Asian Journal of Research in Computer Science

Volume 16, Issue 4, Page 476-489, 2023; Article no.AJRCOS.104270
ISSN: 2581-8260

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

Ruqaia Sharafaldeen [a*] and Mossa Ghurab [a]

[a] Department of Computer Science, Sana'a University, Sana'a City, Republic of Yemen.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJRCOS/2023/v16i4407

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/104270

Review Article

Received: 26/05/2023
Accepted: 03/08/2023
Published: 29/12/2023

ABSTRACT

Breast cancer consider as the second cause of death around the world after heart disease, and it is the primary cause of death for women. Timely detection of breast cancer plays a crucial role in lowering mortality rates, as it enhances the patient's prospects of survival through prompt diagnosis and appropriate treatment. 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 evaluate the deep learning techniqus employed for mitotic number detection.

**Corresponding author: E-mail: ruqeh.abass@su.edu.ye;*

Keywords: Breast cancer; histopathology images; mitotic cell account; deep learning; faster region convolutional neural network.

1. INTRODUCTION

"Breast cancer is a significant global health concern, as highlighted by a recent report from the World Health Organization (WHO)" [1]. According to the report, cancer, including breast cancer, is the second leading cause of death worldwide, following 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, in particular, ranks as the most prevalent cancer globally. The WHO report estimates approximately 2.59 million new cases of breast cancer each year, resulting in approximately 626,679 deaths. Indeed, studies have demonstrated that breast cancer [2] is a prevalent disease that affects a significant number of women. According to Cancer Staging research, approximately one in eight women in the United States will develop invasive breast cancer at some stage of their lives [2]. 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 indeed the fundamental process of cell division, through which a single cell divides into two genetically identical daughter cells [7] and is how fast the tumor is growing spread to other parts of the body.

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

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. The accuracy of recording the other two factors, which are more subjective in nature, relies heavily on the pathologist's level of experience. [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 indeed emerged as a prominent tool in the field of pathology. It involves the utilization of specially designed microscopes that are equipped with powerful cameras to capture high-resolution images of high-power fields (HPFs). These digital images can be stored, analyzed, and shared electronically, enabling pathologists to review and interpret the images remotely. 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 to apply computational techniques in pathology. Computers have the potential to take over many laborious and repetitive tasks currently performed by pathologists, with the ability to achieve or even surpass human accuracy" [10,11]. The introduction of whole slide imaging (WSI) technology [12], which can scan

and digitally store entire pathology slides at high magnification, has accelerated the transition to digital pathology.. Recently, artificial intelligence technologies have made many contributions to various aspects of life, including the medical field. Nowadays, the majority of operations are automated and can serve as a second opinion system in diagnosis or as supportive tools for doctors in suspicious cases. Artificial intelligence techniques can be employed to detect the number of mitotic figures. However, there are several challenges that need to be addressed, such as [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 Fig. 1. “Moreover, certain cell organelles, like apoptotic cells, possess a resemblance to mitotic cells in their appearance. The cleavage process comprises four distinct stages, each with its own distinct characteristics. Consequently, the development of robust techniques is necessary to accurately detect various types of mitotic cells. Maintaining a standardized data preparation environment poses another significant challenge” [13]. Careful execution of biopsy, slide preparation, and scanning procedures is essential, as any issues during these processes can lead to subpar performance and data discrepancies [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 neural networks DNN that are used in deep learning are considered one of the most important areas of their use in the task of detecting multi-scale patterns, and the most important of these networks is the convolutional neural network CNN, where the structure of this network can be adapted to extract high-level features from images to be used in the task of object detection such as detecting cells mitotic. 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.

2. METHODOLOGICAL APPROACHES

2.1 The Techniques for Detecting Mitotic Cells Based on the Extracted Features

There are three main categories of techniques for detecting mitotic cells, which are based on the features extracted from regions of interest (ROIs): handcrafted-features-based, deep-features-based, and combined features (a combination of handcrafted and deep features). In the following sections, we will provide an overview and explanation of each of these three categories.

2.1.1 Mitosis detection using handcrafted features

Handcrafted features involve the extraction of features from regions of interest (ROIs) using traditional image-processing techniques. These features encompass attributes like color, morphology, and texture. Subsequently, machine learning classification algorithms, such as artificial neural networks and support vector machines (SVM), are applied for classification, as illustrated in Fig. 2. This approach has demonstrated promising performance in research and can be utilized in smaller-scale applications. In their study, Huang and Lee [16] introduced a novel algorithm called Exclusive Independent Component Analysis (XICA). This algorithm is an extension of the conventional Independent Component Analysis (ICA) method but focuses on identifying differences between two classes of training patterns (referred to as the exclusive basis set) instead of the major independent components. The automated detection of mitosis is performed based on the residuals obtained from computing the relative exclusive basis set of the training patterns. The proposed approach was tested using an image set provided by the ICPR 2012 contest. The results showed an accurate rate of 100% in training patterns and 83.513% in testing patterns. Khan et al. [17] presented an approach that use statistical methods to detect mitosis on an ICPR 2012 dataset. This algorithm uses a Gamma-Gaussian mixture model to pixel intensities in mitotic and non-mitotic regions, and then this proposed algorithm reduces false positives using a context-aware post-processing in order. This method, despite its simplicity, showed its effectiveness in the detection of mitotic cells. Irshad presented a technique [18] ranked second in the Mitosis Detection Challenge of the International Conference on Pattern Recognition (ICPR) 2012. In the beginning, this technique relies on segmenting all the expected objects and then extracting the statistical and morphological characteristics and classifying them using the decision tree classifier. Paul et al. [19] they used regenerative random forest tree classifier, where this classifier achieved excellent results when

applied to the features of intensity and texture, but this technique cannot be used practically in clinical application because it requires large computational resources.

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

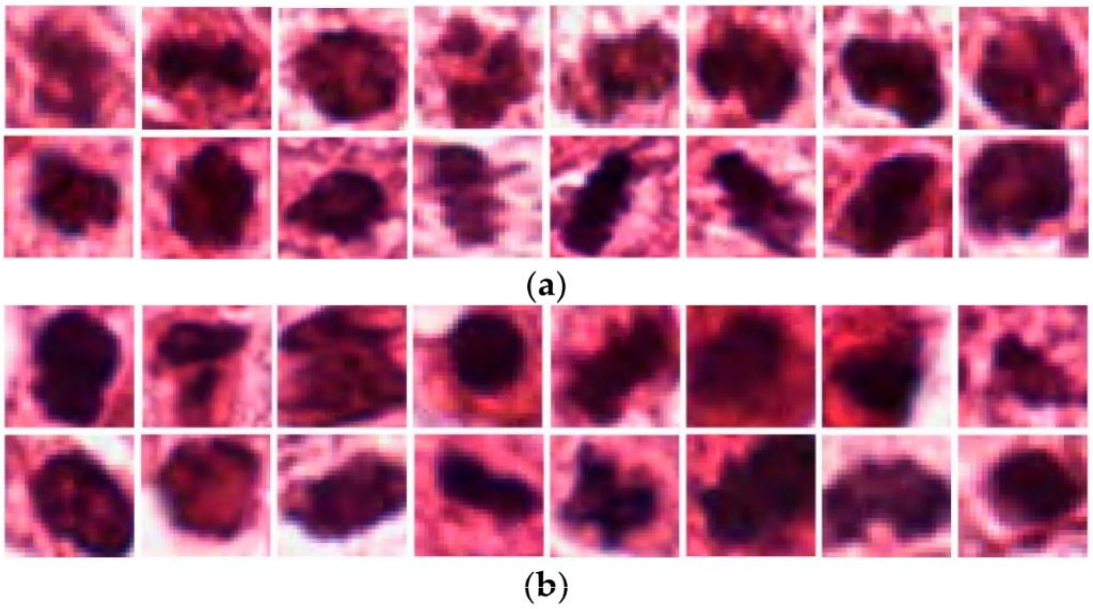

Fig. 1. Examples of (a) mitotic and (b) non-mitotic cells [3]

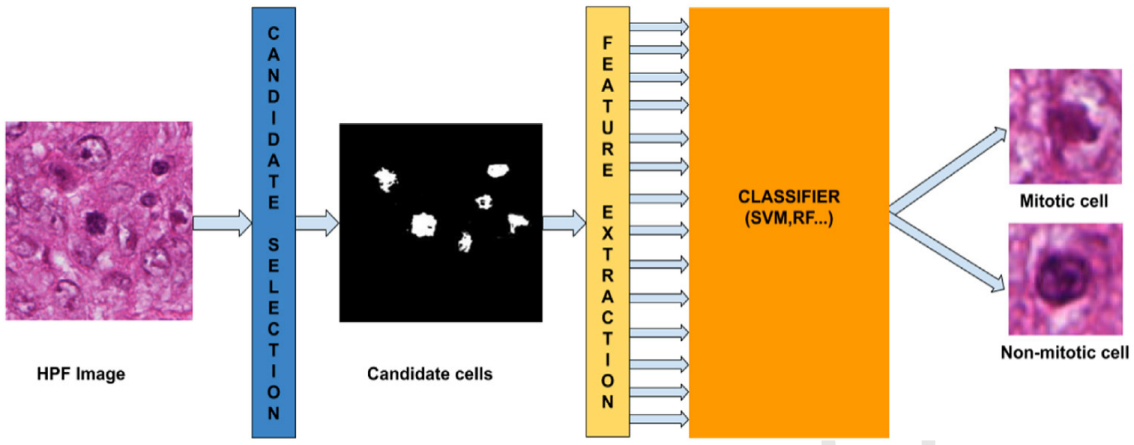

Fig. 2. Typical workflow of a method using handcrafted features [9]

2.1.2 Mitosis detection using deep features

Deep features are extracted from ROIs by using deep-learning techniques as shown in Fig. 3. Li et al. presented a technique [6] that initially detects mitotic cells using Faster region convolutional neural network (Faster R-CNN), where it uses a feature extraction grid using the visual geometry group (VGG)-16. Then the detection results were improved using the residual network (Resnet)-50. This technology based on Faster R-CNN can be used in clinical practices because it is very fast with GBU computing. Ciresan et al. presented a technique [20] that won ranked first in the competition ICPR 2012 in the task of detecting mitosis. This technique extracts deep features from ICPR 2012 images using a sliding window approach. This technique cannot be used in clinical practice because the sliding window approach is computationally expensive. Sohail et al. [21] proposed a deep Convolutional Neural Network (CNN)-based framework called "MP-MitDet" for the detection of mitotic nuclei in breast cancer histopathological images. The framework consists of four distinct phases: (1) refinement of weakly labeled mitosis dataset, (2) selection of mitotic regions at the tissue level, (3) blob analysis, and (4) enhancement of mitosis detection results at the cellular level. The performance evaluation of this framework on the challenging TUPAC16 dataset demonstrates its strong discriminatory ability, achieving favorable metrics such as F-score (0.75), recall (0.76), precision (0.71), and area under the precision-recall curve (0.78).Lakshmanan and et al. [22] they classified mitosis on a MITOS-ATYPIA 14 data set and images were selected from the Hammamatsu (H) scanner and obtained effective results by building a built-in DenseNet model for Principal Component Analysis (PCA). This model is a supervised deep work environment that consists of a three level, the first level uses the DenseNet 121 architecture to extract the deep features of the instance level, in the second level PCA-based features are identified and then a subset of them is selected, the third level is a classification of mitosis. 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. In a separate study, Chen et al. [24] presented a technique consisting of two components. In the first stage, mitotic cells were segmented using a fully convolutional network (FCN), while in the second stage, all detected objects were further refined using an additional CNN. This approach demonstrated superior performance compared to other methods in terms of detection accuracy, as evidenced by its performance in the 2014 ICPR MITOS-ATYPIA challenge. 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).

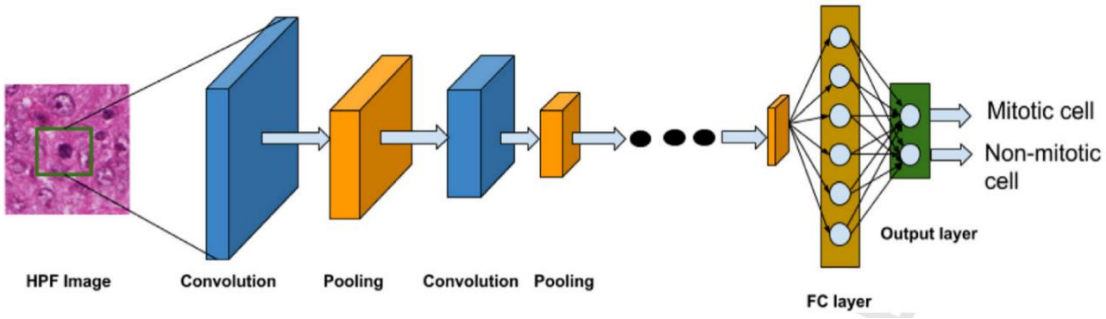

Fig. 3. Typical workflow of a method using deep learning [9]

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%
	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 multispect

Category	Authors	year	Method	Datasets	Results		
					precision	**Recall**	**F-score**
							ral scanner
	Wang et al. [25]	2014	Handcrafted and CNN features, random forest classifier, and CNN	ICPR 2012	0.84	0.65	0.73
Combination Hand-crafted (H.C.F)	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. [27]	2019	Mask R-CNN for object detection and handcrafted and CNN features	ICPR 2012	0.93	0.80	0.87
				ICPR 2014	0.62	0.67	0.64
Deep features (DF)	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

2.1.3 Mitosis detection using combination features (handcrafted with deep features)

Mahmood et al. [3] proposed a multi-CNN approach for mitosis detection. In the first stage, they employed Faster R-CNN for the initial detection of mitotic cells. This was the first time Resnet-50 was used as the feature extraction network. However, this technique generated a large number of false positives due to the subtle differences between mitotic and non-mitotic objects. To mitigate the false positives, the researchers conducted post-processing based on statistical, texture, shape, and color features. Additionally, they employed score-level fusion of Resnet-50 and a dense convolutional network (Densenet)-201 to further reduce the number of false positives. The results obtained using this method were as follows: for the ICPR 2012 dataset, precision of 0.876, recall of 0.841, and F1-measure of 0.858; and for the ICPR 2014 dataset, precision of 0.848, recall of 0.583, and F1-measure of 0.691. Wang et al. [25] introduced a cascaded technique that utilizes two independent classifiers. The first classifier is trained using handcrafted features such as morphology, intensity, and texture, which are extracted and classified using a Random Forests classifier. The second classifier is trained using CNN features. During the testing stage, if the outputs of the two classifiers differ, a third classifier is employed. The final decision is made by considering the consensus of predictions from all three classifiers. This technique offers the advantage of being fast and requiring fewer computing resources. However, it is important to note that the performance of ROI selection using conventional image processing is lower compared to 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] proposed a technique for mitotic detection using mask R-CNN, the feature network was extracted by Resnet-50. After that, when the results appeared, many false positives appeared, to reduce them, the Xception network was used. This technique showed high results when implemented on the two data sets ICPR 2012 and ICPR 2014, but this technology is not suitable for practical clinical application because it uses very expensive graphic processing units GPUs. Malon et al. [28] proposed a method that combines manually designed nuclear features with features learned by convolutional neural networks (CNN) for mitosis detection. The nuclear features capture color, texture, and shape information from segmented regions surrounding a nucleus. By incorporating a CNN, the method is able to handle the diverse appearances of mitotic figures, reducing the sensitivity to variations in feature extraction and thresholds. The trained system achieved F1 scores up to 0.659 on color scanners and 0.589 on multispectral scanners.

Li et al. [29] introduced “a method called SegMitos, which addresses the mitosis detection task through semantic segmentation. Their approach involves predicting the category of each pixel in the image and inferring the locations of mitotic cells directly from the segmentation map. They trained a segmentation network based on a fully convolutional network (FCN) using mitosis data. The SegMitos model generates a segmentation map where each pixel represents its confidence of belonging to the mitosis class. To reduce image noise, a Gaussian filter is applied to the response map. The method calculates the areas and mean confidence scores of the detected blobs in the segmentation map”. Following the segmentation map generation, a filtering mechanism was employed by Li et al. [29] that utilized the two aforementioned features to obtain the final detection results. One notable advantage of this model is its speed and efficiency, as it operates in an end-to-end manner (image-to-image) without relying on a sliding window approach. The model achieved an F-score of 0.562 on the ICPR 2014 MITOSIS dataset, 0.673 on the AMIDA13 dataset, and 0.669 on the TUPAC16 dataset, showcasing its performance across different datasets. Ali et al. [30] proposed a method for detecting mitosis using deep learning called Representation Differential Learning Method (RDLM) and this method was implemented on the ICPR 2014 dataset. This method was divided into two parts, in the first part GLB features are combined with FPN and the second part contains focal loss (FL). In the first part, (GLB-FPN) this combined method calibrates the decoder and makes it extract the regions of interest (ROIs). GLB works in three

phases: 1) by feature embedding the encoder correlates the layer with multiple scales, 2) feature map of the regions of interest (ROIs) of mitotic cells is obtained through noise removal and reconnection, 3) convolutions are used to transfer the feature map to the module decryption. This method achieved 0.685 precision, 0.70 recall and 0.692 F-score. Sohail et al. [31] proposed a novel Deep Convolutional Neural Network (CNN) based technique called "DHE-Mit-Classifier" for analyzing mitotic nuclei in breast histopathology images. This technique involves multiple levels: (1) identifying candidate mitotic patches within the histopathological biopsy regions, (2) classifying these patches into mitotic and non-mitotic nuclei using the proposed DHE-Mit-Classifier, and (3) constructing a heterogeneous ensemble by designing and utilizing five different deep CNNs as base classifiers.

Sigirci et al. [32] introduced a method that combines statistical-based conventional handcrafted methods with deep learning techniques. Their approach involves preprocessing the images with median filtering to reduce noise, applying the k-means algorithm for segmentation, and utilizing shape, texture, and statistical-based feature extraction algorithms along with CNN-based deep feature extraction. The classification step employs the RUSBoost method. The method was tested on the ICPR 2014 histological images dataset, which included approximately 180,000 non-mitotic and 748 mitotic cells extracted from 1200 images cropped from 10 histopathological whole slides. The achieved results were 96.78% precision, 79.42% recall, and 86.97% F-measure values.

Razavi et al. [33] proposed an automatic mitosis and nuclear segmentation method named MiNuGAN, which utilizes a conditional generative adversarial network. The architecture consists of an encoder-decoder with ResNet blocks, comprising 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 additional convolution layers. The output is a generated segmentation mask for both mitosis and nuclear classes. The proposed method was evaluated using images from multiple centers and scanners, including the TUPAC16, ICPR14, and ICPR12 datasets. Results on the TUPAC16 dataset, which consisted of 618 carefully annotated images, showed a mean Dice Similarity Coefficient (DSC) of 0.784 for nuclear segmentation and 0.721 for mitosis segmentation on 200 held-out testing images. On the ICPR12 dataset, the mean DSC for mitosis segmentation was 0.782, indicating good generalization to unseen datasets. For datasets with mitosis centroid annotations, a mean F1-score of 0.854 demonstrated high mitosis detection accuracy.

2.2 The Techniques on Deep Features Based on the Formulation of the Problem

Techniques that use deep features in the task of detecting breast cancer mitotic cells can be divided into three main sections based on problem identification and then formulation. The first part of the researchers considered the mitotic cell detection task as a classification task, because the final result of the task was two categories, either mitotic or non-mitotic.

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]		✓	

The second section of the researchers considered the task of detecting mitotic cells as a semantic segmentation task because of the annotations based on pixels that define the shape of the cells, while the third section of the researchers considered the detection of mitotic cells as a task of object-detection because the main goal is to calculate the mitotic number and not to determine the shape or size mitotic cells.

2.3 Datasets

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

2.3.1 ICPR 2012 MITOSIS dataset

The ICPR 2012 MITOSIS dataset was introduced in the ICPR 2012 contest [39]. Prof. Fr´ed´erique Capron and Dr. Catherine Genestie, two pathologists of Piti´e-Salpˆetri`ere Hospital in Paris, France presented 5 biopsy slides of breast cancer. These slides were stained with hematein and eosin. For each slide, pathologists selected 10 high-power fields at 40X magnification Each HPF has a file size of 512 × 512 µm 2. These 50 HPFs contain more than 300 mitosis, two-thirds of the images were used for training and the other third for testing. Three different scanners were used to scan these slides, namely • an Aperio XT scanner (scanner A)with resolution of 0.2456 µm per pixel; • a Hamamatsu NanoZoomer scanner with resolution of 0.2273 µm (horizontal) and 0.22753 µm (vertical) per pixel; • and a 10 bands multi-spectral microscope M with the best resolution of 0.185 µm per pixel.

2.3.2 ICPR 2014 dataset

Professor Fr´ed´erique Capron team presented the ICPR 2014 dataset for the MITOS-ATYPIA-14 grand challenge [40]. This dataset contains a set of breast cancer biopsy slides stained with hematein and eosin for this competition. To scan these slides two types of scanners an Aperio and a Hamamatsu were used. The training data contains about 1200 images, and for each image there is an excel file showing the coordinates of the mitosis centers, while the testing data contains about 496 images. The aim of this competition consisted of two parts: - detect mitosis on biopsies by writing the coordinates of the mitosis center on an Excel file for each of the testing images, - The second objective was to evaluate the score of nuclear atypia. The contestants had the right to choose which goal they wanted to work on.

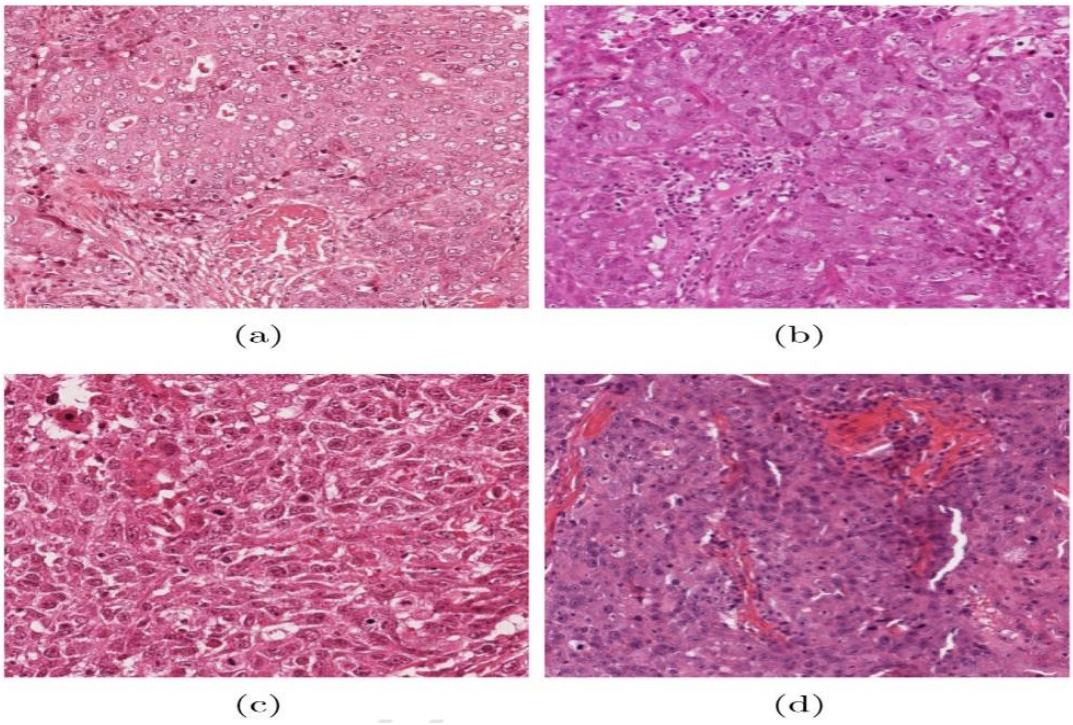

Fig. 4. Representative HPF images from public datasets(a) MITOS(Aperio scanner), (b)MITOS(Hamamatsu scanner), (c)MITOS-ATYPIA, (d)TUPAC [9]

2.3.3 Dataset TUPAC16

The database was provided in TUmor Proliferation Assessment 2016 (TUPAC16) challenge in whole-slide images (WSIs), where the aim of this challenge was to predict the degree of tumor spread in breast cancer through the detection of mitosis. The data set for this challenge contains 500 training and 321 testing breast cancer histopathology WSIs. The training data was provided only to the contestants, while the training data was maintained by the challenge organizers. The first task of the challenge was to predict the degrees of mitosis, while the second task of the challenge was to predict the gene expression based PAM50 proliferation scores from the WSI [14].

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, Mitosis like, Granulocyte, and Tumor cell. 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 Non mitosis.

3. DISCUSSION

Recently, including the medical sector, artificial intelligence (AI) technologies have made significant advancements. One area that has greatly benefited from these advancements is digital pathology. The introduction of full-slide imaging technology, which enables the scanning and storage of entire pathology slides at high magnification, has accelerated the adoption of digital pathology. This shift towards digital pathology has created numerous opportunities for the application of computational techniques in pathology, allowing for faster and more efficient analysis and diagnosis of medical specimens.One of the most important of these applications is the detection of the mitotic number in breast cancer, where high-resolution microscopes are used to photograph pathological slides, as these images can be stored and sent via the Internet with very high accuracy, which prompted doctors in hospitals to classify these images using pathologists and then send them to workers in the field of intelligence Artificial intelligence to train and test their different models. As happened with Prof. Fr´ed´erique Capron , a pathologist at Hospital in Paris, where he provided several pathological anatomy pictures and organized many competitions to detect patterns and reveal the mitotic number, as artificial intelligence techniques showed their effectiveness greatly, especially deep techniques

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.

AVAILABILITY OF DATA AND MATERIAL

The ICPR 2014 dataset it’s available on https://mitos-atypia-14.grand-challenge.org/.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. WHO - Cancer key facts; 2018. Available:https://www.who.int/news-room/fact-sheets/detail/cancer (Accessed20 November 20 2020).
2. Rao S. Mitos-rcnn: A novel approach to mitotic figure detection in breast cancer histopathology images using region based convolutional neural networks. arXiv preprint arXiv. 2018; 1807:01788.
3. Mahmood T, Arsalan M, Owais M, Lee MB, Park KR. Artificial intelligence-based mitosis detection in breast cancer histopathology images using faster R-CNN and deep CNNs. Journal of clinical medicine. 2020;9(3):749.
4. Ghoncheh M, Pournamdar Z, Salehiniya H. Incidence and mortality and epidemiology of breast cancer in the world. 2016;17:43–46.
5. Elston CW, Ellis I. Pathological prognostic factors in breast cancer. i. the value of histological grade in breast cancer: experience from a large study with long-term follow-up. c. w. elston & i. o. ellis. histopathology 1991;19;403-410. author commentary. 2002;41:151–2. discussion 152.
6. Li C, Wang X, Liu W, Latecki LJ. DeepMitosis: Mitosis detection via deep detection, verification and segmentation networks. Med. Image Anal. 2018;45:121–133.
7. Sebai M, Wang X, Wang T. Maskmitosis: a deep learning framework for fully supervised, weakly supervised, and unsupervised mitosis detection in histopathology images. Med Biol Eng Comput. 2020;58:1603–1623. Available:https://doi.org/10.1007/s11517-020-02175-z.
8. Beevi KS, Nair MS, Bindu GR. Automatic mitosis detection in breast histopathology images using convolutional neural network based deep transfer learning. Biocybernetics and Biomedical Engineering. 2019;39(1):214-223.
9. Mathew T, Kini JR, Rajan J. Computational methods for automated mitosis detection in histopathology images: A review. Biocybernetics and Biomedical Engineering. 2021;41(1):64-82.
10. Al-Janabi S, Huisman A, Van Diest PJ. Digital pathology: current status and future perspectives. Histopathology. 2012;61(1):1-9.
11. Higgins C. Applications and challenges of digital pathology and whole slide imaging. Biotechnic & Histochemistry. 2015;90(5):341-347.
12. Al-Janabi S, Huisman A, Vink A, Leguit RJ, Offerhaus GJA, Ten Kate FJ, Van Diest PJ. Whole slide images for primary diagnostics of gastrointestinal tract pathology: a feasibility study. Human pathology. 2012;43(5):702-707.
13. Piansaddhayanon C, Santisukwongchote S, Shuangshoti S, Tao Q, Sriswasdi S, Chuangsuwanich E. ReCasNet: Improving consistency within the two-stage mitosis detection framework. arXiv preprint arXiv: 2022;2202:13912.
14. Veta M, van Diest PJ, Willems SM, Wang H, Madabhushi A, Cruz-Roa A, Gonzalez F, Larsen ABL, Vestergaard JS, Dahl AB, et al. Assessment of algorithms for mitosis detection in breast cancer histopathology images. Med. Image Anal. 2015;20:237–248.
15. Ren S, He K, Girshick R, Sun J, Faster r-cnn: Towards real-time object detection with region proposal networks, in: C. Cortes, N. D. Lawrence, D. D. Lee, M. Sugiyama, R. Garnett (Eds.), Advances in Neural Information Processing Systems 28, Curran Associates, Inc. 2015;91–99. Available:http://papers.nips.cc/paper/5638-faster-r-cnn-towards-real-time-object-detection-with-region-proposal networks. Pdf
16. Huang CH, Lee HK.). Automated mitosis detection based on exclusive independent component analysis. In Proceedings of the 21st International Conference on Pattern Recognition (ICPR2012). 2012;1856-1859.
17. Khan AM, El-Daly H, Rajpoot NM. A gamma-gaussian mixture model for detection of mitotic cells in breast cancer histopathology images. In Proceedings of the 21st International Conference on Pattern Recognition (ICPR2012). 2012;149-152.
18. Irshad H. Automated mitosis detection in histopathology using morphological and multi-channel statistics features. J. Pathol. Inf. 2013;(4):1–6.
19. Paul A, Dey A, Mukherjee DP, Sivaswamy J, Tourani V. Regenerative random forest with automatic feature selection to detect mitosis in histopathological breast cancer images. In Proceedings of the International Conference on Medical Image Computing and Computer-Assisted Intervention,

Munich, Germany, 5–9 October. 2015;94–102.
20. Ciresan DC, Giusti A, Gambardella LM, Schmidhuber J. Mitosis detection in breast cancer histology images with deep neural networks. In Proceedings of the Medical Image Computing and Computer-Assisted Intervention, Nagoya, Japan, 22–26 September. 2013;411–418.
21. Sohail A, Khan A, Wahab N. et al. A multi-phase deep CNN based mitosis detection framework for breast cancer histopathological images. Sci Rep. 2021;11:6215. Available:https://doi.org/10.1038/s41598-021-85652-1
22. Lakshmanan B, Priyadharsini S, Selvakumar B. Computer assisted mitotic figure detection in histopathology images based on DenseNetPCA framework. Materials Today: Proceedings; 2022.
23. Cai D, Sun X, Zhou N, Han X, Yao J. Efficient mitosis detection in breast cancer histology images by RCNN. In Proceedings of the IEEE 16th International Symposium on Biomedical Imaging, Venice, Italy, 8–11 April. 2019;919–922.
24. Chen H, Dou Q, Wang X, Qin J, Heng PA. Mitosis detection in breast cancer histology images via deep cascaded networks. In Proceedings of the Thirtieth AAAI Conference on Artificial Intelligence, Phoenix, AZ, USA, 12–17 February. 2016;1160–1166.
25. Wang H, Cruz-Roa A, Basavanhally A, Gilmore H, Shih N, Feldman M, Tomaszewski J, Gonzalez F, Madabhushi A. Cascaded ensemble of convolutional neural networks and handcrafted features for mitosis detection. In Proceedings of the SPIE Medical Imaging, San Diego, CA, USA, 15–20 February. 2014;1–10.
26. Saha M, Chakraborty C, Racoceanu D. Efficient deep learning model for mitosis detection using breast histopathology images. Computerized Medical Imaging and Graphics. 2018;64:29-40.
27. Dodballapur V, Song Y, Huang H, Chen M, Chrzanowski W, Cai W. Mask-driven mitosis detection in histopathology images. In Proceedings of the IEEE 16th International Symposium on Biomedical Imaging, Venice, Italy, 8–11 April. 2019;1855–1859.
28. Malon CD, Cosatto E. Classification of mitotic figures with convolutional neural networks and seeded blob features. J. Pathol. Inform. 2013;4:1–5.
29. Li C, Wang X, Liu W, Latecki LJ, Wang B, Huang J. Weakly supervised mitosis detection in breast histopathology images using concentric loss. Med. Image Anal. 2019;53:165–178. [CrossRef]
30. Ali H, Li H, Afele Retta E, Haq IU, Guo Z, Han X, Feng J. Representation of Differential Learning Method for Mitosis Detection. Journal of Healthcare Engineering; 2021.
31. Sohail A, Khan A, Nisar H, Tabassum S, Zameer A. Mitotic nuclei analysis in breast cancer histopathology images using deep ensemble classifier. Medical image analysis. 2021;72: 102121.
32. Sigirci IO, Albayrak A, Bilgin G. Detection of mitotic cells in breast cancer histopathological images using deep versus handcrafted features. Multimedia Tools and Applications. 2022;81(10):13179-13202.
33. Razavi S, Khameneh FD, Nouri H, Androutsos D, Done SJ, Khademi A. MiNuGAN: Dual Segmentation of Mitoses and Nuclei Using Conditional GANs on Multi-center Breast H&E Images. Journal of pathology informatics. 2022;13:100002.
34. Alom MZ, Aspiras T, Taha TM, Bowen TJ, Asari VK. MitosisNet: end-to-end mitotic cell detection by multi-task learning. IEEE Access. 2020;8:68695-68710.
35. He K, Zhang X, Ren S, Sun J. Deep residual learning for image recognition," in Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition, LasVegas, NV, USA. 2016; 770–778.
36. Ren S, He K, Girshick R, Sun J. Faster r-cnn: towards real-time object detection with region proposal networks," in Proceedings of the Advances in Neural Information Processing Systems, Montreal, Canada. 2015;91–99.
37. He K, Gkioxari G, Dollár P, Girshick R. Mask r-cnn. In Proceedings of the IEEE international conference on computer vision. 2017;2961-2969.
38. Long J, Shelhamer E, Darrell T. Fully convolutional networks for semantic segmentation," in Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition, Boston, MA, USA. 2015;3431–3440.
39. Roux L, Racoceanu D, Loménie N, Kulikova M, Irshad H, Klossa J, Capron F, Genestie C, Le Naour G, Gurcan MN.

Mitosis detection in breast cancer histological images An ICPR 2012 contest. J Pathol Inform. 2013;4:8.
DOI: 10.4103/2153-3539.112693.
PMID: 23858383; PMCID: PMC3709417.

40. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology. 1991;19(5):403-410.
41. MITOS-ATYPIA-14 Grand Challenge. Available:https://mitos-atypia-14.grand-challenge.org/ (accessed on 14 November 2019).
42. Bertram CA, Aubreville M, Marzahl C. et al. A large-scale dataset for mitotic figure assessment on whole slide images of canine cutaneous mast cell tumor. Sci Data. 2019;6:274.
Available:https://doi.org/10.1038/s41597-019-0290-4
43. Marc Aubreville, Christof Bertram, Taryn Donovan, Christian Marzahl, Andreas Maier, and Robert Klopfleisch. A completely annotated whole slide image dataset of canine breast cancer to aid human breast cancer research. Scientific Data. 2020;7:11.
DOI:10.1038/s41597-020-00756-z.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/104270