016 | Tumor mitosis    | 821 H&E slides         | \                      |
| Camelyon16  | 2016 | Breast cancer    | 400 slides             | \                      |
| Camelyon17  | 2017 | Breast cancer    | 1000 slides            | 200 patients           |
| Kimia Path24| 2017 | Pathology        | 24 WSIs                | \                      |

**Fig. 6** An example of WSI in an adrenal cortical carcinoma in the TCGA database (Atlas 2006)
The significance of the entire competition is to advance an algorithm that automatically detects the extent of breast cancer metastasis in Hematoxylin and Eosin (H&E) stained lymph node slices (Bejnordi et al. 2017a; Bandi et al. 2018). This is the first time in medical image analysis that image analysis has been raised to the WSI level. This task has extremely high clinical significance, which greatly reduces the time for pathologists to observe the slices, and reduce the subjectivity of the diagnosis. The entire competition lasts for two years, so the entire image dataset contains the Camelyon16 dataset and Camelyon17 dataset (Litjens et al. 2018).

The entire competition dataset comes from the sentinel lymph nodes of breast cancer patients, provided by the Radboud University Medical Centre and the University of Utrecht Medical Centre. The Camelyon16 dataset consists of 170 stage I lymph node WSIs (100 normals and 70 metastatic) and 100 stage II lymph node WSIs (60 normals and 40 metastatic). The test dataset consists of two universities. It consists of 130 WSIs. The Camelyon16 dataset is used as the training set for evaluating Camelyon17. Figure 7 is a histopathological picture of the lymph nodes in the Camelyon dataset. The left side belongs to normal cell tissue, and the cells on the right have been swallowed and occupied by cancer cells.

2.1.3 TUPAC16 database

Because tumor proliferation represents an important biomarker for the prognosis of breast cancer patients. Moreover, in clinical practice, the evaluation of tumor value is a subjective and work-intensive task, and thus a TUPAC16 challenge is proposed (Veta et al. 2019). The challenge is to score the value of tumors. The challenge dataset includes 500 pieces of training data and 321 pieces of test data of breast cancer histopathology WSI. In addition to this dataset, there are two small datasets to detect tissue ROI and mitosis. The dataset used

![Fig. 7 A histopathological image of a lymph node in Camelyon (Litjens et al. 2018). Normal tissue is seen on the left, and cells that have been gobbled up and occupied by cancer cells are seen on the right](image-url)
to detect ROI is 148 cases randomly selected from the training set of the challenge dataset. The mitosis detection dataset comes from WSIs of 73 breast cancer cases in three pathology centers. Among them, 23 cases come from the AMIDA13 challenge (Veta et al. 2015), and the remaining 50 cases come from two other pathology centers in the Netherlands. Figure 8 shows some examples of mitotic maps in H&E breast cancer slices. The green circles indicate mitosis.

2.1.4 Kimia path24 database

Kimia Path24 is a dataset for image classification and retrieval in digital pathology. It includes Kimia Path24 composed of 24 WSIs, manually selected from more than 350 scans, depicting different body parts with different texture patterns. The observation focus of this dataset is not on anatomy and tumors, but on the diversity of patterns (Babaie et al. 2017). So this dataset is not a pathology dataset, but a computer vision dataset. The 24 WSIs thumbnails in this dataset are shown in Fig. 9.

2.2 Evaluation method

This subsection introduces the evaluation methods of classification, segmentation, and detection algorithms and related formulas.

The confusion matrix is a situation analysis table of the prediction results of the total machine learning model. In the form of a matrix, the records in the dataset are judged according to the two criterias of the real category and the category predicted by the model. The rows of the matrix represent the true values, and the columns represent the predicted
values. The form of the confusion matrix is shown in Table 2. Pos stands for Positive, and Neg stands for Negative.

In predictive analysis, the confusion matrix is a table with two rows and two columns composed of False Positives (FP), False Negatives (FN), True Positives (TP) and True Negatives (TN). Furthermore, some other evaluation indicators are derived from the confusion matrix as shown in Table 3 (Sokolova and Lapalme 2009).
Image segmentation (Haralick and Shapiro 1985) is the segmentation of images with existing targets and precise boundaries. The commonly used indicators are accuracy, precision, recall, F-measure, sensitivity, and specificity in Table 2. Besides, Dice co-efficient and Jaccard index are popular segmentation evaluation indices in recent years (Tustison and Gee 2009).

As shown in Table 2, accuracy, precision, recall, sensitivity, specificity, and F1 score are widely used to evaluate classification performance. With the continuous improvement of grading requirements in practical applications, Receiver Operating Characteristic (ROC) and Area Under ROC Curve (AUC), these two non-traditional measurement standards have emerged (Fan et al. 2006).

Detection (Pal and Pal 1993) is another common task similar to the classification task. In addition to the common classification indicators we have discussed, the classical ROC method cannot solve the practical problem of evaluating multiple anomalies on an image. So Free Receiver Operating Characteristic Curve (FROC) (Egan et al. 1961) is proposed. This allows multiple lesion areas to be detected on a single WSI.

### 2.3 Summary

In this section, we have introduced the commonly used datasets used in the fields of WSI and CAD and summarized the evaluation indicators of segmentation, classification and detection tasks. It is observed that the commonly used public datasets in this field are TCGA, TUPAC16, and Kimia Path24. In addition to the basic evaluation indicators listed in Table 3, there are some indicators with more comprehensive measurement indicators. For example, the Dice co-efficient and Jaccard index in the segmentation metrics, the AUC in the classification metrics, and the FROC in the detection metrics.

### 3 Feature extraction

Traditional image feature extraction is generally separated into three steps: preprocessing, feature extraction, and feature processing. Then the machine learning method is used to segment and classify the features. The purpose of preprocessing is to eliminate interference factors and highlight characteristic information. The main methods are: image standardization (Shen et al. 2003); image normalization (Khan et al. 2014). The main purpose of feature processing is to eliminate features with a small amount of information and reduce the amount of calculation. The common feature processing method is principal components analysis (Jhajharia et al. 2016).

Feature extraction is a crucial step. The process of transforming the input data into a set of features is called feature extraction (ping Tian et al. 2013). The main goal of feature extraction is to obtain the most relevant information from the original data and represent the information in a lower-dimensional space (Kumar and Bhatia 2014). Therefore, in this section, we mainly summarize the features extracted in WSI for CAD. The types of extracted features are shown in Fig. 10.
3.1 Traditional feature extraction

In the process of segmentation, classification, or detection combined with CAD and WSI analysis technique, the commonly used extracted features include color features, texture features, and shape features.

3.1.1 Color feature extraction

Color features are important and widely used in image representation (Kodituwakku and Selvarajah 2004). In histopathological images, color differences can indicate differences in substances or structures. Because the images are stained, different cell structures or histopathological tissues can be stained with different colors, so the color characteristics can accurately describe WSIs. Color features are defined according to a specific color space or model (ping Tian et al. 2013). Many color spaces are used in the literature we summarized, such as RGB (Roullier et al. 2010b), hue saturation value (HSV) (Mercan et al. 2016b) and Lab (Mercan et al. 2016a). Common color features include color histograms, color moments, and color coherence vectors (CCV) (Pass et al. 1997). Generally, before extracting color features of WSIs, a specific color space should be selected first, then the color space conversion should be performed, and the color space should be quantized into a color histogram. The color histogram provides the global features of WSI, which are then transformed into feature vectors. Finally, feature vectors can be sent to a classifier or segmenters. Among the papers, we summarized, 24 papers use color features. We find five papers based on Lab-based color feature extraction (Kong et al. 2009; Akakin and Gurcan 2012; Mercan et al. 2014, 2016b, 2017). There are four papers based on HSV color feature extraction (Samsi et al. 2012; Akakin and Gurcan 2012; Homeyer et al. 2013; Bautista et al. 2014). There are also 12 studies using the RGB feature extraction technique. Some of these papers even use two or more color features.

The papers (Kong et al. 2009; Akakin and Gurcan 2012; Mercan et al. 2014, 2016b, 2017) all perform operations on WSI to extract ROI. After the candidate ROI is determined, its color feature is extracted according to the Lab color histogram. Then, its feature vector is used to subdivide and classify the histopathological WSI. Lab theory includes all color modes that the human eye can see. Therefore, the features extracted from the Lab space represent the intensity and color information of WSI respectively.

The papers related to HSV color feature extraction are (Samsi et al. 2012; Akakin and Gurcan 2012; Homeyer et al. 2013; Bautista et al. 2014). The color features based on HSV are more in line with the perceived characteristics of the human eye (Smith 1978). Its three components represent Hue, Saturation, and Value. Among the four papers, only Samsi
et al. (2012) uses HSV as a color feature to facilitate the identification of follicles in the immunohistochemistry (IHC) stained tissue of lymphoma. Other three papers (Akakin and Gurcan 2012; Homeyer et al. 2013; Bautista et al. 2014), in addition to HSV, the two-color space features of RGB and Lab are also used. This is since these WSI histopathological images are specially stained to highlight related cell structures, and the single color space has a limited color spectrum. Therefore, more color information can be extracted by combining different color spaces. In these three papers, color moments are used to extract color features. In histopathology WSI, first-order moments (mean, etc.) and second-order moments (standard deviation, etc.) are generally used. Compared with the color histogram, another advantage of this method is that it can clearly express the color distribution in the image without vectorizing the features.

The papers related to RGB feature extraction are the most numerous of these three color spaces, which are Kong et al. (2009), Roullier et al. (2010b), Akakin and Gurcan (2012), Collins and Collins (2013), Veta et al. (2013a), Homeyer et al. (2013), Hiary et al. (2013), Bautista et al. (2014), Yeh et al. (2014), Litjens et al. (2015), Cruz-Roa et al. (2018), Morkūnas et al. (2018). Among these papers, the ones that only use RGB are (Roullier et al. 2010b; Veta et al. 2013a; Hiary et al. 2013; Litjens et al. 2015; Morkūnas et al. 2018). In Roullier et al. (2010b), Veta et al. (2013a), WSI histopathological images are used to detect mitosis. Since the color of mitosis is close to brown, it can be emphasized by the chromaticity information of the red-green difference, the RGB color space is more suitable. Figure 11 shows the RGB feature extraction and classification in Homeyer et al. (2013).

Papers that combine RGB color space features with other color space features are Kong et al. (2009), Akakin and Gurcan (2012), Collins and Collins (2013), Homeyer et al. (2013), Bautista et al. (2014), Yeh et al. (2014), Cruz-Roa et al. (2018). The reason is that they want to express limited color information in more detail. These papers also use color moments to represent features.

3.1.2 Texture feature and shape feature extraction

Texture features describe the surface properties of objects corresponding to an image or an image area. Unlike color features, texture features are not pixel-based features. They need to be calculated in an area that contains multiple pixels. They describe the measurement of characteristics such as smoothness, roughness, and regularity. In the field of histopathology WSI analysis, because WSI histopathological images have rich texture details and a large amount of information, even some diseases are judged benign and malignant based

![Fig. 11 An image after RGB feature extraction and classification in Homeyer et al. (2013). a is original image, b is classification result after color feature extraction. Red represents the light-colored tissue in (a), and green represents the dark-colored tissue in (a). This figure corresponds to Fig. 2 (2) in the original paper](https://example.com/fig11.png)
on changes in texture, so it is very common to use texture features to describe histological images.

According to the papers we review, common texture features used in WSI histopathology image analysis include co-occurrence matrix (CM) (Mohanaiah et al. 2013), local binary pattern (LBP) (Mercan et al. 2016a), and image filter (Pichler et al. 1996). There are nine papers about CM and five papers about filter-based. There are also texture features derived from random field models (Chellappa and Chatterjee 1985). Here, we introduce the most widely used CM (Zucker and Terzopoulos 1980), LBP (Ojala et al. 2002), and Gabor filtering (Nguyen et al. 2011) these three textures features.

Through these papers, we find that in the process of detecting prostate cancer using WSI histopathology images, the methods of combining CM and Gabor filters are commonly used to extract texture features, such as Doyle et al. (2010), Jiao et al. (2013), Gadermayr et al. (2016). Because textures are formed by the gray distribution in an image repeatedly appearing in space, the CM is a method of expressing the texture by describing the spatial correlation characteristics of the image, that is, the joint distribution of two pixels with a certain spatial position relationship. However, it is reflected in the paper that due to a large amount of calculation of this feature extraction method, the patch level is generally used for feature extraction. For example, Weingant et al. (2015), Morkūnas et al. (2018), Jiao et al. (2013) all crop the image into image blocks for CM feature extraction. After all pixels in the image blocks are formed into a CM, and features are calculated from the matrix, such as energy, correlation, inertia, entropy, a moment of inverse difference, sum average, sum variance, sum entropy, difference average, difference variance, difference entropy, and two related information measures. The experimental images in Leo et al. (2016) and the extracted CM texture features are shown in Fig. 12.

LBP is also a texture feature commonly used in WSI histopathology image analysis. It has the characteristics of rotation invariance and gray invariance. In papers we investigated (Sertel et al. 2008, 2009b; Roullier et al. 2010a, 2011; Homeyer et al. 2013; Bejnordi et al. 2015; Mercan et al. 2016b, a; Babaie et al. 2017; Mercan et al. 2017), the original LBP operator is generally used. Then the LBP value in each patch or each small area of the image is calculated and converted into LBP histograms. Finally, the obtained LBP histograms of each patch or each small area are connected into feature vectors, and the LBP feature vectors of the WSI histopathology images are obtained.

The Gabor filter texture feature extraction uses a set of filters to filter WSI histopathology images (Nguyen et al. 2011). Because in histopathology images, different textures generally have different center frequencies and bandwidths, each Gabor filter only allows the texture corresponding to its frequency to pass. Hence, WSI feature analysis and extraction can be performed from the filter output result (Grigorescu et al. 2002).

Fig. 12  a, b are the WSI cancer areas annotated by the pathologist. c, d are the CM texture features extracted in (a, b). This figure corresponds to Fig. 2 in Leo et al. (2016)
There are some papers whose final task is WSI classification and the ROI is extracted before feature extraction. Characteristics are analyzed according to the structure of the ROI or the nucleus. Because nuclear morphology plays a central role in tumor characteristics, and many pathologists associate nuclear characteristics with cancer prognosis and molecular classification (Brieu et al. 2016; Cooper et al. 2015; Saltz et al. 2017; Valkonen et al. 2017). However, these articles do not mention in detail what the extracted texture features are.

In the process of CAD analysis of WSI histopathology images using machine learning, in addition to color features and texture features, there are also shape features. The shape feature is the least used in this field. In these papers, there is no detailed introduction, only a simple mention of the extracted feature group contains shape features (Kothari et al. 2013b; Barker et al. 2016; Swiderska et al. 2015a; Lu and Mandal 2012). The introduction of these functions is kept simple because the focus is on the machine learning part later.

### 3.2 Deep learning feature extraction

Convolutional Neural Network (CNN) is widely used to extract deep learning features in various WSIs analysis tasks. In these papers we summarized, a total of three papers use CNN for deep learning feature extraction (Bychkov et al. 2018; Kumar et al. 2018; Li et al. 2019b).

In Bychkov et al. (2018), the prognosis of colorectal cancer is predicted based on images of tumor tissue samples. Tumor tissue microarrays are assembled using sections of colorectal cancer tissue. Due to the large size of assembled tumor tissue microarray images, they are cropped into patches with the size of 224 × 224 pixels. Then transfer learning is applied using intermediate activation of VGG-16 from the penultimate fully connected layer. VGG-16 activation is extracted separately from each tile. A total of 256 tiles (16 rows and 16 columns) are generated from each input image, allowing adjacent tiles to overlap by 15 pixels. Then, each of these tiles is passed through the VGG-16 pre-trained CNN and obtained a 4096-dimensional feature vector by preserving the activation of the second and last fully connected layer. Long Short Term (LSTM) (Ren et al. 2018b) models and traditional machine learning classifiers, including logistic regression, Naive Bayes, and Support Vector Machine (SVM), are then used for classification to obtain 5-year specific disease outcome predictions. The process of VGG extracting features (Bychkov et al. 2018) is shown in Fig. 13.

![Fig. 13](image)

*Fig. 13* The VGG-16 network produces a high-dimensional feature vector for each individual tile from an input image. This figure corresponds to Fig. 1 in Bychkov et al. (2018)
3.3 Potential methods for feature extraction applied to WSI analysis technique

In addition to the feature extraction methods we reviewed, some other feature extraction methods grab our attention and can be used in the WSI analysis technique.

In Wang et al. (2020), a method is proposed to extract the structural features of building facades through texture fusion. After texture fusion, the gradient amplitude of elements is reduced, and the gradient amplitude of structural features can be kept constant. The interference of texture to structural feature extraction can be eliminated by this method of texture fusion. If we apply this method to the extraction of traditional features, it may improve the availability of features and get better results.

In Toğaçar et al. (2020), LeNet, AlexNet, and VGG-16 based deep learning models are used to realize the detection of lung cancer. This experiment is applied to the Computed Tomography (CT) image dataset. The combination of the AlexNet model and k-Nearest Neighbor (k-NN) classifier is used to obtain the best accuracy of 98.74%. Then, the minimum redundancy and maximum correlation feature selection method proposed in this paper is applied to the deep learning features, and the pruning operation is carried out to select the most effective features. This method improves accuracy to 99.51%. Next, we can try to apply this approach to WSI datasets as well. We can then try to replace CT images with WSI and use this method to extract features. The effect selected in this way is more effective and effective, which not only improves accuracy, but also improves efficiency.

In Hao et al. (2021), a fast hyperspectral image feature extraction algorithm is introduced. The proposed method is a multi-scale feature extraction method that uses the curvature filter’s multi-scale superpixel segmentation constraint, which can use progressive curvature filtering and down-sampling operations. This can effectively extract global multi-scale spectral-spatial features. This method is similar to the image pyramid decomposition method. The classification accuracy of the features produced by this method is higher than that of the standard method. So we can also apply this method to the WSI dataset.

3.4 Summary

It can be seen from the content we reviewed above, in the traditional feature extraction, color, texture, and shape features are the three most commonly used features. Especially, texture features are the most used. Among the papers, we summarized, from 2004 to 2019, a total of 51 papers used texture features. The second is color features, which are generally based on three color spaces of RGB, HSV, and Lab. Among them, RGB color space is the most commonly used. The least frequently used are shape features. For more details and analysis in this regard, see the detailed introduction in the following chapters.

Over time, the level of science and technique has also continuously improved. As can be seen from the papers we summarized, since 2016, deep learning features have been gradually applied to this day. The specific deep learning network architecture will be introduced in a separate method analysis later. Table 4 is a summary of the CAD methods used for feature extraction in WSI.
| Method | Reference | Details |
|--------|-----------|---------|
| Color  | Kong et al. (2009) | Combined Color and entropy information extracted from RGB and Lab image channels |
| Color  | Roullier et al. (2010b) | RGB feature vector |
| Color  | Samsi et al. (2012) | Hue channel for HSV color space conversion |
| Color  | Kothari et al. (2012) | RGB, CIELab, HSV, mean and standard deviation in each channel in three spaces |
| Color  | Akakin and Gurcan (2012) | Nuclear RGB features |
| Color  | Collins and Collins (2013) | Color information |
| Color  | Nayak et al. (2013) | The average, standard deviation, minimum and maximum values of each color channel in the RGB space |
| Color  | Veta et al. (2013a) | \ |
| Color  | Kothari et al. (2013b) | PVS for each R, G, B and H, S, V channel |
| Color  | Homeyer et al. (2013) | Variance of RGB, \( \mu \) hue of HIS |
| Color  | Hiary et al. (2013) | RGB color and color saturation and value in HSV space |
| Color  | Bautista et al. (2014) | RGB color and color saturation and value in HSV space RGB |
| Color  | Mercan et al. (2014) | Lab space color histogram |
| Color  | Yeh et al. (2014) | RGB color channels |
| Color  | Litjens et al. (2015) | RGB histogram features |
| Color  | Weingant et al. (2015) | Color channel histogram |
| Color  | Li and Huang (2015) | Histogram of the three-channel HSD color model |
| Color  | Mercan et al. (2016b) | Lab histograms for color |
| Color  | Barker et al. (2016) | \ |
| Color  | Mercan et al. (2016a) | Lab histograms for Color |
| Color  | Brieu et al. (2016) | \ |
| Color  | Mercan et al. (2017) | Color histogram of each channel in CIE-Lab space |
| Color  | Cruz-Roa et al. (2018) | Color histograms 8 3 8-bin histogram for each RGB channel |
| Color  | Morkūnas et al. (2018) | The average and standard deviation of the pixel values of each color channel and its RGB superpixels. |
| Method     | Reference                        | Details                                                                 |
|------------|----------------------------------|-------------------------------------------------------------------------|
| Texture    | Diamond et al. (2004)            | \                                                                        |
| Texture    | Petushi et al. (2006)            | 9 texture parameters: DNM1, DNM2, DNM3, DNM1-2, DNM1-3, DNM2-3, DNM1-2-3, DT, DN |
| Texture    | Sertel et al. (2008)             | LBP features, Haralick features                                         |
| Texture    | Sertel et al. (2009a)            | \                                                                        |
| Texture    | Kong et al. (2009)               | Four textural Haralick features                                         |
| Texture    | Sertel et al. (2009b)            | LBP features                                                            |
| Texture    | Roullier et al. (2010a)          | LBP histogram                                                           |
| Texture    | DiFranco et al. (2011)           | Feature maps (the mean and standard from HS), Co-occurrence texture features |
| Texture    | Kong et al. (2011)               | Texture and gradient features                                           |
| Texture    | Roullier et al. (2011)           | LBP                                                                     |
| Texture    | Grunkin et al. (2011)            | \                                                                        |
| Texture    | Nguyen et al. (2011)             | Gabor filter features                                                   |
| Texture    | Doyle et al. (2010)              | Co-occurrence features                                                  |
| Texture    | Akakin and Gurcan (2012)         | Mean, standard deviation, contrast, correlation, energy, entropy and uniformity |
| Texture    | Sharma et al. (2012)             | Texton-based texture                                                    |
| Texture    | Nayak et al. (2013)              | \                                                                        |
| Texture    | Jiao et al. (2013)               | Combine mean, variance and other 17 features which are extracted by GLCM method |
| Texture    | Veta et al. (2013a)              | \                                                                        |
| Texture    | Kothari et al. (2013b)           | \                                                                        |
| Texture    | Kong et al. (2013)               | \                                                                        |
| Texture    | Homeyer et al. (2013)            | \                                                                        |
| Texture    | Hiary et al. (2013)              | \                                                                        |
| Texture    | Apou et al. (2014)               | \                                                                        |
| Texture    | Mercan et al. (2016b)            | LBP                                                                     |
| Texture    | Bejnordi et al. (2015)           | LBP                                                                     |
| Method  | Reference                  | Details                  |
|---------|----------------------------|--------------------------|
| Texture | Sharma et al. (2015a)      | GLCM features            |
| Texture | Swiderska et al. (2015a)   | \                        |
| Texture | Weingant et al. (2015)     | GLCM features            |
| Texture | Li and Huang (2015)        | \                        |
| Texture | Zhang et al. (2015)        | \                        |
| Texture | Cooper et al. (2015)       | \                        |
| Texture | Apou et al. (2015)         | \                        |
| Texture | Peikari et al. (2015)      | \                        |
| Texture | Mercan et al. (2016b)      | LBP                      |
| Texture | Barker et al. (2016)       | \                        |
| Texture | Bejnordi et al. (2016)     | \                        |
| Texture | Zhao et al. (2016)         | GLCM                     |
| Texture | Harder et al. (2016)       | Co-occurrence feature    |
| Texture | Shirinifard et al. (2016)  | \                        |
| Texture | Gadermayr et al. (2016)    | HOG,LBP,FV               |
| Texture | Leo et al. (2016)          | Haralick features        |
| Texture | Mercan et al. (2016a)      | LBP                      |
| Texture | Brieu et al. (2016)        | \                        |
| Texture | Saltz et al. (2017)        | \                        |
| Texture | Babaie et al. (2017)       | LBP                      |
| Texture | Hu et al. (2017)           | Haralick texture         |
| Texture | Bejnordi et al. (2017a)    | SIFT,LBP,GLCM            |
| Texture | Valkonen et al. (2017)     | VlFeat implementation of MSER and SIFT |
| Texture | Nirschl et al. (2018)      | \                        |
| Texture | Xu et al. (2018)           | \                        |
| Method   | Reference                  | Details                      |
|----------|----------------------------|------------------------------|
| Texture  | Yoshida et al. (2018)      | \                           |
| Texture  | Han et al. (2018)          | \                           |
| Texture  | Morkūnas et al. (2018)     | \                           |
| Texture  | Mercan et al. (2017)       | \                           |
| Texture  | Simon et al. (2018)        | LBP,mrcLBP feature          |
| Texture  | Klimov et al. (2019)       | \                           |
| Shape    | Diamond et al. (2004)      | \                           |
| Shape    | Kong et al. (2011)         | \                           |
| Shape    | Grunkin et al. (2011)      | \                           |
| Shape    | Lu and Mandal (2012)       | \                           |
| Shape    | Kothari et al. (2012)      | \                           |
| Shape    | Veta et al. (2012)         | \                           |
| Shape    | Lopez et al. (2013)        | Multiple sharpness features |
| Shape    | Collins and Collins (2013) | \                           |
| Shape    | Veta et al. (2013a)        | \                           |
| Shape    | Kothari et al. (2013b)     | \                           |
| Shape    | Kong et al. (2013)         | \                           |
| Shape    | Cooper et al. (2015)       | \                           |
| Shape    | Barker et al. (2016)       | \                           |
| Shape    | Wang et al. (2016)         | \                           |
| Shape    | Saltz et al. (2017)        | \                           |
| Shape    | Xu et al. (2018)           | \                           |
| CNN      | Kumar et al. (2018)        | VGG,AlexNet                 |
| CNN      | Bychkov et al. (2018)      | VGG                         |
| CNN      | Li et al. (2019b)          | VGG                         |
4 Segmentation methods

In recent years, with the increasing size and quantity of medical images, computers must facilitate processing and analysis. In particular, computer algorithms for delineating anatomical structures and other ROI are becoming increasingly important in assisting and automating specific histopathological tasks. These algorithms are called image segmentation algorithms (Pham et al. 2000).

Image segmentation refers to the process of dividing a digital image into multiple segments, namely a set of pixels. The pixels in a region are similar according to some homogeneity criteria (such as color, intensity, or texture), to locate and identify objects and boundaries in the image (Gonzalez and Woods 2007). The practical applications of image segmentation include filtering noise images, medical applications (locating tumors and other pathologies, measuring tissue volume, computer-guided surgery, diagnosis, treatment planning, anatomical structure research) (Patil and Deore 2013), locating objects in satellite images (roads, forests, etc.), facial recognition, fingerprint recognition, etc. The selection of segmentation techniques and the level of segmentation depends on the specific type of image and the characteristics of the problem being considered (Dass and Devi 2012).

In the process of medical image segmentation, the details required in the segmentation process largely depend on the clinical application of problems (Masood et al. 2015; Zuva et al. 2011). The purpose of segmentation is to improve the visualization process to deal with the detection process more effectively. Medical image segmentation is facing many problems because the quality of the segmentation process is affected (Shrimali et al. 2009). When there is noise in the image, there will be uncertainty, which makes it difficult to classify the image (Birkfellner 2016). The reason is that the intensity value of the pixel has been modified due to noise in the image. Such a change in pixel intensity value will disturb the uniformity of the image intensity range (Al-Amri et al. 2010). Therefore, to deal with this uncertainty, image segmentation plays a crucial role in medical diagnostic systems (He et al. 2013).

As a crucial step in CAD pathologists, segmentation techniques have flourished in recent years. As shown in Fig. 2, from 2010 to 2020, the number of papers using the segmentation WSI analysis technique to assist doctors in diagnosis has increased from 2 to 28. According to the papers we have reviewed, segmentation is separated into five different techniques including thresholding-based, region-based, graph-based, clustering-based, deep learning, and other image segmentation methods. Its composition and structure diagram is shown in Fig. 14.
4.1 Traditional segmentation method

Threshold-based methods are a sort of classical image segmentation techniques. They take advantage of the difference between the grayscale of objects to be extracted from the foreground and background in an image. The grayscale is separated into several levels by setting thresholds (Petrou and Petrou 2010). Commonly used threshold selection methods are the manual empirical selection method, histogram method (Rosenfeld and De La Torre 1983), maximum between-class variance method (OTSU) (Otsu 1978) and adaptive threshold method. Among these papers, five are threshold-based segmentation (Kong et al. 2011; Lu and Mandal 2012; Shu et al. 2013; Vo et al. 2016; Arunachalam et al. 2017). In Kong et al. (2011); Shu et al. (2013); Vo et al. (2016, 2019), the methods proposed are all segmentation of cell nuclei in WSI histopathology. Kong et al. (2011) and Shu et al. (2013) both use the preprocessing that separates the foreground from the background, and then use a threshold method to identify the nucleus. But Kong et al. (2011) point out that the image studied is a microscopic image of glioblastoma. Vo et al. (2016) and Vo et al. (2019) propose a cost-effective image analysis framework based on MapReduce and realize parallelized overlap segmentation based on a grid. Lu and Mandal (2012) and Arunachalam et al. (2017), both are segmentation studies for clinical purposes. Lu and Mandal (2012) are about the segmentation of the epidermal area for the diagnosis of skin melanoma, and the global threshold method is used for multi-resolution image analysis to achieve higher performance. The main purpose of Arunachalam et al. (2017) is to segment tumor and non-tumor regions on the WSI dataset of osteosarcoma histopathology. The segmentation technique used is multi-threshold OTSU segmentation, which is used to further separate the tumor area into active and inactive areas.

Region-based segmentation is a segmentation technique based on finding regions directly. Generally, region-based image segmentation methods include two categories: watershed segmentation and region growing. The watershed algorithm draws on the theory of morphology and is equivalent to an adaptive multi-threshold segmentation algorithm (Vincent and Soille 1991). In the papers we have summarized, the watershed algorithm is used in Kong et al. (2011), Veta et al. (2012, 2013b), Shu et al. (2013), Vo et al. (2016, 2019). Among them, (Kong et al. 2011; Veta et al. 2012; Shu et al. 2013; Vo et al. 2016, 2019) are all about the separation of nuclei, except for Veta et al. (2012) which uses segmentation of nuclei to achieve the purpose of prognostic analysis in male breast cancer, the rest are separation of overlapping nuclei. Some segmentation results are shown in Fig. 15. In Veta et al. (2013b), the H&E stained breast cancer histopathological images

![Fig. 15](image-url)
are segmented using the watershed algorithm. Region growth is an image segmentation method for continuous region segmentation. Region growth refers to starting from a certain pixel. It gradually increases neighboring pixels according to a specific standard and achieves the purpose of segmentation (Adams and Bischof 1994; Shu et al. 2013). In the papers we summarized, only Shu et al. (2013) uses the region growing algorithm.

Graph-based segmentation is a kind of clustering algorithm (Van de Sande et al. 2011). Among the papers we have summarized, the papers that use graph-based segmentation are Roullier et al. (2010a, b, 2011). They all use this method in combination with multi-resolution, low-resolution to determine ROI, high-resolution to classify images. These three papers are all about WSI mitosis of breast tissue.

Clustering-based segmentation uses the relationship between each pixel and its neighboring pixels to group them into different categories. If a pixel and its neighbors are similar in color, texture or grayscale, they will be merged into the same class. Among clustering methods, the \( k \)-means algorithm is a commonly used algorithm in clustering algorithms (MacQueen et al. 1967). In the papers we reviewed, Hiary et al. (2013) and Arunachalam et al. (2017) use \( k \)-means clustering for tissue region segmentation. Arunachalam et al. (2017) use \( k \)-means clustering for tumor separation. In Hiary et al. (2013), the accuracy of the WSI segmentation results finally obtained is as high as 95.5%. In Xu and Mandal (2015), a technique for segmenting the skin histopathological WSI is proposed. First, rough segmentation is carried out, and then \( k \)-means fine segmentation is used to separate it into two categories, namely dermal pixels and epidermal pixels. The results of \( k \)-means segmentation of the epidermis are shown in Fig. 16.

### 4.2 Deep learning based segmentation

Among the papers we reviewed, 10 papers use deep learning methods for WSI segmentation (Bándi et al. 2017; Xu et al. 2017; Dong et al. 2018; Cui et al. 2019; Sirinukunwattana et al. 2018; Mehta et al. 2018; Vo et al. 2019; Seth 2019; Seth et al. 2019; Feng et al. 2020).

In Bándi et al. (2017), three methods are proposed to segment and accurately identify tissue sections WSI. The three methods are fully convolutional network (FCN), U-net, and the traditional foreground extraction (FESI) algorithm. The experimental data is 54 tissue sections WSIs. These three methods are applied to these WSIs for segmentation. The average and standard deviation of the Yakoka index are used to evaluate the segmentation results. The evaluation result shows that U-net has the best result, and its Jaccard index is 0.937.

![Fig. 16](image_url) An example of skin tissue WSI using \( k \)-means to perform epidermal segmentation. a Coarse segmentation. b Skin result of \( k \)-means fine segmentation. This figure corresponds to Fig. 5 in Xu and Mandal (2015)
In Xu et al. (2017), CNN-based ImageNet is used to extract features and convert them into histopathological images. And SVM is used to define segmentation as a classification problem. This method is applied to the digital histopathology and colon cancer dataset of the Medical Image Computing and Computer Assisted Intervention Society (MICCAI) 2014 Challenge, and finally won first place with 84% test data accuracy.

In Dong et al. (2018), a network architecture called Reinforced Auto-Zoom Net (RAZN) is proposed. The network has the function of automatically enhancing the zoom, and the structure is simple and effective. RAZN can zoom in on a specific ROI. This magnifying function is learned from a strategy network. And the network has certain robustness to imbalance and noise, which can effectively reduce over-fitting. Finally, the method is applied to the public breast cancer dataset. From the results, we can see that the single-scale baseline method and the multi-scale baseline method are not as good as RAZN. RAZN can obtain higher segmentation accuracy at a lower cost.

In Cui et al. (2019), the cell nucleus is segmented, and the network used is an end-to-end deep neural network (DNN). First, color normalization is performed on the image, and then FCN is used to predict the nucleus and its boundary. And the core and boundary are output. After post-processing, the final segmented core is produced. A method for extracting and assembling overlapping blocks is designed to seamlessly predict the cores in a large WSI. The final result proves the effectiveness of the data expansion method for cell nucleus segmentation tasks. The experiment shows that this method is superior to the prior art method and it is possible to accurately segment WSI within an acceptable time.

In Sirinukunwattana et al. (2018), different architectures are systematically compared to evaluate how the inclusion of multi-scale information affects segmentation performance. The architectures are shown in Fig. 17. It uses a public breast cancer dataset and a locally

![Fig. 17 Network architecture in Sirinukunwattana et al. (2018). This figure corresponds to Fig. 2 in Sirinukunwattana et al. (2018)](image)
collected prostate cancer dataset. The result shows that the visual environment and scale play a vital role in the classification of histological images.

In Mehta et al. (2018), semantic segmentation is performed on breast biopsy WSI. The proposed method is a new structure that utilizes the encoder-decoder. This new structure includes four modules: (1) Input Perception Coding Block. Since this module can enhance the connection between the encoders, it can compensate for the loss of information due to downsampling. (2) and (3) are respectively densely connected and additional sparsely connected decoding networks. These two networks can effectively combine multi-level features. (4) It is a multi-resolution network based on context-aware learning. This network can combine input feature fusion blocks to obtain outputs of different resolutions. The entire segmented frame is shown in Fig. 18.

Fig. 18 Multi-resolution encoder-decoder network structure diagram. This figure corresponds to Fig. 4 in Mehta et al. (2018)
In Seth et al. (2019), several U-net architectures deep convolutional neural networks (DCN) designed to output probability maps are trained to segment ductal carcinoma in-situ (DCIS) WSI in wireless sensor networks and verified the minimum required to achieve excellent accuracy at the slide level good patch vision. U-net is trained five times to achieve the best test results \(DSC = 0.771, \ F1 = 0.601\), which means that U-net benefits from seeing wider contextual information.

In Feng et al. (2020), a multi-scale image processing method is proposed to solve the segmentation problem of liver cancer in histopathological images. These eight networks are compared, and then the network most suitable for liver cancer segmentation is selected. Through a comprehensive comparison of performance, U-net is selected. The local color normalization method of histopathological images is used to solve the influence of the background, and then a seven-layer Gaussian pyramid representation is established for each WSI to obtain a multi-scale image set. The trained U-net is fine-tuned at each level to obtain an independent model. Then, shift cropping and weighted overlap are used in the prediction process to solve block continuity. Finally, the predicted image is mapped back to the original size, and a voting mechanism is proposed to combine the multi-scale predicted
images. The experimental data are the verification images of the 2019 MICCAI PAIP Challenge. The evaluation results show that this algorithm is better than other algorithms.

There are also three papers on the classification of pixels, but in essence, they have achieved the purpose of segmentation. DiFranco et al. (2011) are about the WSI classification of prostate tumors, but in the end, the goal of tumor segmentation is achieved. In DiFranco et al. (2011), different feature subsets are used to compare the performance of different classifiers. Experiments prove that Radial Basis Function (RBF) kernel SVM gets the best classification result, and its AUC value is 95.50%. The final heat map is shown in Fig. 19.

In Nayak et al. (2013), sparse autoencoder is used to automatically learn features from the image, and then multi-class regularization support vector classification is used. This method is applied to the TCGA glioblastoma multiforme (GBM) dataset, and the classification accuracy rate is 84.30%. The classification results of GBM tissue sections are shown in Fig. 20. The final result is equivalent to the tumor segmented from GBM tissue sections.

Kwok (2018) et.al use a deep learning framework to multi-classify WSI breast cancer. The framework is mainly separated into two parts. After the image is preprocessed, the patch-level image is first input into the InceptionResNet-v2 classifier for training. The

![Diagram](image_url)

**Fig. 21** Overview of the framework. This figure corresponds to Fig. 1 in Kwok (2018)
WSIs are then converted from RGB space to CIE-LAB color space. After the conversion, the foreground and background are segmented. The segmented patch-level classifier is trained. Then, the patch-level classification results are aggregated to get the final classification results. Finally, the method is applied to International Conference on Image Analysis and Recognition (ICIAR2018) breast cancer tissue image challenge, and the result is much higher than the second-place 87%. The final result is equivalent to the segmentation of breast cancer tissue. The specific workflow chart is shown in Fig. 21.

4.3 Other segmentation methods

In Bergmeir et al. (2012), a new algorithm for segmenting cell nuclei is used. Before determining the precise shape of the cell nucleus by the elastic segmentation algorithm, the proposed algorithm uses a voting scheme and prior knowledge to locate the cell nucleus. After removing noise through the mean shift and median filtering, the Canny edge detection algorithm is used to extract edges. Since the nucleus is observed to be surrounded by cytoplasm, its shape is roughly elliptical, and the edges adjacent to the background are removed. The random hough transform of the ellipse finds the candidate kernel and then processes it through the level set algorithm. The algorithm is tested and compared with other algorithms in a database containing 207 images obtained from two different microscope slides and the results passed the positive predictive value (PPV) and True Positive Rate (TPR). The high value is displayed, resulting in a high measurement value of 96.15%.

In Apou et al. (2014), a fast segmentation method based on WSI is proposed. Due to the large size of the WSI, a set of horizontal and vertical optimal paths that follow the high gradient of the image are used to segment the image so that the relevant segmentation of the image is provided in an effective manner. Then other subsequent steps are executed.

In Zhang et al. (2015), a robust segmentation method is developed to accurately delineate ROI (e.g., cells) using hierarchical voting and repelling active contours. Its segmentation is based on active contours with repelling terms (Cohen 1991). The exclusion term is used to prevent the contour lines from intersecting and merging. Based on the detection result, the circle is associated with each detected cell as the initial contour. The final segmentation result is shown in Fig. 22.

![Fig. 22](image) Segmentation results of different methods on a randomly picked patch. From left to right: original image, level set and segmentation method in Zhang et al. (2015). This figure corresponds to Fig. 3 in Zhang et al. (2015)
In Li and Huang (2015), a new ROI search and segmentation algorithm based on superpixels is proposed. First, the initial recognition of the ROI is obtained by gathering superpixels at low magnification. Then, by marking the corresponding pixels, the superpixels are mapped to the higher magnification image. This process is repeated several times until the segmentation is stable. This method is different from the previous classic segmentation methods based on superpixels (Achanta et al. 2012; Yamaguchi et al. 2014). This algorithm provides image segmentation with topology preservation.

In Brieu et al. (2016), threshold processing is performed on the foreground posterior image to detect the foreground area, and spot detection algorithms such as MSER and

Fig. 23 The schematic diagram after segmentation is shown in the figure. Left: H&E (a)–(b), IHC-nuclei (c), and CD8 (d) regions; center: posterior maps for marked nuclei and cells (blue channel if applicable), for homogeneous nuclei (red channel) and for textured nuclei (green channel); right: outline of the segmentation result. This figure corresponds to Fig. 3 in Brieu et al. (2016)
Gaussian differences are used further to identify the brightness of the image. According to the classification function combining suitable candidate parameters is selected. The remaining area is further divided by calculating the minimum path of the posterior mapping between the concave points and checking the goodness of fit of the candidate area in turn. The schematic diagram after segmentation is shown in Fig. 23.

4.4 Analysis of segmentation applications in WSI

According to the various segmentation methods reviewed in Sects. 4.1, 4.2, and 4.3, we can analyze that most of them use deep learning algorithms. Because of the different data-sets used in each effort, it is impossible to evaluate each segmentation method’s effectiveness vertically. The use of multi-resolution U-net architecture is undoubtedly a common one, as shown in Fig. 24.

Its U-shaped structure and its skip-connection are its structural characteristics. The U-shaped structure can be used to extract deep features by down-sampling and down-dimension reduction, and then up-sampling to obtain more accurate output images. This kind of end-to-end network can achieve good results in medical image segmentation. There is another multi-resolution encoder-decoder network for breast cancer segmentation (Mehta et al. 2018), which is similar to the U-net method. However, the U-net structure can only be predicted on a single scale, so it cannot cope with scale changes well. Moreover, training does not have a good generalization ability when the convolutional layer is increased (Du et al. 2020). Breast cancer is the most commonly used (Dong et al. 2018; Mehta et al. 2018; Apou et al. 2014; Veta et al. 2013b, 2012; Roullier et al. 2010a, b; Seth 2019; Seth et al. 2019) tasks in segmenting WSI.

4.5 Potential methods for segmentation applied to WSI analysis technique

Some segmentation methods are worth noting in other fields and can be tried with WSI for CAD.

In Sun et al. (2020), the cancer nest information in the gastric image is automatically located. The proposed method is a segmentation based on the hierarchical conditional random field (CRF). Because CRF can represent spatial information, it can refine the edges of the segmented image. In this way, CRF can be used as an image post-processing step, which improves the overall segmentation performance. Similarly, in Zhang et al. (2020), CRF is also applied to the segmentation of environmental microbial images. So we can also apply it to the WSI analysis technique.
In Galvão et al. (2020), a faster image segmentation method than the superpixel method is proposed. This method can be separated into two strategies: dense and sparse. The intensive strategy is a new method. This method can achieve excellent boundary compliance by exploring alternative intermediate segmentation strategies. Therefore, the performance of hierarchical segmentation is improved. However, here it is applied to natural images. We can also try to apply it to the WSI analysis technique. Because the boundaries of natural images are obvious, the hierarchical segmentation method can achieve high-precision segmentation. We can also try to apply this method to WSI images, and adjust the method according to the characteristics of histopathological images.

In Cui et al. (2020), a method of automatically segmenting coronary arteries is proposed. The method is based on the growth algorithm. Firstly, the initial growth point is located by using a 2-D U-net, and then a new growth algorithm combined with a 3-D triangulation network is proposed. According to the new algorithm and 3-D U-net to complete the segmentation. This method uses residual structure and two-stage training. This method is hopefully extended to the WSI datasets. This method uses residual structure and two-stage training, and is rarely used for histopathological images. This method is expected to be extended to the WSI dataset, and it will be a novel method for the segmentation of histopathological images.

4.6 Summary

As can be seen from the content we have reviewed above, machine learning is used in combination with the WSI analysis technique to assist diagnosis. In the field of image segmentation, popular methods include thresholding-based segmentation, region-based segmentation, graph-based segmentation, clustering-based segmentation, deep learning-based segmentation and other segmentation methods.

The graph-based segmentation method is a very classical algorithm, and later many algorithms are developed based on this method. Thresholding-based segmentation methods are often used in WSI in combination with the watershed algorithm in region-based segmentation methods. Among the papers we reviewed, three of them use both methods at the same time. Then clustering-based segmentation methods and some other segmentation methods are appeared to be used. Beginning in 2017, deep learning-based methods starts to apply in segmentation and appear in the research of WSI segmentation. Among them, the U-net architecture based on the multi-resolution method gained popularity. Table 5 is a summary of the CAD method for segmentation technique in WSI.

5 Classification methods

Image classification has a fixed set of classification labels and assigns the classification label to the input image. It is at the heart of computer vision and is the most fundamental issue that forms the basis for other computer vision tasks such as positioning, detection, and segmentation (Rawat and Wang 2017; Karpathy and Fei-Fei 2015). It is widely used in practice.

In the analysis of histopathological images, the most studied task is CAD. It also helps the pathologist make a diagnosis. The diagnostic process is the task of mapping one or more WSIs to a disease category. Since errors produced by machine learning systems are
### Table 5 Summary of the CAD methods used for segmentation in WSI

| Method                  | Reference                  | Details                                                                                       |
|-------------------------|----------------------------|------------------------------------------------------------------------------------------------|
| Thresholding            | Kong et al. (2011)         | Simple threshold watershed method                                                             |
| Thresholding            | Lu and Mandal (2012)       | OTSU threshold                                                                                 |
| Thresholding            | Shu et al. (2013)          | Automatic threshold method (foreground and background classification), region growth, watershed segmentation (seriously clustered overlapping cores for segmentation) |
| Thresholding            | Vo et al. (2016)           | Parallelization of image segmentation based on MapReduce                                        |
| Thresholding            | Arunachalam et al. (2017)  | The combination of pixel-based and object-based methods (k-means and non-tumor images, and multi-level OTSU threshold segmentation) |
| Region-based (Watered)  | Kong et al. (2011)         | Simple threshold watershed method                                                             |
| Region-based (Watered)  | Veta et al. (2012)         | Watershed segmentation controlled by multi-scale markers                                        |
| Region-based (Watered)  | Veta et al. (2013b)        | Marker-controlled watershed segmentation, with multiple scales and different markers (automatic nuclear segmentation) |
| Region-based (Watered)  | Shu et al. (2013)          | Automatic threshold method (foreground and background classification), region growth, watershed segmentation (seriously clustered overlapping cores for segmentation) |
| Region-based (Watered)  | Vo et al. (2016)           | TCGA Parallelization of Image Segmentation Based on MapReduce                                  |
| Region-based (Watered)  | Vo et al. (2019)           | TCGA Core segmentation (MapReduce architecture)                                               |
| Region-based (Region growing) | Shu et al. (2013) | Automatic threshold method (foreground and background classification), region growth, watershed segmentation (seriously clustered overlapping cores for segmentation) |
| Graph-based             | Roullier et al. (2010b)    | Integrates graph-based segmentation (discrete semi-supervised clustering) and multi-resolution segmentation (cluster space refinement) |
| Graph-based             | Roullier et al. (2010a)    | Integrates graph-based segmentation (discrete semi-supervised clustering) and multi-resolution segmentation (cluster space refinement) |
| Graph-based             | Roullier et al. (2011)     | Multi-resolution segmentation method (regularization framework, histogram construction, histogram 3 mean clustering, partition and spatial refinement) |
| Clustering              | Hiary et al. (2013)        | k-means clustering                                                                             |
| Clustering              | Arunachalam et al. (2017)  | The combination of pixel-based and object-based methods (k-means and multi-level OTSU threshold) |
| Deep Learning           | Bándi et al. (2017)        | Using FCN and U-net to organize background segmentation                                          |
| Method          | Reference                          | data       | Details                                                                 |
|-----------------|------------------------------------|------------|-------------------------------------------------------------------------|
| Deep Learning   | Xu et al. (2017)                    | MICCAI 2014| SVM-CNN                                                                 |
| Deep Learning   | Dong et al. (2018)                  | \          | High-resolution image semantic segmentation framework-Reinforced Auto-Zoom Net (RAZN) (FCN) |
| Deep Learning   | Cui et al. (2019)                   | \          | Supervised FCN method for nuclear segmentation in histopathological images |
| Deep Learning   | Sirinukunwattana et al. (2018)      | \          | Combining multiple CNNs of different scales with LSTM                   |
| Deep Learning   | Mehta et al. (2018)                 | \          | Multi-resolution encoder-decoder network semantic segmentation          |
| Deep Learning   | Vo et al. (2019)                    | \          | Core segmentation (MapReduce architecture)                              |
| Deep Learning   | Seth (2019)                         | \          | Multi-resolution U-net architecture                                     |
| Deep Learning   | Seth et al. (2019)                  | \          | Multi-resolution U-net architecture                                     |
| Deep Learning   | Feng et al. (2020)                  | MICCAI 2019| Multi-resolution seven-layer pyramid U-net                               |
| Other           | Bergmeir et al. (2012)              | \          | Random Hough transform ellipse fitting cell nucleus to segment the nucleus (level set algorithm) |
| Other           | Apou et al. (2014)                  | \          | The path calculation in the horizontal and vertical strips              |
| Other           | Zhang et al. (2015)                 | TCGA       | (Robust segmentation method) Use Euclidean distance. Based on active contours with repelling terms |
| Other           | Li and Huang (2015)                 | NLST       | The superpixels are clustered at low magnification to obtain ROI. Then, the superpixels are mapped to the higher magnification image. This process is repeated several times. |
| Other           | Brieu et al. (2016)                 | \          | It is further divided by calculating the minimum path of the posterior mapping between the concave points and checking the goodness of fit of the candidate area in turn |
different from those produced by human pathologists (Wang et al. 2016), the use of CAD systems can improve classification accuracy (Komura and Ishikawa 2018).

In recent years, due to the progress of computer techniques, histopathological image classification has gradually become a research hotspot in the field of medical image processing. This is of great significance to the further diagnosis of doctors and the further treatment of patients.

In the papers we summarized, there are around 54 articles from 2004 to 2020 on image classification using WSI techniques to assist pathologists in diagnosis. We can see from the development trend in Fig. 2 that the application of classification has increased. This reflects the wide application of classification techniques. From these papers, we can briefly summarize the classification methods they applied including traditional machine learning algorithms, deep learning algorithms, and other methods.

5.1 Traditional machine learning based classification method

Among the papers we reviewed, 18 papers involve the classification of WSI by using traditional machine learning algorithms for CAD.

**SVM-based Classification Method** SVM is a supervised machine learning technique. In 1963, Vladimir N. Vapnik and Alexander Y. Lerner first published (Vapnik and Lerner 1963). It uses hypothesis space of linear function in the hyperspace (Roweis and Saul 2000) and uses the learning algorithm of the optimization theory for training. The purpose of SVM classification is to find an effective calculation method to learn a better separation hyperplane in the hyperspace (Kumar et al. 2012). It is generally used for two classifications. When the designed task is multi-classification, it can also be separated into multiple two-classification tasks (Kamath et al. 2018; Madzarov et al. 2009). In our review, there are a total of nine papers (DiFranco et al. 2011; Nayak et al. 2013; Jiao et al. 2013; Lu and Mandal 2015; Weingant et al. 2015; Peikari et al. 2015; Gadermayr et al. 2016; Shukla et al. 2017; Xu et al. 2018) related to the use of SVM for WSI classification.

In the work of Xu et al. (2018) and Lu and Mandal (2015), WSI is used for skin diagnosis and analysis of melanoma. Both papers use multi-class SVM classifiers to classify skin tissue features. In the end, an accuracy of rate more than 90.00% is obtained in the classification of melanoma and normal skin.

In the paper (Jiao et al. 2013), texture features are extracted and SVM is used to classify whether it is colorectal cancer. In the end, an accuracy rate of 96.67% is obtained. In the paper (Peikari et al. 2015), texture features are also used to classify clinically important areas. In Shukla et al. (2017), sentinel lymph nodes WSI uses SVM to predict the presence of cancer. Its characteristic lies in the use of 50 support vectors to establish a fuzzy rule-based model (FRBS) to improve the interpretability of the method. The final accuracy rate of FRBS is 91.89%. In Gadermayr et al. (2016), SVM is used to propose a domain adaptive method to improve the generalization ability of the kidney WSI classification model.

**Random Forest-based Classification Method** Random Forest (RF) is a popular machine learning algorithm, which is often used for classification tasks in various fields (Cutler et al. 2007; Ghimire et al. 2010; Gislason et al. 2006; Guo et al. 2011; Chen and Liu 2005; Özçift 2011; Seera and Lim 2014; Titapiccolo et al. 2013). RF is a collection of tree structure classifiers (Breiman 2001). Each tree in the forest votes once and assigns each input to the most probable category label. This method has strong robustness and a fast response to noise and is a successful integration method for identifying non-linear patterns in data.
It can easily handle numerical and categorical data (Titapiccolo et al. 2013). Among the papers we summarized, five papers (Homeyer et al. 2013; Sharma et al. 2016; Wang et al. 2016; Jamaluddin et al. 2017; Klimov et al. 2019) mainly use RF classifiers for related WSI classification.

In Homeyer et al. (2013), it is mainly to quantify the necrotic part of histological WSIs. After the feature classification, the misclassified isolated blocks are post-processed. It can be seen from the experimental results that the result of the RF classifier is the best among post-processing classifiers. Necrosis is identified as an important prognostic marker for survival in a variety of tumors, so this method can be applied to a variety of cancers. But the paper does not indicate what type of WSI is used in the experiment. In Sharma et al. (2016), gastric WSI is classified into cancer, and the traditional method and deep learning methods are quantitatively compared. The traditional method uses an RF classifier. In Wang et al. (2016), based on generating a heat map, the RF classifier is used to classify metastatic breast cancer, and the final AUC is 92.50%. In Jamaluddin et al. (2017), the CNN model is the first used to segment the tumor area of lymph node tissue, and then the RF classifier is used to classify the tumor. Finally, an AUC score of 94.00% is obtained. In Klimov et al. (2019), the recurrence risk of DCIS is classified, the extracted texture features are input into RF classifier, and the 10-year recurrence risk is finally predicted.

**Others Traditional Machine Learning Classification Method**

In addition to the two commonly used classification methods, SVM and RF, some other methods are also used for histopathological WSI classification, such as Bayesian classifier (Domingos and Pazzani 1997) and $k$-Nearest Neighbor ($k$-NN) (Hastie and Tibshirani 1996) classifier.

In Sertel et al. (2008, 2009b); Kong et al. (2009), neuroblastoma WSIs are graded. Among them, Sertel et al. (2008, 2009b) use the multi-resolution Gaussian pyramid method for parallel processing and use sequential floating forward selection (SFFS) to select features, and finally through $k$-NN classification. Experimental results show that the overall classification accuracy rate is 95.00%, and the amount of calculation is reduced by 60.00%. In Kong et al. (2009), weighted voting of multiple classifiers is used to select the output of neuroblastoma WSI classification results. In the end, the classification accuracy rate reaches 87.88%. In Doyle et al. (2010), the multi-resolution Gaussian pyramid method is also used to process the prostate cancer area in WSIs. Here, the AdaBoost ensemble method is used to select 10 image features and classify them. According to experiments, the Bayesian classifier has higher AUC and accuracy.

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![Fig. 25](image)

**Fig. 25** Categorization of papers in this section by medical application field
5.2 Deep learning based classification method

This subsection is separated into six parts according to the medical application field. They are classified based on breast cancer, prostate cancer, colon disease, gastric cancer, and other diseases. The summarized bar graph is shown in Fig. 25.

5.2.1 Classification methods based on breast cancer

In Geçer (2016) and Gecer et al. (2018), deep convolutional networks are used to detect and classify WSIs ROI in breast cancer. The detection part is described in detail in Sect. 6. In this part, the classification is mainly introduced, that is, the ROI includes five diagnostic categories. The classifier is designed based on CNN, which uses the features learned by CNN to classify the detected ROI. The CNN structure diagram designed is shown in Fig. 26. Then the post-processing of WSI classification is carried out. WSIs are classified according to the prediction of most categories in the remaining cancer areas. The results show that the efficiency is improved by about 6.6 times with sufficient accuracy.

Araújo et al. (2017) are to classify breast biopsy WSI. The method used is the CNN architecture, which can retrieve information of different scales. First, the image is separated into 12 non-overlapping patches, and then CNN and CNN with SVM are respectively used in combination with these two classifiers to calculate the patch-level image classification probability. Finally, the classification probability obtained at patch-level is fused to obtain the classification result at image-level. There are three probability fusion methods, which are majority voting (select the most common patch as the image label), maximum probability (select the patch category with high probability as the image label), and probability (the category with the largest sum of patch-level probability). Finally, the tumor is separated into four types: normal tissue, benign tumor, carcinoma in situ, and invasive cancer. The overall sensitivity of classification is 81%.

The task in Bejnordi et al. (2017b) is to classify histopathological WSI into normal tissue, benign tumor, DCIS, and invasive ductal carcinoma (IDC). The method used is a context-aware stacked CNN. The first CNN is pre-trained and high pixel resolution is used to get cell-level features. The features are entered into the second CNN. Then the two used CNNs are stacked together. The AUC of the binary classification of the whole model for non-malignant and malignant slides is 0.962, and the three-level accuracy of the normal/benign classification of DCIS and IDC is 81.3%.

In Mercan et al. (2017), a weakly supervised method for multi-classification of breast histopathology WSIs is proposed. Firstly, ROI is extracted by zooming, translation, and
fixation. Then, the color and texture information and structural features are extracted in CIE-LAB space. Next, four different multi-instance multi-label (MIML) learning algorithms are used to predict the slide-level and ROI levels in the image. The result is an average classification accuracy of 78% at slide-level 5-Class.

The author of Das et al. (2018) proposes a multiple instance learning (MIL) framework. This framework is based on CNN to classify breast cancer WSI model. To integrate more features in this network framework, a new pooling layer is introduced to achieve better classification results. Under the four magnifications, the classification accuracy of the obtained public datasets is 93.87%, 95.81%, 93.17%, and 88.95%.

5.2.2 Classification methods based on prostate cancer

Ren et al. (2018a) use an unsupervised domain adaptive method to classify prostate histopathology WSI. The unsupervised domain used is to minimize the difference in the distribution of the feature spaces of the two domains. These two domains are labeled source domain and unlabeled target domain. The loss function uses a Generative Adversarial Network (GAN). In this method, a Siamese architecture is still used to standardize the patch of WSIs. The flowchart of this method is shown in Fig. 27. The application of this method to public prostate cancer datasets shows that the classification accuracy of the Gleason score is significantly improved.

The study in Campanella et al. (2018) is also based on the MIL classification for prostate cancer. Slide tiling is the first run at different magnification and its bags are generated. Then, model training is carried out to find the tiling with the highest positive and negative probability in the slide, which is used to give more importance to the under-representative examples. Based on AlexNet, ResNet, VGG classification, given a threshold, if at least one instance is positive, then the WSI is called positive and the slide is negative if all instances are negative. The optimal models are ResNet34 and VGG11-BN, with AUC of 0.976 and 0.977, respectively. The method of Campanella et al. (2019) is roughly the same as that of Campanella et al. (2018).

![Flowchart of the unsupervised domain adaptation method](image)

**Fig. 27** The architecture of the networks for the unsupervised domain adaptation. This figure corresponds to Fig. 1 in Ren et al. (2018a)
In Li et al. (2019b), a multi-resolution classification of prostate WSIs based on attention mechanism is performed. The MIL model based on attention is used to extract transient features. The overall process is separated into two parts. The first part is to classify cancer and non-cancer, using attention-based clustering tile selection. The second part is to conduct cancer classification research with higher resolution. Finally, an average classification accuracy rate of 85.11% is obtained, and the new performance of prostate cancer classification is realized.

5.2.3 Classification methods based on colon disease

In Sirinukunwattana et al. (2016), the cell nucleus is detected and classified. The detection part is introduced in detail in Sect. 6. The main method is to use CNN to detect the space-constrained core. In the classification part, CNN is used in combination with a new NEP. Finally, the whole process method proposed is applied to colorectal adenocarcinoma WSIs, and a higher classification F1 score is obtained. The final result of detection and classification is shown in Fig. 28.

In Korbar et al. (2017a), different types of colorectal polyps on WSI are classified. First, the WSI is separated into small patches, and then the improved version of ResNet is used for classification. If at least 5 patches are classified into a certain category on WSI, they will be recognized as that category. If there is no cancer type in the patches, then WSI is considered normal. The final experimental results show that the accuracy rate is 93.0%. The recall rate is 88.3%. The F1 score is 88.8%.

In Morkūnas et al. (2018), WSI colorectal cancer tumor tissue is classified. The simple linear iterative clustering (SLIC) algorithm is proposed by Achanta et al. (2012) is mainly applied to generate superpixels, and superpixels are used to annotate the image. Therefore, the selected area is divided into superpixels. Then, color and texture features are extracted.
and dimensionality reduction is used to regenerate composite features. Experiment shows that the superpixel method is suitable for using different classification algorithms based on machine learning.

5.2.4 Classification methods based on gastric cancer

In Sharma et al. (2017), gastric cancer WSI is automatically classified. The traditional image analysis method and deep learning method are proposed and compared quantitatively. In the traditional analysis method, GLCM, Gabor filter bank response, LBP histogram, gray level histogram, HSV histogram, and RGB histogram are used for classification and RF. In terms of the deep learning method, AlexNet is proposed as a deep convolution framework. The structure of the network is shown in Fig. 29. According to the experiment, the overall classification accuracy of the cancer classification proposed by AlexNet is 0.6990, and the overall classification accuracy of necrosis detection is 0.8144.

Shou et al. (2018) are to classify gastric cancer in WSI. First, the tissue extraction is performed based on the threshold difference and the color difference. After the processed image is segmented into patches, the expanded data is obtained by data inversion. And then, DenseNet-201 is used to conduct experiments on patch-level and slide-level respectively, and good experimental results are obtained.
In Wang et al. (2019b), a method named Recalibrated Multi-instance Deep Learning (RMDL) is proposed to classify WSI gastric cancer images. The method of MIL is also used in the process of classification, which is similar to the MIL method. The whole process is separated into two stages. Firstly, the localization network is trained to select different instances, and then RMDL is used for image-level label prediction. The network consists of local-global feature fusion, instance re-calibration, and multi-instance pool. The specific workflow is shown in Fig. 30.

### 5.2.5 Classification methods based on other disease entities

In Arevalo et al. (2015), basal cell carcinoma WSIs are studied as an integrated unsupervised characteristic. First, a set of feature detectors are learned from a set of patches randomly sampled in the image set. The detectors can capture the most common patterns by simulating the automatic encoder neural network. The image is then represented using the convolution or Bag-of-Features (BOF) method. This representation is achieved using the feature detector learned in the previous step. Next, the representation obtained from the convolution or BOF method to train the binary classification model, the softmax regression classifier. Basal cell carcinoma includes different categories of cancer and non-cancer carcinoma. The final result of the system is shown in Fig. 31. The best results in AUC are obtained, which are superior to the most advanced 7% and 98.1%.

In Barker et al. (2016), brain tumor types in WSIs are automatically classified. The main method is to analyze local features from coarse to fine in histopathological images. Firstly, the diversity of rough areas in WSIs is analyzed, including the spatial local characteristics of shape, color, and texture of WSIs. Then the clustering-based method is used to create the representative group. The individual representative tiles in each group are then concretely analyzed. An Elastic Net classifier produces the diagnostic decision value for tile to obtain the WSI level diagnosis. Finally, 302 cases of brain cancer included automatically two possible diagnoses (glioblastoma multiforme (182 cases) and glioblastoma low grade (120 cases)) to evaluate the method with an accuracy rate of 93.1% ($P \ll 0.001$).

| True class | Cancer | Cancer | Cancer | Non-cancer | Non-cancer | Non-cancer |
|------------|--------|--------|--------|------------|------------|------------|
| Input image | ![Image](image1.png) | ![Image](image2.png) | ![Image](image3.png) | ![Image](image4.png) | ![Image](image5.png) | ![Image](image6.png) |
| Prediction | Cancer | Cancer | Cancer | Non-cancer | Non-cancer | Non-cancer |
| Probability | 0.901 | 0.925 | 0.672 | 0.083 | 0.147 | 0.460 |
| Digital staining | ![Image](image7.png) | ![Image](image8.png) | ![Image](image9.png) | ![Image](image10.png) | ![Image](image11.png) | ![Image](image12.png) |

*Fig. 31* Outputs produced by the system for different cancer and non-cancer input images (red stain indicates cancer regions, blue stain indicates normal regions). This figure corresponds to Table 2 in Arevalo et al. (2015)
In Hou et al. (2016), an expectation-maximization method is proposed. The spatial relationship of patches is used to locate the distinguished patches robustly. This method is applied to the subtype classification of glioma and non-small cell lung cancer. The classification module uses patch-level CNN and trains a decision fusion model as a two-level model. The first level (patch-level) model is based on expectation maximization, combined with CNN output patch-level prediction. In the second level (image-level), the patch-level predicted histogram is input to the image-level multiple logistic regression or SVM.

In Korbar et al. (2017b), an image analysis method based on deep learning is proposed to classify different polyp types on WSIs. This classification model is based on the ResNet architecture, with minor modifications to the architecture. Specifically, the last fully connected layer is replaced by a convolution layer. Finally, the average accuracy rate is 91.3%, which is better than other deep learning architectures.

In Courtiol et al. (2018), a detection method to classify and locate weak diseases is proposed. Firstly, background separation, color normalization, and other pretreatments are carried out for WSIs. These are then segmented into patches. The segmented patches are fed into ResNet to extract features, which are then refined and adjusted using the Weakly Supervised Learning of Deep Convolutional Neural Networks (WELDON) method proposed by Durand et al. (2016). At the same time, an additional set of fully connected layers is introduced that can be used to reclassify the context from the instance. After this series of operations, the final classification result is obtained. The classification result is shown in Fig. 32.

In Wang et al. (2018), a weakly supervised learning approach is used to classify WSI lung cancer. Firstly, the improved FCN based on patch-level from WSI is used for cancer prediction to find the different regions as the prediction model of patch-level. When the probability of a block exceeds the threshold, it is retrieved. Then, context-based feature selection and aggregation from the retrieved parts are performed to construct the global feature descriptor. Finally, the global feature descriptor is input into the standard RF classifier. Finally, a high classification accuracy of 97.1% is obtained.

A new dataset is proposed in Babaie et al. (2017), named Kimia Path24. This dataset is mainly used for the classification and retrieval of digital histopathology images.

**Fig. 32** The classification result of the proposed method in Camelyon16 dataset. This figure corresponds to Fig. 4 in Courtiol et al. (2018)
dataset scans various parts of the body and selects 24 WSIs with different textures to test the patch. In this paper, LBP histogram, bag-of-words approach, and CNN are used to classify patch-level images.

In Hu et al. (2017), a DNN (an 11-layer CNN model) is trained to automatically learn valid features and classify protein images of eight subcellular locations. First, image preprocessing and data balance are carried out. Then, the processed data is passed through the 11-layers of the CNN model. Details of the structure are shown in Fig. 33. Finally, the classification accuracy rate reached 47.31% in the test data and 100% in the training data.

In Xu et al. (2017), a deep CNN is proposed to conduct large-scale histopathological image classification, segmentation, and visualization. In the part of the classification, WSI is first divided into patches, and the background is discarded, and then the selected patches are input into the network to obtain 4096-dimensional CNN feature vectors. The final feature vectors of the image are assembled through softmax. Then feature selection is carried out to remove redundant and irrelevant features. Finally, SVM is used for classification. When using the MICCAI challenge dataset, the classification accuracy is 97.5%.

The author of Ghosh et al. (2017) classifies white blood cells of WSIs. The method is a deep learning network based on CNN. The network first uses the average pool level to find the location of white blood cells in WSI. Then the pre-trained AlexNet is fine-tuned.
according to the dataset used. Finally, the adjusted network is used on the patch-level dataset. The trained network structure is shown in Fig. 34.

Das et al. (2017) propose a method combining multi-resolution and CNN to classify WSI tissue slices. Firstly, the class posterior estimation of each view at a specific magnification is obtained from CNN, and then the class posterior estimation of random multiple views at a specific magnification is filtered by voting to provide image-level classification results. According to the experimental results, the final classification accuracy is $94.67 \pm 14.60\%$, sensitivity is $96.00 \pm 8.94\%$, specificity is $92.00 \pm 17.85\%$, and $F$-score of $96.24 \pm 5.29\%$.

In Tellez et al. (2018b), a deep learning algorithm is proposed to classify WSI. The method is separated into two parts. Firstly, the unsupervised method is used to train the encoder. The organization block on WSI is mapped to the embedding vector, and the sliding window is used to form the stack of WSI feature mapping. Secondly, the CNN classifier is trained based on WSIs compact representation. Three types of encoders are trained: convolutional automatic encoder (CAE), variational automatic encoder (VAE), and a new method based on contrast training. Experiments show that the new contrast encoder is better than CAE and VAE.

### 5.3 Other classification methods

Among the papers we have reviewed, seven papers are based on classification (Diamond et al. 2004; Harder et al. 2016; Petushi et al. 2006; Sertel et al. 2009a; Yeh et al. 2014; Yoshida et al. 2017, 2018), and they involve techniques related to machine learning.

In Diamond et al. (2004), a machine vision system is developed, which uses its morphological features and texture analysis to classify the sub-regions in WSIs. However, it focuses on the application of features and does not introduce the classification part of the machine vision system in detail. Experimental results show that 79.3% of WSI sub-regions are correctly classified. This also illustrates the effectiveness of the system in small scenarios to a certain extent. The study in Harder et al. (2016) also does not make a special description of the classifier, but only focused on the features. The proposed feature is superior to clinical features, achieving a classification accuracy of 70%.

In Petushi et al. (2006), the LNKnet software package is used to classify breast cancer WSIs. LNKnet integrates neural networks, statistical and machine learning classification, clustering, and feature selection algorithms into a modular package. The software correctly identified spots caused by staining and other artifacts as non-nuclei in 250 times and the accuracy is 95.6%.

In Sertel et al. (2009a), a classification framework is proposed to classify the degree of neuroblastoma differentiation. The main point here is that a new method of structuring structural features is introduced, and its classification method is also based on probability, namely mapping decision rules. 34 independent WSIs are used to evaluate the framework, and classification accuracy is 94.1%.

In Yeh et al. (2014), pixel-based stain classification is carried out to classify the IHC stain, mainly using the nearest neighbor and morphological methods. Then, the density distribution of the identified IHC stains is calculated by the kernel density estimator. After that, the staining distribution on WSI is obtained. The IHC WSIs used in the experiment is obtained by labeling the ED1+ macrophages in the tissue section and digitizing the stained glass slide with a whole-slide scanner. After analysis, the correlation coefficient between the number of IHC
stains counted by the stain recognition algorithm and the manual count is 0.8961, results are in good agreement. It has a positive effect on assisting clinical diagnosis.

Both Yoshida et al. (2017) and Yoshida et al. (2018) are used to evaluate the classification accuracy of an automated image analysis system, E-pathologist. Among them, (Yoshida et al. 2017) is for colorectal biopsy, and E-pathologist classification accuracy is as high as 90%. (Yoshida et al. 2018) is for gastric biopsy. The detection sensitivity of E-pathologist is 90%.

The seven papers Diamond et al. (2004), Harder et al. (2016), Petushi et al. (2006), Sertel et al. (2009a), Yeh et al. (2014), Yoshida et al. (2017, 2018) all create software or design a machine vision system for WSI classification. These systems are different from the previous networks and cannot adjust parameters, so there are some limitations in the application of the clinical environment, and the accuracy rate needs to be improved. However, its work efficiency is improved compared to networks, and it can reduce the workload of pathologists. There is a high potential in the realization of automatic screening.

5.4 Analysis of classification methods in WSI

According to the review of classification applications of WSI in CAD, it can be seen that SVM is the most frequently used technique in traditional machine learning. However, basic SVM cannot achieve excellent classification results. For example, in Nayak et al. (2013), multi-class regularized SVM is used to classify tumors, and the accuracy rate is only 84%. In Peikari et al. (2015), the RBFSVM is used for classification, and only 0.87 AUC is obtained. However, if SVM is combined with SVM of other kernel functions or other kinds of classifiers to train ensemble learning classifiers, the results will be highly improved. For example, in DiFranco et al. (2011), the AUC of prostate cancer is 0.95 when it is classified. However, this ensemble learning method has low efficiency, slow running speed, and requires a large number of parameters. For some more complex tasks, a large number of calculations are needed (Weihua 2013).

In the traditional machine learning algorithm, the Gaussian pyramid method is also commonly combined with k-NN to improve classification accuracy (Goceri et al. 2017). The Gaussian pyramid is based on simple down-sampling plus Gaussian filtering. The original image is continuously sampled by decreasing order, and a series of images of different sizes are obtained, from large to small, from bottom to top, to form a tower model. In this way, images of different resolutions can be obtained, thus improving the accuracy of classification. For example, in Sertel et al. (2008), the improved k-NN combined with the Gaussian pyramid is used to classify neuroblastoma, and the classification accuracy of 95% is obtained. However, in the classification problem of unbalanced datasets, the defects of k-NN are obvious. Due to the influence of sample distribution, the minority class will be more biased towards the majority class discrimination (Li and Zhang 2011).

In the deep learning classification algorithm, most of them are based on CNN. CNN is better than traditional machine learning methods in processing high-dimensional data, and because of the convolutional layer, it can automatically extract features for learning. In recent years, MIL and neural networks are often used to carry out classification tasks for medical WSIs. For example (Mercan et al. 2017; Das et al. 2018; Campanella et al. 2018, 2019; Wang et al. 2019b). MIL is a learning problem with multiple example packages as training units. A bag is marked as a positive-class multi-example package if it contains at least one positive instance. Conversely, the negative example is also true. The multi-example learning method can effectively reduce the noise and improve the classification accuracy of the prediction. In Campanella et al. (2018, 2019), the AUC of its classification
is 0.98. However, the CNN-based neural network is an end-to-end architecture, similar to a black box, which is weak in interpretation (Zhang 2013). The popular methods in classification for WSIs are as shown in Fig. 35.

In the task of WSIs classification, the classification of breast cancer (Peikari et al. 2015; Wang et al. 2016; Gecer 2016; Araújo et al. 2017; Bejnordi et al. 2017b; Gecer et al. 2018; Kwok 2018; Das et al. 2018), prostate cancer (DiFranco et al. 2011; Doyle et al. 2010; Li et al. 2019b; Weingant et al. 2015; Ren et al. 2018a), and colon cancer (Jiao et al. 2013; Sirinukunwattana et al. 2016; Morkūnas et al. 2018; Korbar et al. 2017a) is commonly used. Gastric cancer (Sharma et al. 2016, 2017; Shou et al. 2018), neuroblastoma (Sertel et al. 2008; Kong et al. 2009), and melanocytic tumor on the skin (Lu and Mandal 2015; Xu et al. 2018) have also been studied.

5.5 Potential methods for classification in WSI

The following is an introduction to some classification methods used in other fields, which can be used in WSI for CAD.

In Mu et al. (2020), a spectral-spatial classification algorithm based on spectral-spatial feature fusion of spatial coordinates is proposed to classify hyperspectral images. Active learning is introduced to improve performance. The method of combining spectral information with spatial information can solve noise interference. Although WSI does not have spectral information, deep active learning can select the most useful samples from unlabeled datasets, thereby reducing labeling costs as much as possible while maintaining performance.

In Devi et al. (2020), two new Privacy Supporting Binary Classifier Systems are proposed to classify the Magnetic Resonance Imaging (MRI) of the brain. It can effectively protect the privacy of patients. We can apply this approach to histopathological WSI. In this way, patient privacy can be protected to a certain extent in the field of histopathology.

In Li et al. (2019a), a Content-Based Microscopic Image Analysis (CBMIA) approach is proposed to classify microscopic images of microorganisms. This method is based on the computer semi-automatic or automatic method, so it is very effective and saves manpower and material resources. We can also apply this approach to medicine.

In Manyala et al. (2019), a CNN-based gender classification method for near-infrared periocular images is proposed. The first method is to use a neural network to extract features, and SVM is used for classification. The second method uses the CNN model...
obtained by fine-tuning VGG-Face for direct classification. We can learn that when using DCN in an application, the network can be built from scratch, pre-trained models can be used as off-the-shelf feature extractors or existing models can be fine-tuned. Therefore, we can also try to apply this method to WSI for image classification, which can achieve a balance between classification and computing performance.

5.6 Summary

From what we have summarized above, we can see that the combination of CAD and WSI analysis techniques are used for classification, including traditional machine learning methods, deep learning methods, and some other methods.

In traditional machine learning algorithms, the commonly used algorithms used in WSI classification are SVM and RF. There are other algorithms, such as k-NN. Since 2008, traditional machine learning algorithms have taken the mainstream position in WSI classification. In 2015, deep learning algorithms began to be widely used, obtaining classification results with higher accuracy than traditional machine learning algorithms. Among them, MIL has many applications. Table 6 is a summary of the CAD method of classification technique in WSI.

6 Detection methods

To completely understand an image, one should accurately estimate the objects’ concept and location in each image (Zhao et al. 2019). Detection determines whether one or more specific category instances exist in an image or not (Vedaldi et al. 2009). Detection can provide valuable information for various fields. For example, remote sensing image detection (Zhang et al. 2013) can provide useful information related to geology, meteorology, water conservancy, and face recognition (Hsu et al. 2002). It is widely used in military and public security criminal investigations, and biomedical image detection (Szczypański and Klepaczko 2017) makes it convenient for doctors in clinical diagnosis and histopathological research.

As one of the most common tasks for CAD to view WSI, the detection method has developed rapidly in recent years. It can be seen from Fig. 2 that the number of detection cases is increasing from 2009 to 2019, which reflects the development of detection techniques. Besides, the basic content of the CAD view WSI detection method is shown in Fig. 36. As shown in Fig. 36, all CAD WSI methods for disease detection can be roughly divided into three categories. The first category is traditional detection methods (such as SVM, image enhancement, etc.), the second category is an ensemble learning method, and the last category is the deep learning method.

6.1 Traditional detection method

In this part, we select the traditional detection methods that appear in papers and summarize these methods. The methods involved are detection based on SVM (Vapnik 1964),
| Method | Reference | Data | Details |
|--------|-----------|------|---------|
| T      | DiFranco et al. (2011) | \ | RF, linear SVMs, RBFSVMs are used to classify a collection of 19 B * channel features |
| T      | Nayak et al. (2013) | TCGA | Multi-class regularized SVM classification with regularized parameters 1 and 3 polynomial kernels |
| T      | Jiao et al. (2013) | \ | SVM |
| T      | Lu and Mandal (2015) | \ | SVM |
| T      | Weingant et al. (2015) | \ | RF feature selection, class balance training sample subsampling and SVM classification |
| T      | Peikari et al. (2015) | \ | An SVM with a RBF kernel |
| T      | Gadermayr et al. (2016) | \ | The efficient linear C-SVM |
| T      | Shukla et al. (2017) | Camelyon 16 | SVM |
| T      | Xu et al. (2018) | \ | MSVM |
| T      | Homeyer et al. (2013) | \ | Naive Bayes classifier, k-NN classifier, RF classifier |
| T      | Sharma et al. (2016) | \ | RF |
| T      | Wang et al. (2016) | Camelyon 16 | The post processing uses the RF classifier for classification |
| T      | Jamaluddin et al. (2017) | Camelyon 16 | RF |
| T      | Klimov et al. (2019) | \ | RF |
| T      | Sertel et al. (2008) | \ | A multi-resolution classification system is developed based on the improved k-NN classifier |
| T      | Sertel et al. (2009b) | \ | Multi-resolution decomposition of training images is performed by Gaussian pyramid method, and improved k-NN |
| T      | Doyle et al. (2010) | \ | Strong Bayesian multi-resolution classifier |
| T      | Kong et al. (2009) | \ | A simple two-step classifier combination mechanism consisting of voting and weighting processes is chosen to aggregate the output of multiple classifiers. |
| DL     | Arevalo et al. (2015) | \ | Softmax, Linear-SVM |
| DL     | Barker et al. (2016) | TCGA | Elastic Net classifier |
| DL     | Geçer (2016) | \ | CNN |
| DL     | Sirinukunwattana et al. (2016) | \ | NEP is combined with CNN |
| DL     | Hou et al. (2016) | TCGA | CNN, EM algorithm, SVM |
| DL     | Babaie et al. (2017) | Kimia Path24 | Applied LBP, the dictionary approach and CNNs to classify patches |
| DL     | Araújo et al. (2017) | \ | CNN |
| Method | Reference            | Data                | Details                                                                 |
|--------|----------------------|---------------------|-------------------------------------------------------------------------|
| DL     | Bejnordi et al. (2017b) | \                  | Contextual Awareness Stacked CNN                                       |
| DL     | Sharma et al. (2017) | \                  | The AlexNet deep convolutional comparison with RF is made, and a CNN architecture is proposed |
| DL     | Korbar et al. (2017a) | \                  | ResNet                                                                  |
| DL     | Hu et al. (2017)     | HPA                 | CNN                                                                     |
| DL     | Xu et al. (2017)     | MICCAI 2014         | CNN                                                                     |
| DL     | Korbar et al. (2017b) | \                  | ResNet                                                                  |
| DL     | Ghosh et al. (2017)  | \                  | AlexNet                                                                 |
| DL     | Das et al. (2017)    | BreaKHis2           | CNN                                                                     |
| DL     | Ren et al. (2018a)   | TCGA                | Siamese neural network and GAN network                                 |
| DL     | Courtiol et al. (2018)| TCGA, Camelyon 16   | Modify the pre-trained DCN model to introduce an additional set of full connection layers for context reclassification from instances |
| DL     | Gecer et al. (2018)  | \                  | CNN                                                                     |
| DL     | Tellez et al. (2018b)| Camelyon 16         | CNN                                                                     |
| DL     | Morkūnas et al. (2018)| \              | CNN                                                                     |
| DL     | Kwok (2018)          | \                  | Inception-ResNet-v2                                                     |
| DL     | Mercan et al. (2017) | \                  | MIMIL framework                                                         |
| DL     | Das et al. (2018)    | BreaKHis1           | Based on VGG                                                            |
| DL     | Campanella et al. (2018)| \              | AlexNet, VGG11-BN, ResNet18, ResNet34 (MIL)                            |
| DL     | Wang et al. (2018)   | \                  | CNN (find discriminative region) RF (classification)                    |
| DL     | Shou et al. (2018)   | \                  | CNN                                                                     |
| DL     | Li et al. (2019b)    | \                  | Attention-based clustering and CNN                                      |
| DL     | Campanella et al. (2019)| \              | CNN RNN                                                                 |
| DL     | Wang et al. (2019b)  | \                  | New RMDL network                                                        |
| Others | Diamond et al. (2004)| \                  | A machine vision system is developed, but the emphasis is on the application of features |
| Others | Petushi et al. (2006)| \                  | LNKnet package                                                          |
| Others | Sertel et al. (2009a)| \                  | Classified according to the distance between classes and the distance between classes |
| Method | Reference         | Data | Details                                           |
|--------|-------------------|------|--------------------------------------------------|
| Others | Yeh et al. (2014) | \    | Classification to calculate IHC stain density distribution |
| Others | Harder et al. (2016) | \   | Emphasis is on the application of features       |
| Others | Yoshida et al. (2017) | \  | Compare human pathologist and E-Pathologist      |
| Others | Yoshida et al. (2018) | \  | E-Pathologist                                     |
RF (Breiman 2001), other traditional machine learning methods and non-machine learning methods.

SVMs are used in Jiao et al. (2013), Sharma et al. (2015a), Han et al. (2018), Simon et al. (2018), Swiderska et al. (2015b), Nguyen et al. (2011), but their applications are not the same. In Jiao et al. (2013), WSIs are used to detect colon cancer. Sharma et al. (2015a) are to detect the heterogeneity of WSI necrosis. Han et al. (2018) are to calculate the WSI tissue composition map. Simon et al. (2018) are to detect glomeruli by WSIs. In Swiderska et al. (2015b), the tumor proliferation area is detected and in Nguyen et al. (2011), RBF-SVM is used to detect prostate cancer.

Among the papers we summarized, papers related to RF are (Valkonen et al. 2017; Litjens et al. 2015; Bejnordi et al. 2016, 2015; Li and Huang 2015). These papers are based on the background simplification of WSI and the use of RF to detect cancer areas. Among them, Valkonen et al. (2017) use the watershed segmentation method, and Litjens et al. (2015) use the SLIC algorithm to calculate superpixels and remove the pixel background. The methods in Bejnordi et al. (2016) and Bejnordi et al. (2015) are similar to those in Litjens et al. (2015), both of which use multi-scale super-pixel methods to detect breast cancer. In Li and Huang (2015), the super-pixel method is also used to quickly detect the ROI in WSI.

There are also some traditional detection methods, such as decision tree (DT) classifier, clustering algorithm, linear discriminator, and machine learning organization classifier (Lopez et al. 2013, 2012; Veta et al. 2013a; Shirinifard et al. 2016). In Lopez et al. (2013), the multi-sharpness feature method is used to identify fuzzy areas on WSI, the obtained fuzzy features are detected using the DT classifier. In Lopez et al. (2012), a hybrid clustering method called Seedlink is used to improve the detection of hot spots in WSI. In Veta et al. (2013a), linear discrimination is used to detect mitosis. In Shirinifard et al. (2016), a tissue classifier based on machine learning is used to detect phenotypic changes in live tumor tissues and finally reaches an accuracy of 95.00%.

We find three papers using non-machine learning to perform WSI-related inspections for CAD. In Bautista and Yagi (2009) and Bautista and Yagi (2010), the motion operator is introduced to amplify the chromaticity difference between tissue folds and other tissue components to detect tissue folds in WSI. In Vyas et al. (2016), the effectiveness of WSI is verified by comparing WSI with traditional microscopes.
6.2 Deep learning based detection methods

In this subsection, the relevant content of using deep learning algorithms to detect histopathological images with WSI are briefly summarized.

6.2.1 CNN-based deep learning detection method

The following Zanjani et al. (2018), Cruz-Roa et al. (2017), Bejnordi et al. (2017a), Tellez et al. (2018a), Kohlberger et al. (2019), Jamaluddin et al. (2017), Cruz-Roa et al. (2014) are all detection classifiers based on CNN. In Zanjani et al. (2018), CRF and CNN are used for the classification and retrieval of breast cancer. First, WSIs are input into CNN to extract the compact feature. The fully connected domain CRF is then used to detect invasive breast cancer. The method is to take the compact feature as the observed value of CRF. The whole model is applied to the Camelyon17 ISBI challenge dataset, and second place is obtained with a kappa score of 0.8759.

In Cruz-Roa et al. (2017), involved images from five different cohorts from different institutions/ histopathology labs in the United States and TCGA. The training dataset has 349 estrogen receptor-positive (ER+) invasive breast cancer patients. The approach yielded a Dice-coefficient of 75.86%, a positive predictive value of 71.62% and a negative predictive value of 96.77% in terms of pixel-by-pixel evaluation compared to manually annotated regions of IDC.

The author of Bejnordi et al. (2017a) evaluates the performance of automated deep learning algorithms in detecting metastasis in lymph node H&E tissue sections of women with breast cancer and compares it with a diagnostic environment. The dataset is collected from 399 patients who underwent breast cancer surgery at the Radboud University Medical Center (RUMC) and Utrecht University Medical Center (UMCU) in the Netherlands. The algorithm in the paper is significantly better than the pathologist’s artificial algorithm.

In Tellez et al. (2018a), a CNN method is proposed for the detection of mitosis in breast cancer WSIs. In the three tasks challenged by Tupac, the performance of the method is independently evaluated.

In Kohlberger et al. (2019), an automatic focusing mass detector is developed. The detector is called ConFocus. It can accurately detect and quantify the out-of-focus (OOF) on WSIs. ConFocus achieves Spearman rank coefficients of 0.81 and 0.94 on both scanners compared to the focus quality of the pathology grade. It also allows the expected OOF pattern to be reproduced in the Z-stack scanning. The paper also evaluates the impact of OOF

![Fig. 37](image.png)

12 convolutional layer including the fully connected layer. This model was also inspired from VGG model

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on the accuracy of state-of-the-art metastatic breast cancer detectors and finds that as OOF increases, the performance continues to decline.

Jamaluddin et al. (2017) is separated into two parts: detection and classification. First, the possible tumor areas in WSI are detected by CNN. After the possible areas are detected, the second part is classified. The experiment uses the Camelyon16 dataset. There are 160 negative and 110 positive WSIs in the training set and 50 positive and 80 negative WSIs in the test set. Finally, the AUC value is 0.94. The overall network architecture is shown in Fig. 37.

In Cruz-Roa et al. (2014), a method using CNN to detect IDC in WSI is proposed. The overall detection process of this method is shown in the figure. The experimental result is that $F$-measure (F1) is 71.80% and the balance accuracy is 84.23%. The overall detection framework of (Cruz-Roa et al. 2014) is shown in Fig. 38.

### 6.2.2 FCN-based deep learning detection method

The following Geçer (2016), Gecer et al. (2018), Lin et al. (2018, 2019) are processed with 4-layers of FCN to achieve the purpose of detection.

The study in Geçer (2016) is composed of two tasks, retrieval and classification. The retrieval part is composed of four layers of FCN. Through the feedforward processing of FCN-1, the salient area is detected from WSI, and each connected component above the threshold is enlarged on the input image and processed by FCN-2. This process lasts four times, and a significant area of WSI can be detected. Then CNN classifies and finally determines the breast cancer diagnosis results.

The authors of Gecer et al. (2018) use a neural network to diagnose WSI in breast tissue. Firstly, ROI is extracted, and saliency detection and multi-scale localization are used as preparation. In this step, the fuzzy neural network is used. Then CNN is used to classify the processed images. Finally, the classification result graph is combined with the saliency graph. Through experiments, it can be known that the accuracy of this method is basically the same as the results obtained by pathologists.

In Lin et al. (2018), an improved FCN layer is used to input the WSI of any size, and the standard FCN layers are converted into the anchor layer. Fast and dense ScanNet inference with the anchor layer makes the network faster. The result of its detection of cancer metastasis shows excellent performance on the Camelyon16 Challenge dataset. A similar method is applied in Lin et al. (2018) and Lin et al. (2019).
6.2.3 Other deep learning based detection methods

The following references (Cruz-Roa et al. 2018; Sirinukunwattana et al. 2016; Bilaloglu et al. 2019) are used for detection after combining or simplifying the CNN structure with other methods.

In Cruz-Roa et al. (2018), invasive breast cancer in WSIs is detected. The method used is an efficient adaptive sampling method. The method combines probability gradient and quasi-Monte Carlo sampling. After the sampling, CNN is used for the classification experiment and the results show that the method can get 76% detection Dice-coefficient.

The authors of Sirinukunwattana et al. (2016) proposes a nuclear detection method for conventional colon cancer in WSI. This method combines CNN with the newly developed NEP method. This provides more accurate results for cell testing. The final experimental results produced a high average F1 score of detection.

In Bilaloglu et al. (2019), a method is proposed to detect outliers in WSI containing cancer tissues. This method is called PathCNN, which is a variation of CNN. The data used in the experiment is WSIs downloaded from the TCGA database.

In Liu et al. (2019), Lymph Node Assistant (LYNA), a tool for breast cancer lymph node metastasis detection based on InceptionV3, is evaluated for its application and clinical practice. The data is obtained from two sources: the Camelyon16 challenge containing 399 slides, and a private dataset containing 108 slides from 20 patients (86 tissue blocks). When applying the second dataset, LYNA achieved an AUC of 99.6%.

6.3 Ensemble learning based detection method

This section provides a summary of the contents related to the use of WSIs by the ensemble learning algorithm to detect histopathological images.

In Huang and Racoceanu (2017), the image is sampled based on the kernel density, and the taint deconvolution and feature description are used to extract image features. Then, an enhanced version of the rank boost integrated method (using multiple weak classifiers to obtain better performance of the final rank) is utilized to rank and detect high-level prostate cancer. The experiment shows the mean AUC is 0.9486 ± 0.005 and the mean accuracy achieves 95.57% ± 2.1%.

In the first step in Doyle et al. (2010), WSIs are decomposed into an image pyramid containing multiple resolution levels. At a lower resolution level, the Bayesian classifier identifies the infected areas like cancer, and then a higher resolution level is used for more detailed examination. At each resolution level, the AdaBoost ensemble method is used to collect more than 900 first-order statistics, ten image features are selected from the second-order co-occurrence and Gabor filter feature pool, and an enhanced Bayesian multi-resolution system is used to detect the coronary artery lesion area on the digital biopsy slice.

6.4 Potential detection methods in WSI

Several detection methods are used in other areas that can be attempted for WSI and CAD.

In Park et al. (2020), Mask R-CNN is used to detect the target in the video. This method can determine whether there is a candidate target in the video, and then segment it.
In Mukherjee et al. (2020), a soft-computing based approach for automatic detection of pulmonary nodules is proposed. This method is applied to the CT images. Firstly, threshold processing, gray-scale morphology, and other preprocessing are used, and then random undersampling is used to deal with unbalanced problems. Then, a combination of particle swarm optimization (PSO) and stacking integration is used to detect.

In Mohammadi et al. (2020), to deal with the complex scene of the target, a Feature Guide Network is proposed. The multi-scale feature extraction module (MFEM) is used to obtain multi-scale context information for each level of abstraction. Finally, a loss function that outperforms the widely used cross-entropy loss is designed. This method does not require pretreatment and is efficient. Singh et al. (2019) is also used for significance detection, an artificial neural network regressor is trained to refine the significance map. If it can be used in the WSI detection of histopathology, it will be very promising.

In Hamadi et al. (2020), semantic context is used to carry out multiple concept detection of still images. The first is to generate semantic descriptors using a set of test scores for a single concept. This advanced feature is pushed as input to the target multi-concept detector. The second method detects the target multiple concepts and their categories and then aggregates the results of the two treatments. The combination of semantic context and feature usage based on deep learning produces good results.

6.5 Summary

Among the papers we have summarized, it can be separated into traditional detection methods, detection methods based on deep learning, and detection methods based on ensemble learning.

There are many articles on medical WSIs detection that are related to classification. For example, Geçer (2016); Sirinukunwattana et al. (2016); Jamaluddin et al. (2017); Gecer et al. (2018), they are all detected first and then classified. Most of the tasks that use WSIs alone as an adjunct to treatment are for breast cancer detection (Cruz-Roa et al. 2017, 2018; Valkonen et al. 2017; Lin et al. 2018; Tellez et al. 2018a; Zanjani et al. 2018; Veta et al. 2013a; Liu et al. 2019).

There are traditional machine learning algorithms and some non-machine learning algorithms in traditional detection methods. Among the traditional detection method, six articles (Jiao et al. 2013; Sharma et al. 2015a; Han et al. 2018; Simon et al. 2018; Swiderska et al. 2015b; Nguyen et al. 2011) use SVM methods and five articles (Valkonen et al. 2017; Litjens et al. 2015; Bejnordi et al. 2015, 2016; Li and Huang 2015) use RF, DT, clustering, linear discriminator, and organization classifier algorithms. Two non-machine learning papers (Bautista and Yagi 2009, 2010) construct a color transfer factor to enhance the image folds for detection. There are 15 papers (Zanjani et al. 2018; Cruz-Roa et al. 2017; Bejnordi et al. 2017a; Tellez et al. 2018a; Kohlberger et al. 2019; Jamaluddin et al. 2017; Cruz-Roa et al. 2014, 2018; Sirinukunwattana et al. 2016; Liu et al. 2019; Geçer 2016; Gecer et al. 2018; Lin et al. 2018, 2019) related to detection based on deep learning, most of which use CNN. In Huang and Racoceanu (2017); Doyle et al. (2010), an ensemble learning-based detection, uses RankBoost and the other uses AdaBoost. It can be seen from the summary paper that before 2010, traditional non-machine learning algorithms are used for detection. Since 2011, machine learning has entered the public arena and methods such as SVM and RF has been widely used. Until 2016, the emergence of deep learning enables better results. From the detection results, we can also see that CNN obtain high accuracy. Table 7 is a summary of the CAD methods used for detection in WSI.
| Type | Reference               | Data                          | Details                                           |
|------|-------------------------|-------------------------------|--------------------------------------------------|
| T    | Nguyen et al. (2011)    |                               | SVM with RBF kernel and c = 1                    |
| T    | Jiao et al. (2013)      |                               | SVM                                              |
| T    | Sharma et al. (2015a)   |                               | SVM                                              |
| T    | Swiderska et al. (2015b)|                               | SVM with Gaussian kernel function                |
| T    | Han et al. (2018)       |                               | SVM                                              |
| T    | Simon et al. (2018)     |                               | SVM                                              |
| T    | Litjens et al. (2015)   |                               | RF                                               |
| T    | Li and Huang (2015)     | NLST                          | RF                                               |
| T    | Bejnordi et al. (2015)  |                               | RF                                               |
| T    | Bejnordi et al. (2016)  |                               | RF                                               |
| T    | Valkonen et al. (2017)  |                               | RF                                               |
| T    | Bautista and Yagi (2009)| Massachusetts General Hospital| Color shift factor                                |
| T    | Bautista and Yagi (2010)| Massachusetts General Hospital| Color shift factor                                |
| T    | Veta et al. (2013a)     | UMCU                          | Linear discriminator                              |
| T    | Lopez et al. (2012)     |                               | A hybrid clustering method                        |
| T    | Lopez et al. (2013)     |                               | DT                                               |
| T    | Shirinifard et al. (2016)|                              | A tissue classifier based on machine learning    |
| T    | Vyas et al. (2016)      |                               | Compare WSI and traditional microscopy           |
| DL   | Cruz-Roa et al. (2014)  |                               | CNN                                              |
| DL   | Jamaluddin et al. (2017)| Camelyon16                    | CNN                                              |
| DL   | Bejnordi et al. (2017a) | RUMC and UMCU                 | CNN                                              |
| DL   | Cruz-Roa et al. (2017)  | TCGA                          | CNN                                              |
| DL   | Zanjani et al. (2018)   | Camelyon17                    | CNN                                              |
| DL   | Tellez et al. (2018a)   | TNBC,TUPAC                    | CNN                                              |
| DL   | Kohlberger et al. (2019)|                               | CNN                                              |
| DL   | Geçer (2016)            |                               | FCN                                              |
| DL   | Geçer et al. (2018)     | registries associated with the BCSC Consortium | FCN                        |
| DL   | Lin et al. (2018)       | Camelyon16                    | FCN                                              |
| DL   | Lin et al. (2019)       | Camelyon16                    | FCN                                              |
| DL   | Sirinukunwattana et al. (2016)|                        | New NEP is used in conjunction with CNN         |
| DL   | Cruz-Roa et al. (2018)  | HUP,CWRU,CINJ,TCGA           | CNN and adaptive sampling                        |
| DL   | Bilaloglu et al. (2019) | TCGA                          | PathCNN                                          |
| DL   | Liu et al. (2019)       | Camelyon16, a separate dataset | LYNA (Based on Inception-v3)                     |
| EL   | Doyle et al. (2010)     |                               | AdaBoost                                         |
| EL   | Huang and Racocecanu (2017)|                              | TCGA                                             | Rankboost
7 Conclusions and future work

This paper summarizes the histopathological image analysis methods based on CAD and WSI. We summarized and analyzed the datasets, evaluation indicators, feature extraction, image segmentation, classification and detection methods commonly used in WSI analysis tasks. After summarizing all previous related work, we find that in the early stage of WSI analysis tasks, the main methods are edge detection, texture feature extraction, morphological filtering, SVM, and RF. These types of analysis methods have a common feature and are designed for specific tasks, so they can be collectively referred to as manual custom design methods. In addition, there is a different method that is currently popular deep learning. It is a data-driven analysis method that can automatically learn the characteristics of related models from large-scale datasets for specific problems. Therefore, deep learning methods can learn hidden deep features from large datasets and extract complex structures from high-dimensional data. In essence, the data-driven learning process can be summarized as the process of solving the optimal solution to the problem. The learning model can extract the features most needed to complete the target task from the training data, so as to show better decision-making results when the new data is input for testing.

Since 2016, with the rapid development of the software and hardware industry, the computing power and speed of computers have increased significantly, and the available datasets have also increased significantly. Deep learning has achieved various positive developments. Deep learning models and algorithms are constantly improving. At present, deep learning is widely used in speech recognition (Deng and Platt 2014), natural language processing (Kamath et al. 2019), weather forecast (Rodrigues et al. 2018), gene expression (Chen et al. 2016), content recommendation (Wang and Wang 2014), and various other fields.

In the future, the combination of WSI technology and machine learning will perform CAD. At present, CAD research mainly focuses on the breast, prostate, colon, nervous system, etc. The future research field can be extended to other diseases and other body areas. Second, in terms of data collection, there is still a lack of large-scale, comprehensive and fully annotated WSI datasets. Moreover, the data needs to be judged and labeled manually by doctors, so the labeling standards are not uniform. Furthermore, what deep learning must learn is not only to recognize according to the marked image features but also to understand the inevitable connection between pathology, and image features, so in the future, we can in-depth study high-dimensional image data processing technology. Finally, it will be very useful to develop a network that requires less computation, less hardware, and interpretability, which will benefit for CAD.

Acknowledgements This work is supported by National Natural Science Foundation of China (No. 61806047). We thank Miss Zixian Li and Mr. Guoxian Li for their important discussion. We also thank B.E. Xiaoming Zhou, B.E. Jinghua Zhang and B.E. Jining Li, for their Important technical supports.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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