Review Article

The Techniques Used in Mitosis Detection in Breast Cancer Histopathology Images. A Survey

Abstract:

Breast cancer is the second cause of death around the world after heart disease, and it is the primary cause of death for women. The early diagnosis of breast cancer can reduce the death rate, as early diagnosis and treatment at the right time can increase the patient's chance of survival. The discovery of the mitotic number is one of the necessary procedures that must be performed for a person suffering from breast cancer because it is an important marker for determining the aggressiveness of the tumor. According to the Nottingham scale, it gives 3 degrees to determine the degree of the tumor, whether it is of the first degree, the second degree, or the third degree of seriousness. Deep learning algorithms have many contributions in the medical fields, including in the field of mitotic number discovery, as the mitotic number process is a difficult and tiring task that requires time and effort from pathologists (diagnostic doctors), because the work environment is under microscopes with high magnification degrees, for this reason deep learning techniques were used to reduce the burden on diagnostic doctors and save time for the patient to know the result of his examination, as the biopsy results in developed countries take from 10 days to two weeks for the results to appear. In this survey we will review the deep learning techniques that were used to detect the mitotic number.

Key words: Breast cancer, Histopathology images, Mitotic cell account, Deep learning, Faster R_CNN

1. Introduction:

According to a recent report issued by the World Health Organization [1] that cancer of all kinds is the second dominant cause of death around the world after cardiovascular diseases, and the danger of cancer is that it can multiply and spread to affect other healthy parts of the body (away from the parts) diagnosed such as (lungs, colon, stomach, ...). Breast cancer is the most common cancer with an estimated 2.59 million new cases and 626,679 deaths in the same yearly. Studies show that one in eight women in the United States will develop invasive breast cancer at some point in her life [2].

$$CancerGrade(TS) = \begin{cases} grade: 1, & \text{if } TS \text{ is } 3\text{–}5 \\ grade: 2, & \text{if } TS \text{ is } 6\text{–}7 \\ grade: 3, & \text{if } TS \text{ is } 8\text{–}9 \end{cases}$$

$$TS = Totalscore$$

Early diagnosis of breast cancer is an important factor to reduce the number of deaths[3] and to limit the spread of cancer from the breast to other parts of the body, because the treatment plan depends mainly on the degree of cancer and diagnosis; Early diagnosis and timely treatment can increase the patient's chance of survival [3]. To determine the grade of breast cancer [4], the World Health Organization recommends

using the Nottingham grading system for tumor grading [5]. The Nottingham grading system is derived from the assessment of three major morphological features: nuclear atypia, mitotic count and tubule formation. A karyotype is described as a malformation of the nuclei in a population of cells and is characterized by the following factors: the size of the nuclei, the density of chromatin, the thickness of the nuclear membrane, the regularity of the nuclear contour, and the karyocytosis (size difference within the group of nuclei). Tubule composition is described as a percentage of the cancer cells that are in the formation of regular tubules. When cancer becomes more aggressive, cancer cells multiply via mitosis (the process of cell division), which makes mitosis an important prognostic factor. For this survey we will focus on the most documented and most prominent feature involved in accurate diagnosis of breast cancer which is the mitotic number, as the process of mitotic cell division is directly related to the diagnosis of tumors as it determines the aggressiveness of the tumor [6]. Mitosis is the process of cell duplication, in which one cell divides into two genetically identical daughter cells [7] and is how fast the tumor is growing and how likely it is to spread to other parts of the body.

[4] Cancer Staging

Table 1- [8] Nottingham grading system (NGS) parameters and scoring criteria for breast cancer grading

parameter	score	Score criteria
Mitosis count	1	0-9 mitotic cells in 10 consecutive high power fields (HPFs)
	2	10-19 mitotic cells in 10 consecutive HPFs
	3	>=20 mitotic cells in 10 consecutive HPFs
Nuclear atypia	1	Small, uniform, and regular nuclei
	2	Moderate variations in size and shape
	3	Multiple nucleoli with prominent variation
Tubule formation	1	>75% of the tumor forms tubule
	2	10-75% of the tumor forms tubule
	3	Multiple nucleoli with prominent variation

Mitotic counting needs little or no professional explanation [2], due to simple scales used to determine proliferation rates using a mitotic count for each high power field (HPF's: the Visible area under the maximum magnification power of the microscope): 0-9 dilutions every 10 HPF is low prevalence, 10-19 dilutions per 10 HPF moderate spread and over Of 19 per 10 HPF it is a severe prevalence. While the other two factors are relatively subjective in nature, the accuracy of their recording depends to a large extent on the experience of the pathologist [9]. Despite the prevalence of breast cancer, the current methods of diagnosing breast cancer are very primitive. Trained pathologists are needed to examine hundreds of high-energy fields of tissue images. Biopsies often take two to ten days for results to return patient [4]. Given the increasing number of breast cancer cases [4], the traditional method the diagnosis of breast cancer is unsustainable. The computational approach would be a much time-saving and cost-effective alternative, allowing streamlined diagnosis of pipeline breast cancer. This would allow the spread of sick services to poor areas and improving care centers worldwide. Digital pathology has become a prominent tool in this process. In digital pathology, specially designed microscopes equipped with powerful cameras are used to capture high-energy field (HPF) images with high resolution. These images can be transmitted over the Internet and stored securely in a digital format for future reference. Digital pathology has opened tremendous opportunities for the application of computational techniques in pathology. Many of the arduous and mundane tasks performed by pathologists can be handed over to computers that can complete them to match or exceed human accuracy [10,11]. The advent of whole slide imaging (WSI) [12] technology that can scan and store an entire pathology slide at high magnification has facilitated a faster transition to digital pathology. Recently, artificial intelligence technologies have made

many contributions to various aspects of life, including the medical field. Most of the operations are now automated and can be used as a second opinion system in diagnosis or used as support for the doctor's decision in suspicious cases. Mitotic number can be detected using artificial intelligence techniques, however There are many challenges for example [3], it is Difficulty distinguishing mitotic cells from normal cells without pathological knowledge and use from high-resolution microscopes because mitotic cells have texture and morphological characteristics Similar to normal cells, as shown in Figure 1. Furthermore, some other cell organelles, such as apoptotic cells, they have an appearance similar to mitotic cells. The process of cleavage is Four stages where each has its own unique characteristics, therefore, a strong technique is required They are developed to detect diverse mitotic cells. Another major challenge is maintaining a standard data preparation environment [13]. Biopsy, slide preparation, and scanning procedures are required to be carried out carefully because low performance is obtained if there are data problems assembly, slide preparation, and scanning [14]. However, these challenges include not only computer diagnosis, but also challenges for manual diagnosis, so it is necessary to develop powerful techniques in artificial intelligence to detect the mitotic number. Deep learning is a growing field geared towards multi-scale pattern detection using deep Neural network architectures. Adaptations of models such as a convolutional neural network CNN can extract high-level features from images for use in object detection tasks such as get a mitotic count. One example of this model is the Faster-RCNN proposed by [15], which uses features from an image to produce spatial coordinates for bounding boxes linked to certain categories.

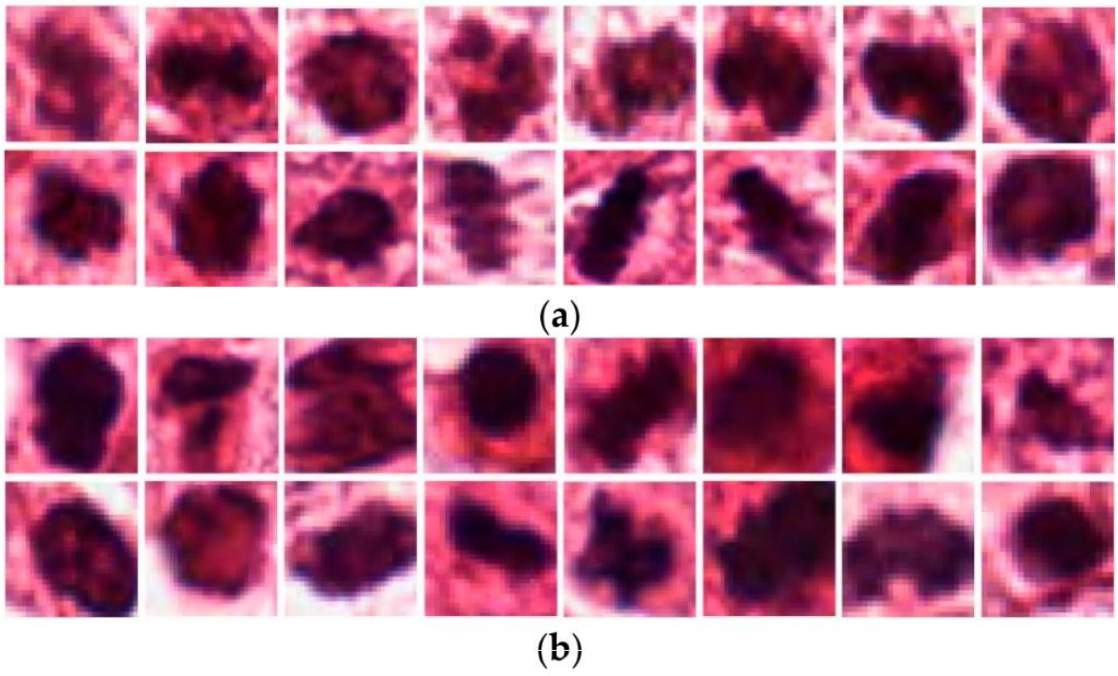

Figure 1. Examples of (**a**) mitotic and (**b**) non-mitotic cells [3].

2. Methodological approaches:

2.1. The techniques for detecting mitotic cells based on the extracted features:

Mitotic-cell detection techniques can be categorized into three divisions based on the features extracted from regions of interest (ROIs): handcrafted-features-based, deep-features-based and combined features (handcrafted with deep) research in the following, we will review an explanation of each of these three categories.

2.1.1. Mitosis Detection Using Handcrafted Features:

Handcrafted features are extracted from ROIs by using conventional image-processing techniques. Features such as color, morphology, and texture are extracted, which is followed by classification using machine-learning classification algorithms such as an artificial neural network and a support vector machine (SVM) as shown in **Figure 2**. Research on this approach has shown good performance and can be used in small-scale applications. Huang and Lee [16] they presented a novel algorithm, named Exclusive Independent Component Analysis (XICA) is proposed. The XICA is an extension of a generic ICA, but focusing the components of differences (called exclusive basis set) between two classes of training patterns rather than the major (independent) components. Based on the residuals obtained from the relative computing involving the exclusive basis set of the relative training patterns, the automated mitosis detection is performed. By computing the residual of the relative exclusive basis set, they have been tested this approach on image set provided by ICPR 2012 contest It achieved accurate rate 100% in training patterns and 83.513% in testing patterns. Khan et al. [17] presented a statistical approach for mitosis detection in breast cancer histological images. The proposed algorithm models the pixel intensities in mitotic and non-mitotic regions by a Gamma-Gaussian mixture model and employs a context-aware post-processing in order to reduce false positives. Experimental results demonstrate the ability of this simple, yet effective method to detect mitotic cells. Irshad presented a technique [18] in which all the expected objects were first segmented, and statistical and morphological features were extracted and classified using a decision-tree classifier. This technique ranked second in the mitosis detection challenge of the international conference on pattern recognition (ICPR) 2012. Paul et al. [19] they used features Intensity and texture then used regenerative random forest tree classifier that demonstrated an excellent performance. However, this technique requires significant computational resources, and thus, it cannot be used in practical clinical application.

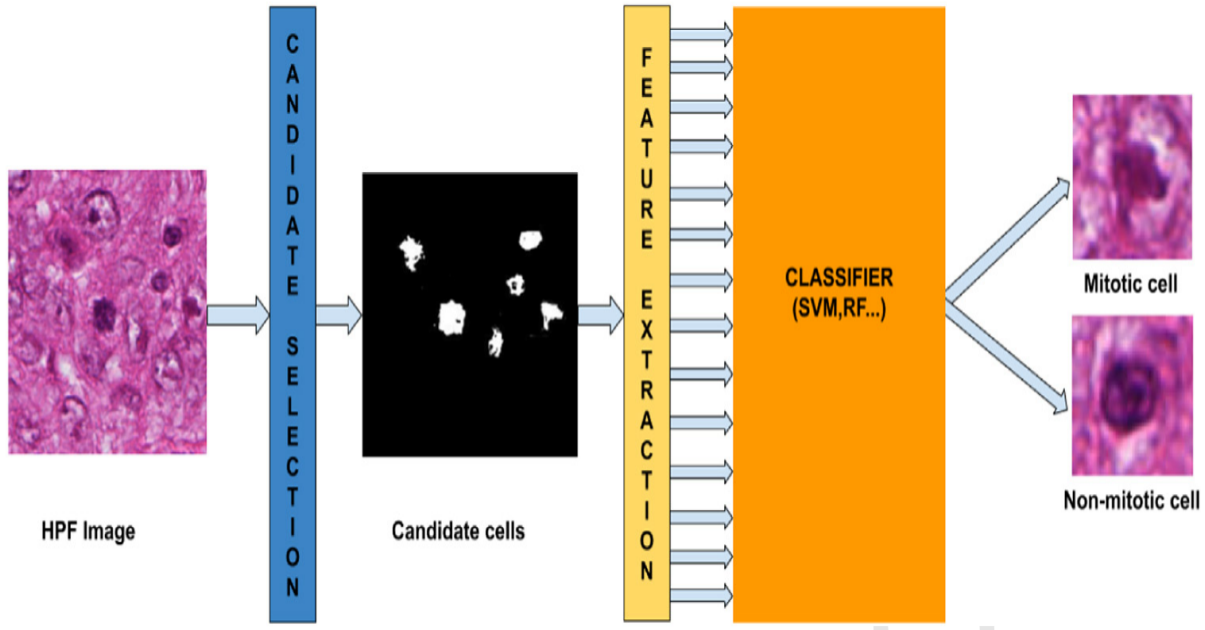

Figure 2. Typical workflow of a method using handcrafted features [9].

2.1.2. Mitosis Detection Using Deep Features:

Deep features are extracted from ROIs by using deep-learning techniques as shown in **Figure 3**. Li et al. presented a technique [6] based on Faster region convolutional neural network (Faster R-CNN) and residual network (Resnet)-50. Faster R-CNN initially detects mitotic cells, which are further refined by Resnet-50. The Faster R-CNN used in this technique comprises visual geometry group (VGG)-16 as a feature-extraction network. This method is very fast with GPU computing, which makes it feasible for clinical practice. Ciresan et al. presented a technique [20] based on the sliding window approach for the extraction of deep features from images. This technique ranked first in the ICPR 2012 mitosis-detection contest. The sliding window approach is computationally expensive, and thus, this technique is not suitable for clinical application. Sohail et al. [21] they proposed deep CNN based multi‑phase mitosis detection framework "MP‑MitDet" for mitotic nuclei identification in breast cancer histopathological images. The workflow is decomposed into 4 phases: (1) refinement of weakly labelled mitosis dataset, (2) mitotic region selection at tissue-level, (^{3}) blob analysis, and (4) enhancement of mitosis detection results at cell-level. The performance of this proposed framework shows good discrimination ability in terms of F‑score (0.75), recall (0.76), precision (0.71) and area under the precision‑recall curve (0.78) on challenging TUPAC16 dataset. Lakshmanan and et al. [22] they constructed a supervised deep framework called DenseNet combined Principal Component Analysis (PCA) model for mitosis classification. this approach has three level (1) Instance level deep features extraction by DenseNet 121 architecture (2) PCA based feature subset selection (3) mitosis classification. they used MITOS-ATYPIA 14 Hammamatsu Scanner images and hey got effective results. Cai et al. [23] they used a modified

regional convolutional neural network (RCNN). They used Resnet-101 for the feature extraction of the Faster R-CNN. This method achieved 0.76 in precision, 0.72 recall and 0.736 F1 score on MICCAI TUPAC 2016 datasets, F1 score of 0.585 is also achieved on ICPR 2014 mitosis dataset. The inference time for a 2000×2000 image is ~0.8 s, this method a promising tool for clinical deployment. Chen et al. presented a technique [24] was composed of two components. First, in mitotic cells were segmented by a fully convolutional network (FCN) in stage 1, while in stage 2, all the detected objects were further refined by an additional CNN. This approach outperformed other methods by a large margin in 2014 ICPR MITOS-ATYPIA challenge in terms of detection accuracy. When compared with the state-of-the-art methods on the 2012 ICPR MITOSIS data (a smaller and less challenging dataset), this method achieved comparable or better results with a roughly 60 times faster speed. Piansaddhayanon et al. [13] they proposed a Refine Cascade Network (ReCasNet), an enhanced deep learning pipeline It consists of first, Window Relocation, a simple effective method that overcomes the weakness of an overlapping sliding window by removing objects around the window border and re-evaluating them as the center of newly extracted patches. Second, they introduced an Object Center Adjustment Stage. Third, they improved the training data sampling process of the verification model. Finally, a classification stage rescores the object confidence of each patch. ReCasNet was evaluated on two large-scale mitotic figure recognition datasets, canine cutaneous mast cell tumor (CCMCT) and canine mammary carcinoma (CMC).

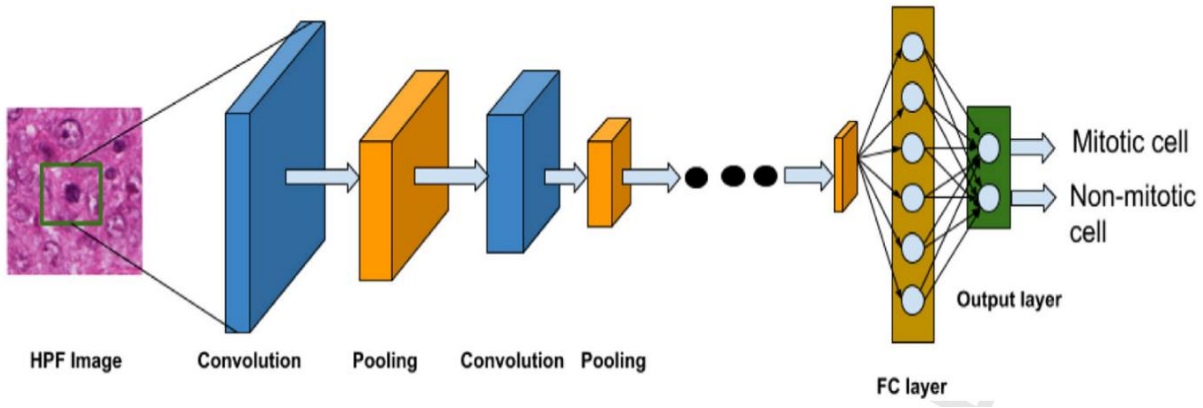

Figure 3. Typical workflow of a method using deep learning [9].

2.1.3. Mitosis Detection Using Combination features (handcrafted with deep features):

Mahmood et al. [3] proposed a multi-CNN for mitosis detection. Faster R-CNN used in the first stage in which the primary detection of mitotic cells was performed. They adopt Resnet-50 as a features-extraction network for the first time. In this technique, a large number of false positives were produced because of the minute differences between mitotic and non-mitotic objects. To reduce the number of false positives, they performed post-processing on the basis of statistical, texture, shape, and color features. To further reduce the number of false positives, they performed a score-level fusion of Resnet-50 and a dense convolutional network (Densenet)-201. This method achieved the results of 0.876 precision, 0.841 recall, and 0.858 F1-measure for the ICPR 2012 dataset, and 0.848 precision, 0.583 recall, and 0.691 F1-

measure for the ICPR 2014 dataset. Wang et al. presented a cascaded technique [25] in which two classifiers were used independently. First classifier is trained with handcrafted features (morphology, intensity and texture) handcrafted features are extracted and classified via a Random Forests classifier, and the second is trained with CNN features. In the testing stage, a third classifier is used if the outputs of the two classifiers are different. That's mean final decision is obtained via a consensus of the predictions of the three classifiers. This technique is fast and requiring far less computing resources, however, the ROI-selection performance with conventional image processing is lower than that obtained with the deep-learning technique. This technique achieved 0.84 precision, recall 0.65, and F-score 0.73. Saha et al. [26] presented mitosis detection in whole slide image (WSI) by combining CNN and a set of 55 handcrafted features. Handcrafted features mainly consist of morphological, intensity, and textural of the nuclei present in WSI. The deep learning architecture mainly consists of five convolution layers, four max-pooling layers, four rectified linear units (ReLU), and two fully connected layers. This technique achieved 92% precision, 88% recall and 90% F-score. Dodballapur et al. [27] presented a technique used mask R-CNN and that comprised Resnet-50 as a feature-extraction network. Xception network was used for the reduction of false positives. This technique provides high accuracy; however, owing to its use of expensive GPUs and intensive training, it is not suitable for use in practical clinical applications. Malon et al. presented a method [28] combined manually designed nuclear features with the learned features extracted by convolutional neural networks (CNN). The nuclear features capture color, texture, and shape information of segmented regions around a nucleus. The use of a CNN handles the variety of appearances of mitotic figures that reduces the sensitivity of mitotic cells during feature extraction and thresholds. this trained system achieved F1 scores up to 0.659 on color scanners and 0.589 on multispectral scanner. Li et al. [29] presented a method, called SegMitos. this method solved the mitosis detection task by the virtue of a semantic segmentation model. they predict the category of each pixel and then directly infer the locations of mitotic cells from the segmentation map they trained a segmentation network based on fully convolutional network (FCN) with the mitosis data. The SegMitos model produces a segmentation map where each pixel represents its confidence of belonging to the mitosis class. They used a Gaussian filter to processed the response map to reduce image noise. For these blobs, they calculate their areas and mean confidence scores. after that they used a filtering mechanism based on these two features to obtained detection results. this model is fast and efficient because they were applied in an end-to-end (image-to-image) without using sliding window method. This model achieved 0.562 F-score on ICPR 2014 MITOSIS dataset, 0.673 F-score on AMIDA13 dataset, and obtained 0.669 F-score on the latest TUPAC16 dataset. Ali et al. [30] proposed a Representation Differential Learning Method (RDLM) for mitosis detection through deep learning to detect the accurate mitotic cell area on pathological images. This method has been divided into two parts: Global bank Feature Pyramid Network (GLB-FPN) and focal loss (FL). The GLB feature fusion method with FPN essentially calibrates the encoder-decoder and further makes encoder-decoder pay attention to extract the region of interest (ROIs) for mitotic cells. GLB has three phases. In the first phase, the encoder connects the layer at multiple-scales by including features. The second phase reconnects and removes the background noise to acquire a suitable feature map that further pays attention to the region of interest for mitotic cells. In the final phase, the feature map is generally transferred to the decoder by convolutions. This method achieved 0.685 precision, 0.70 recall and 0.692 F-score for the ICPR 2014 dataset. Sohail et al. [31] they proposed a new Deep Convolutional Neural Network (CNN) based Heterogeneous Ensemble technique "DHE- Mit-Classifier" for analysis of mitotic nuclei in breast histopathology images. This technique has many levels (1) detects candidate mitotic patches from the histopathological biopsy regions, (2), these patches are classified into mitotic and non-mitotic nuclei using the proposed DHE- Mit-Classifier, (3) for the development of a heterogeneous ensemble, five different deep CNNs are designed and used as base-classifiers. Sigirci et al. [32] they proposed method based statistical based conventional handcrafted methods are employed besides deep

learning. In the preprocessing step they proposed median filtering to reduce noise, for segmentation step they used k-means algorithm, then they used shape, texture and statistical-based feature extraction algorithms and CNN based deep feature extraction. Finally, they used RUSBoost method for Classification. They tested this method on the histological images dataset (ICPR) 2014. In this dataset, approximately 180,000 non-mitotic and 748 mitotic cells were extracted from 1200 images cropped from 10 histopathological whole slides. They achieved 96.78% precision, 79.42% recall and 86.97% F-measure values. Razavi et al. [33] they proposed an automatic mitosis and nuclear segmentation method called MiNuGAN is based on a conditional generative adversarial network to segment both mitoses and nuclei at the same time. An encoder‑decoder architecture with ResNet blocks are used for the generator network, consisting of five convolutional layers and nine residual blocks in the encoding arm, four convolutional upsampling layers in the decoder, followed by three residual blocks after deconvolution, and two more convolution layers. The output is a generated segmentation mask for both mitosis and nuclear classes. The accuracy of this proposed method was investigated using images from multiple centers and scanners, including TUPAC16, ICPR14 and ICPR12 datasets. In TUPAC16, they used 618 carefully annotated images of size 256×256 scanned at 40×. TUPAC16 was used to train the model, and segmentation performance. Results on 200 held-out testing images from the TUPAC16 dataset were mean DSC = 0.784 and 0.721 for nuclear and mitosis, respectively. On 202 ICPR12 images, mitosis segmentation accuracy had a mean DSC = 0.782, indicating the model generalizes well to unseen datasets. For datasets that had mitosis centroid annotations, a mean F1-score of 0.854 was found indicating high mitosis detection accuracy.

Table 2 - shows techniques for detecting mitotic cells based on the extracted features. Arranged from oldest to newest.

Category	Authors	year	method	Datasets	Results		
					precision	Recall	F-score
Hand-crafted features (H.C.F)	Huang And Lee [16]	2012	eXclusive In- dependent Component Analysis (XICA)	ICPR 2012	100% in training patterns & 83.513% in testing patterns.		
	Khan et al. [17]	2012	**textural features** (Phase Gradient (PG), roughness, entropy), **representative features** (mean, standard deviation, skewness, kurtosis) with SVM classifier	ICPR 2012	86% sensitivity		
	Irshad [18]	2013	Morphological and statistical features with decision tree classifier	Aperio ICPR 2012	70%	74%	72%
				Hamamatsu ICPR 2012	56%	71%	63%

	Paul et al [19]	2015	Intensity, texture, and regenerative random forest tree classifier	ICPR 2012	0.8350	0.8113	0.823
Deep features (D.F)	Ciresan et al. [20]	2013	Sliding-window-based classification	ICPR 2012	0.88	0.70	0.782
	Chen et al. [24]	2016	FCN model for objects segmentation and CNN for classification	ICPR 2012	0.804	0.772	0.788
				ICPR 2014	0.460	0.507	0.482
	Li et al. [6]	2018	Faster R-CNN-based detection and Resnet-50 for classification	ICPR 2012	0.854	0.812	0.832
				ICPR 2014	0.431	0.443	0.437
	Cai et al. [23]	2019	Modified Faster R-CNN with Resnet-101 feature-extraction network	ICPR 2014			0.585
				TUPAC-16	0.76	0.72	0.736
	Sohail et al. [21]	2021	Mask R-CNN	TUPAC16	(0.71)	(0.76)	(0.75)
	Lakshmanan et al.[22]	2022	DenseNet combined Principal Component Analysis (PCA)	ICPR 2014	effective results		
	Piansaddhayanon et al. [13]	2022	window relocation, sliding window overlapped, Faster-RCNN-ResNet50.	CCMCT			83.2%
				CMC			82.3%
Combination Hand-crafted (H.C.F)	Malon et al. [28]	2013	Combination of color, texture, and shape features, and CNN features with SVM classifier	ICPR 2012			0.659 on color scanners
							0.589 on multispectral scanner
	Wang et al. [25]	2014	Handcrafted and CNN features, random forest classifier, and CNN	ICPR 2012	0.84	0.65	0.73
	Saha et al. [26]	2018	combining a set of handcrafted features (morphological, intensity, and textural) and CNN.	ICPR 2012 AMIDA-13	92%	88%	90%
	Dodballapur et al.	2019	Mask R-CNN for object detection and	ICPR 2012	0.93	0.80	0.87

& **Deep features (DF)**	[27]		handcrafted and CNN features	ICPR 2014	0.62	0.67	0.64
	Li et al. [29]	2019	FCN trained with concentric loss on weakly annotated centeriode label, and two features on the segmented blob (area and mean)	ICPR14			0.562
				AMIDA13			0.673
				TUPAC16			0.669
	Mahmood et al. [3]	2020	Faster R-CNN and score-level fusion of Resnet-50 and Densenet-201	ICPR12	0.876	0.841	0.858
				ICPR14	0.848	0.583	0.691
	Ali et al. [30]	2021	Global bank Feature Pyramid Network (GLB-FPN) and focal loss (FL)	ICPR14	0.685	0.70	0.692
	Sohail et al. [31]	2021	five different CNN based base-classifiers are developed to appropriately capture the variation in the structure, texture, and morphological properties of the mitotic nuclei	TUPAC16 ICPR12 ICPR14	(0.83)	(0.71)	(0.77)
	Sigirci et al. [32]	2021	(textural/spatial, statistical and shape) with cnn for features, k-means algorithm for segmentation and RUSBoost for classification.	ICPR14	96.78	79.42	86.97
	Razavi et al. [33]	2022	conditional generative adversarial network to segment (MiNuGAN)	TUPAC16 ICPR12 ICPR14			0.854

2.2. The techniques on deep features based on the formulation of the problem:

In the mitotic-cell detection task, deep features-based techniques are further divided into three main categories based on the problem formulation. [3] some researchers consider mitotic-cell detection as a classification task, while others consider it as a semantic segmentation task because of the pixels-based annotations. Few others also consider it to be an object-detection task because the objective was not to determine the shape of the mitotic cells but to count them.

Table 3 - presents researchers' division of mitotic cell detection problem based on deep features into three categories based on problem formulation.

Authors	classification task	semantic segmentation task	object-detection task
Mahmood et al. [3]			✓
Li et al. [6]			✓
Ciresan et al. [20]	✓		
Ali et al. [30]			✓
Li et al. [29]		✓	
Chen et al. [24]	✓		
Wang et al. [25]	✓		
Alom et al. [34]		✓	
Beevi et al. [8]		✓	
Zhang et al. [35]	✓		
Ren et al. [36]			✓
He et al. [37]		✓	
Long et al. [38]		✓	

2.3. Datasets:

There are many histopathological images that are used to detect mitotic cells open source, as shown in **Figure 4.**

2.3.1. ICPR 2012 MITOSIS Dataset:

The ICPR 2012 MITOSIS dataset was introduced in the ICPR 2012 contest [39]. It comprises 50 RGB images of which 35 images are fixed for training and 15 images for testing. For acquiring this dataset, 10 high-power fields (HPFs) of size 512 × 512 μm2 at 40× magnification are selected from the biopsy images of five breast-cancer patients. The resolution of each image is 0.2456 μm per pixel, and each of the HPFs has an area of 512 × 512 μm, which implies that the image size is 2084 × 2084 pixels.Two scanners, namely, Aperio XT (scanner A) scanner and Hamamatsu NanoZoomer Scanner (scanner H) were used.

2.3.2. ICPR 2014 Dataset:

The ICPR 2014 dataset was presented in the MITOS-ATYPIA-14 grand challenge [40], in which researchers were required to compete for nuclear atypia scoring and mitotic-cells count. This dataset

comprised 1200 training images acquired from 16 different biopsies and 496 testing images acquired from five different breast biopsies. The size of each images is 1539 × 1376 pixels at 40× magnification it's available on [41].

2.3.3. Dataset TUPAC16:

The dataset provided the ROIs from 73 patient biopsies in the train set and 34 cases in the test set. The provided ROIs were selected by the pathologists and correspond to 10 HPF. The patient samples were obtained from three different hospitals of the Netherlands and were digitalized using Aperior and Lecia slide scanner [30]. Therefore, this dataset contains different variations in stain colour and tissue sample appearance. The ROIs in the dataset contain either no mitosis or more than a hundred mitoses.

2.3.4. CCMCT & CMC datasets:

In this section, we will discuss two types of databases: ODAEL variant of the CCMCT dataset [42] and the CODAEL variant of the CMC [43] dataset. The prominent characteristic of the two datasets was the availability of a complete mitotic figure annotation on the WSI level using algorithm-aided annotation and the consensus of experts. In addition, hard negative objects (mitosis figures lookalikes) were also annotated, which improve training information. The CCMCT dataset contains an annotation of 44,800 mitotic figures on 32 WSIs, of which 11 of them were held out for testing. The CCMCT dataset consists of four classes: Mitosis, Mitosislike, Granulocyte, and Tumorcell. The first class is a positive class while the rest are considered negative. In the same manner, the CMC dataset contained an annotation of 13,907 mitotic figures on 21 WSIs, of which 7 of them were held out for testing. The CMC dataset consists of two classes: Mitosis, and Nonmitosis.

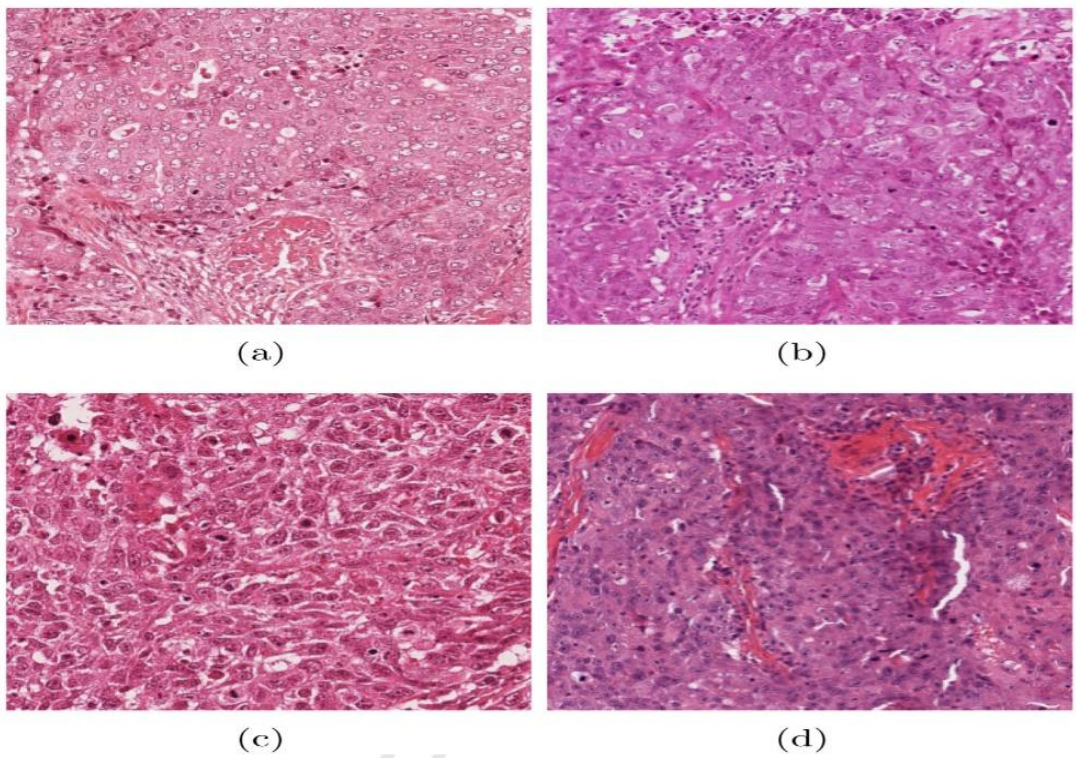

Figure 4. Representative HPF images from public datasets(a) MITOS(Aperio scanner), (b)MITOS(Hamamatsu scanner), (c)MITOS-ATYPIA, (d)TUPAC [9].

3. Discussions:

Recently, artificial intelligence technologies have made many contributions in several fields, including the medical field. Digital pathology has opened tremendous opportunities for the application of computational techniques in pathology, as the advent of full-slide imaging technology (WSI) which can scan and store the entire pathology slide at high magnification has facilitated a faster transition to digital pathology.

4. Conclusions:

We have noticed recently that researchers have focused on the problem of mitotic detection, as it has become a growing field, also provided Mitosis Detection Challenge competitions that are held at conferences provide a resource and communication platform for all ,such competitions have encouraged researchers to solve the problem of detecting mitotic cells and provided them with databases. In this survey we divided the mitosis detection methods into two sections: The first section is based on the methods of mitosis detection based on the features used in each work, some of them used hand-crafted features, some of them used features based on deep learning, and some of them used a combination of features Hand-crafted with deep features. We note from Table 2 that algorithms based on deep learning give more successful results in segmentation and classification problems, where traditional methods are insufficient in medical image analysis. As for the second section, based on the formulation of the problem (in terms of the task) as we noted in Table 3, some of them considered the problem of mitosis detection a classification task, and some considered it the task of semantic segmention, and some of them considered it the task of object detection.

Ethics approval: Not applicable.

Consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and material: The ICPR 2014 dataset it's available on https://mitos-atypia-14.grand-challenge.org/

Code availability: Not applicable.

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