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A Mitosis Detection and Classification Methodology with YOLOv5 and Fuzzy Classifiers

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Abstract – Histopathological images are examined by pathologists to diagnose cancer. A major step in classifying nuclei as cancerous or non-cancerous is to detect and classify mitosis. Detecting and classifying mitosis, however, can be challenging due to its complex form of proliferation and high similarity to non-mitosis. Typically, pathologists use manual methods to diagnose cancer. However, it is a very laborious, time-consuming and costly method. Computer-aided diagnosis helps pathologists in the early detection and recognition of cancer and increases diagnostic precision. Many methods have been proposed over the years, but researchers have not been able to develop a system that provides high accuracy and reliability for a wide range of applications. This issue motivates us to develop a new methodology for identifying and classifying mitosis in breast histopathological images. First, mitotic-shaped cells are detected with YOLOv5. Both mitotic and non-mitotic cells can be detected by YOLOv5. In results of YOLOv5 diagnosis accuracy and reliability are reduced. After the detection process of mitotic-shaped cells with YOLOv5, fuzzy-based classifiers such as Fuzzy-based K Nearest Neighbor, Fuzzy Min-Max, and Fuzzy Random Forest are applied to distinguish mitotic cells from non-mitotic cells. The performance verification of the proposed methodology is conducted on the MITOS ICPR14 dataset in terms of Precision, Recall and F1-Score.

***Keywords*:** Breast Cancer, Mitosis Detection, Mitosis Classification, YOLOv5, Fuzzy Random Forest.

1. Introduction

Cancer is the most dangerous disease of our age, for which there is no definitive cure until now. Cancer refers to a group of diseases that motivate the irrepressible increase of nuclei in the body, forming tumors. Cancer nuclei spread from the prime affected site to other parts of the body. Breast cancer has been the superlative popular cancer between women and a major reason for death globally in the last two decades. Early diagnosis of cancer reduces the risk of death. Therefore, there are research works conducted globally to improve the premature diagnosis of cancer [1]. Computer aided diagnoses (CAD) or digital pathology has become a major tool in this handle. In digital pathology, privately designed microscopes accounted with strong cameras are used to seize High-Power Field (HPF) images at high resolutions [2].

Mitosis detection or count is a predominant objective parameter in the breast cancer grading and staging unlike other types of cancers. Mitosis is the nuclei division process in living organisms, have four major phases: prophase, metaphase, anaphase, and telophase [3]. The task of mitosis detection and classification with high accuracy and reliability is a challenging due to the following reasons: (1) mitosis are small objects with a large range of shapes and texture formats; (2) the different terms for tissue dyeing; and (3) image acquisition process rise the diversity of the mitosis shapes' appearance. In the process of cancer grading and staging [4] the mitosis shapes' appearance plays incisive role. The grading of cancer indicates how much they resemble the parent tissue. Cancer grading primarily aims at determining the aggressiveness of cancer. Cancer staging measures how far the disease has progressed from the primary seeming organ to other parts of the body. Mitosis detection is an index of the nuclei proliferation rate and hence the phase of cancer [5].

The literature contains numerous studies on cancer diagnosis [6], specifically focusing on mitosis detection and classification. With the rapid progress of deep-learning models in cancer diagnosis, there have been significant advancements in cancer staging and grading. However, existing studies have not achieved the desired level of accuracy and reliability for cancer diagnosis. Consequently, there is a growing need for more effective research in this area.

To address this need, this study introduces a novel methodology for accurate and reliable breast cancer diagnosis. The proposed approach involves the detection of mitotic-shaped cells using YOLOv5 and subsequently separating them from non-mitotic cells using fuzzy-based classifiers. The results demonstrate that this methodology enhances both the accuracy and reliability of mitosis detection and classification.

The rest part of the paper is organized as follows. Section 2 summarizes the related studies on mitotic detection. Section 3 describes the proposed methodology. Section 4 discusses the implementation results. Finally, Section 5 presents the conclusions.

2. Related works

Numerous studies have explored mitosis detection and classification using deep learning and fuzzy-based techniques. Several existing works have been summarized below:

Khan et al. [7] proposed SMDetector, which incorporates Feature Pyramid Network (FPN), Region Recommendation Network (RPN), and Region of Interest (ROI) modules for mitosis detection and classification. Their model achieved an overall average precision (AP) of 50.31, an average recall (AR) of 55.90, and an F1-Score of 63.88 on the ICPR14 dataset.

Razavi et al. [8] introduced MiNuGAN, a cGAN architecture for dual mitosis and nuclei segmentation. Their approach achieved a mean F1-Score of 0.854 on the TUPAC16, ICPR12, and ICPR14 datasets.

Banerjee et al. [9] employed U-Net for segmentation, YOLO for object detection, and one-class SVM for binary classification. Their work utilized the ICPR 2012 and Data Science Bowl 2018 datasets to train the object classification model.

Yancey [10] combined faster RCNN for object detection with segmentation features from U-Net. The features from both streams were fused using the bilinear pooling layer, achieving an F1-Score of 0.508 on the ICPR14 dataset.

Cayır et al. [11] proposed MITNET, a two-stage deep learning framework for mitosis classification in Whole Slide Images (WSI). MITNET-det is an architecture that uses CSPDarknet and PANet to extract features from nuclei images and fuse them together. It then proceeds to the classification stage, where isolated nuclei images are fed into MITNET-rec. MITNET-rec's main objective is to identify and classify instances of mitosis within whole-slide images (WSIs). They achieved an F1-Score of 68.7 on the publicly available MIDOG dataset and 49.0 on the ATYPIA dataset.

Nateghi et al. [12] developed a method consisting of region of interest detection, mitosis detection using deep neural networks, and tumor proliferation scoring using Support Vector Machine (SVM). Their approach was evaluated on the TUPAC16 dataset for overall proliferation scoring performance.

Rehman et al. [13] proposed a general method involving feature vector set preparation, weightage assignment, classification using SVM and Random Forest (RF), and majority voting. Their approach achieved high F1-Scores for mitosis detection in ICPR12, ICPR14, AMIDA13, and TUPAC16 datasets.

Thomas and Jisha [14] utilized Fuzzy C-Means clustering for nuclei identification, followed by RF classification for mitosis/non-mitosis classification. Their approach attained an F1-Score of 78.0 on the ICPR14 dataset.

Wang et al. [15] introduced the FMDet algorithm, which included Fourier-based data augmentation, pixel-level annotation generation, and segmentation-based mitosis detection. Their approach achieved an F1-Score of 0.77 on five different datasets.

Hwang et al. [16] employed fuzzy segmentation and thresholding to distinguish mitosis candidate images from the background. Their approach achieved an F1-Score of 88.9 on the TUPAC16 and ICPR12 datasets.

Lakshmanan et al. [17] proposed a supervised deep framework combining DenseNet-121 and Principal Component Analysis (PCA) for mitosis classification. Their approach utilized a Decision Tree (DT) classifier and achieved successful feature training for classification.

Maroof et al. [18] introduced a hybrid feature space combining color, morphological, and texture features for mitosis and non-mitosis discrimination. Their SVM classifier outperformed the RF classifier, achieving an F1-Score of 72.07 on the ICPR14 dataset.

Although deep learning and fuzzy techniques have been applied independently for mitosis detection and classification, the obtained results on the ICPR14 dataset are not satisfactory for accurately and reliably diagnosing breast cancer. In this paper,

we propose combining deep learning and fuzzy techniques to achieve high accuracy and reliability in both mitosis detection and classification.

3. Proposed Mitosis Detection and Classification Methodology

The overall framework of the proposed methodology is presented in Fig. 1. The proposed methodology has four main stages:

1) dataset initialization, 2) preprocessing, 3) mitosis detection and 4) mitosis classification.

In the following subsections, each stage is described.

3.1. Dataset Initialization

The most common datasets used for mitosis detection are as follows: ICPR12 [3], ICPR14 [19], TUPAC16 [20], MIDOG22 [21], and AMIDA13 [22]. In this study, ICPR14 dataset is selected as the dataset to carry out experiments. There are 1200 labeled and 496 unlabeled images in the ICPR14 dataset. Labeled images contain both mitosis and non-mitosis. The central pixels of the mitosis were marked by the pathologists. ICPR14 consists of multiple HPFs that differ in different aspects caused by unlike factors such as tissue acquisition, staining, lighting, and tissue portability. The ICPR14 dataset is thus the most suitable for detecting and classifying mitosis in histopathological images.

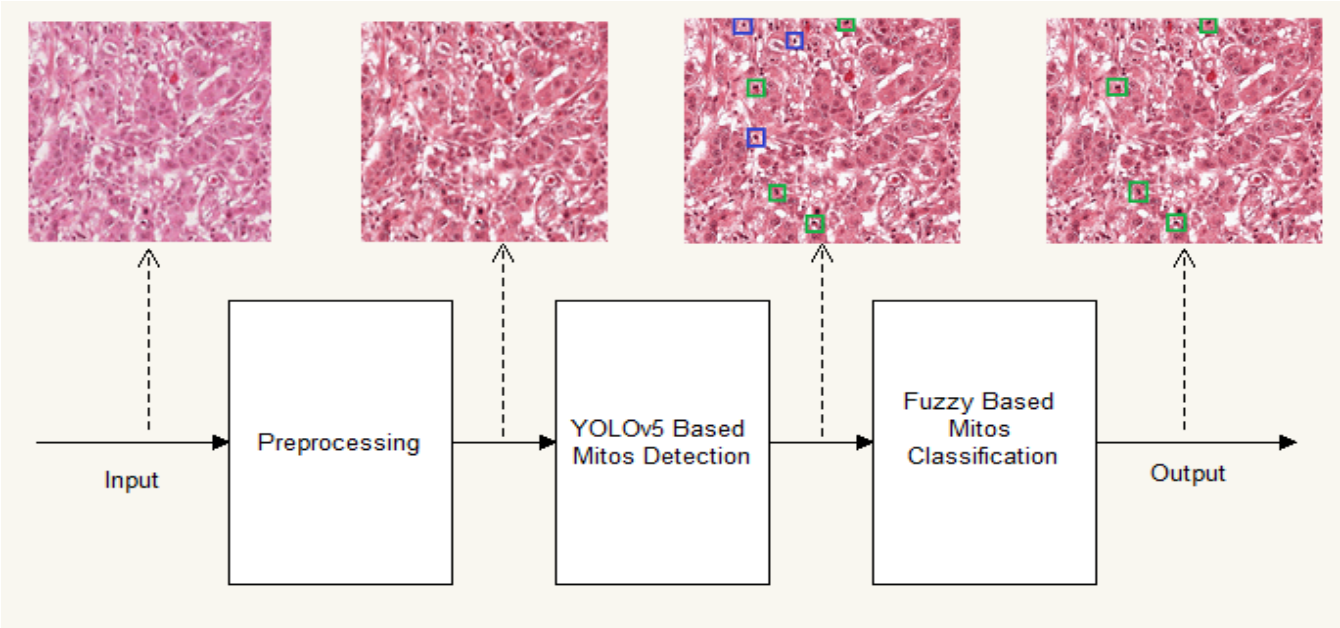

Fig. 1: Proposed Mitosis Detection and Classification Methodology

3.2. Preprocessing

In the second stage of the methodology, preprocessing is performed on the ICPR14 dataset. The purpose of preprocessing is to improve the quality of the images in the dataset so that they can be analyzed more effectively. Before model training and feature extraction, preprocessing processes should be applied to the images in the dataset. In the scope of preprocessing, size, direction, color, etc. settings are made. Preprocessing allows the removal of undesired deterioration and achieves certain properties required for the application being studied [23].

In the proposed methodology, we apply a color normalization technique, namely Macenko [24]. In this method, stain vectors are determined for each image based on the colors present. A pixel with an Optical Density (OD) value of 0 represents no light absorption. It is then necessary to project OD-transformed pixels onto the geodesic direction to determine the stain vector endpoints [25].

3.3. Mitosis Detection

The Histogram of Oriented Gradients (HOG) is used for the purpose of object detection in many image processing and computer vision studies. HOG decomposes an image into small, squared patches, computes a histogram of oriented gradients for each patch, normalizes the result using a block-wise pattern, and returns a descriptor for each patch. HOG features have been used as input to the YOLOv5 [26] model. The HOG features may serve as additional information or be combined with other features in a fusion step.

YOLOv5 is a novel convolutional neural network (CNN) that detects objects in real-time with high accuracy [26] (Fig. 2). This model uses a single neural network to process the entire image. At the results, mitosis and non-mitosis are detected and the bounding boxes for them are created. An original image applied to model is resized into 224×224 pixels. The coordinates of the detected mitosis are saved into a data frame. YOLOv5 consists of three important components. backbone, neck, and output. The backbone network is responsible for feature extraction from the input image, capturing both low-level and high-level features that are important for object detection. The neck component combines the extracted features and produces feature maps at three different scales. Finally, the output section is responsible for detecting objects based on the generated feature maps.

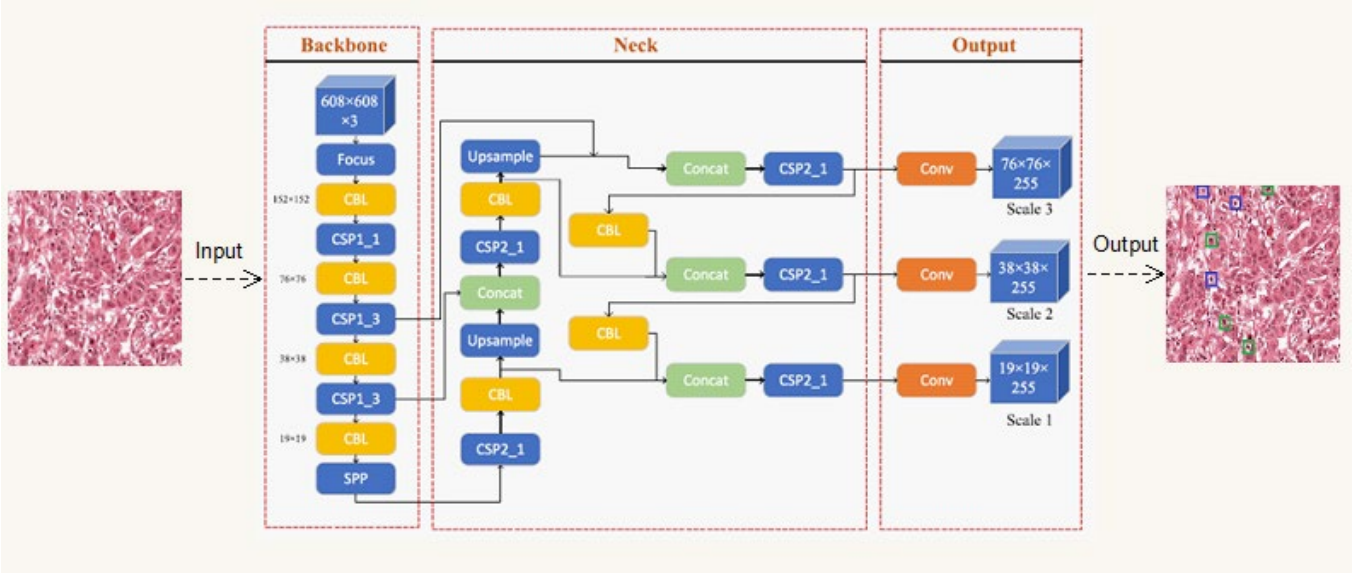

Fig. 2: The Architecture of YOLOv5

3.4. Mitosis Classification

On the output of YOLOv5 of the proposed architecture, mitosis (TPs - green squares in Fig. 1 and Fig. 2) and non-mitosis (FPs - blue squares in Fig. 1 and Fig. 2) are detected. This case decreases the accuracy and reliability of cancer diagnosis. FPs need to be decreased to increase the accuracy and reliability of detecting and classifying only real mitosis. In the proposed architecture and methodology three different fuzzy-based classifiers are used to remove FP mitosis. Fuzzy-based classifier algorithms have been employed to address the challenge of false positive (FP) detection in mitosis identification. Fuzzy-based classifiers can be trained using labeled data to learn the subtle patterns and characteristics that distinguish true mitoses from other structures. By considering the uncertainty and imprecision associated with mitosis identification, these algorithms assign membership degrees to each candidate, allowing for a more nuanced classification process. By leveraging fuzzy logic principles, these classifiers can effectively reduce the occurrence of FP mitosis detections, improving the accuracy and reliability of automated mitosis detection systems in cancer research and diagnosis.
We employ the following fuzzy-based classifiers:

a) ***Fuzzy Random Forest (FRF)*** is an ensemble method based on fuzzy decision trees. This approach combines the stability of multiple classifier systems, the power of randomness to increase the diversity of the trees, and the flexibility of fuzzy logic and fuzzy sets for imperfect data management. This algorithm is used to reduce bias in random data feature selection caused by associated features. Fuzzy random forest can handle imbalanced data effectively by adjusting the fuzzy membership degrees according to the class distribution. This ensures that the algorithm gives appropriate consideration to minority classes, leading to more balanced and accurate predictions. FRF, according to its assumptions, combines the robustness of ensemble classifiers and the power of randomness to decrease the relation between the trees and increase their range of them and the flexibility of fuzzy logic to deal with imperfect data [28].

b) ***Fuzzy K Nearest Neighbor (FKNN)*** assigns class membership to a sample vector rather than assigning the vector to a particular class. The advantage is that no arbitrary assignments are produced by the algorithm. The FKNN classifier finds the memberships of data instances into classes rather than assigning the whole class label. By adjusting the fuzziness parameters, such as the shape of membership functions or the degree of fuzzification, FKNN can handle data with varying degrees of uncertainty and imprecision. It is useful that how much its neighbors belong to a class to improve accuracy [29].

c) ***Fuzzy Min-Max (FMM)*** is a machine learning method that learning stage is completed just with one pass over the learning samples and used for classification or clustering. One of the most major properties of this approach is that most of the processing is related with detection and fine-tuning the boundaries of the classes [30]. In FMM, there are mainly 3 processes: expansion process, overlap test, and contraction process.

4. Implementation

The experiments were conducted using a PC with an NVDIA RTX 4000 GPU, Intel(R) Xeon(R) W-2245 CPU@3.90GHz and a 64GB System RAM with python programming language via Google Colab platform. MITOS ICPR 2014 dataset was used to implement the proposed architecture and methodology.

To evaluate the performance of the proposed methodology for mitosis detection and classification the following metrics are used:

$$Precision = \frac{N_{TP}}{N_{TP} + N_{FP}}, \tag{1}$$

$$Recall = \frac{N_{TP}}{N_{TP} + N_{FN}}, \tag{2}$$

$$F1 - Score = 2 \times \frac{Precision \times Recall}{Precision \times Recall}, \tag{3}$$

where N_{TP} represents the number of true positives, which is recognized as mitosis and is actually the number of mitosis; N_{FP} represents the number of false positives, which is actually the number of non-mitosis among detected mitosis; N_{FN} represents the number of false negatives, which is recognized as non-mitosis and is actually the number of mitosis; N_{TN} represents the number of true negatives, which is recognized as non-mitosis and is actually the number of non-mitosis.

Table 2: Implementation results

Methods	Precision	Recall	F1-Score
YOLOv5	0.818	0.757	0.79
YOLOv5 + Fuzzy Min-Max	0.822	0.684	0.750
YOLOv5 + Fuzzy K Nearest Neighbor	0.865	0.752	0.805
YOLOv5 + Fuzzy Random Forest	**0.895**	**0.848**	**0.873**

The experimental results are presented in Table 2 in terms of Precision, Recall and F1-Score. From Table 2, it can be indicated that YOLOv5 with fuzzy versions of K Nearest Neighbor and Random Forest significantly improves the classification performance compared to YOLOv5 without a classification stage. YOLOv5 only performs better than

YOLOv5 with a Fuzzy Min-Max classifier. When comparing the fuzzy version of K Nearest Neighbor and Random Forest, it can be observed that Random Forest outperforms K Nearest Neighbor. It can therefore be inferred that YOLOv5 with an additional classification stage can perform well in terms of classifying mitosis and Fuzzy Random Forest is the most appropriate classifier as an additional stage for YOLOv5.

5. Conclusion

The accurate detection and classification of mitosis are critical for cancer staging and grading. However, this task poses challenges due to the similarity between the shapes of nuclei and mitotic cells, often leading to the misclassification of nuclei as mitosis. Consequently, the reliability of cancer grade and stage analysis is compromised. To address this challenge, we propose a two-stage methodology for the detection and classification of mitosis in breast histopathological images. Our methodology begins by utilizing YOLOv5 for the initial detection of mitotic cells. Subsequently, the detected mitotic cells undergo classification using fuzzy classifiers, specifically Fuzzy K Nearest Neighbor, Fuzzy Min-Max, and Fuzzy Random Forest. Notably, the inclusion of fuzzy classifiers as an additional stage for mitotic cell classification is a novel contribution in the literature.

In future research, we intend to enhance the performance of our methodology by incorporating the latest versions of the YOLO architecture. Additionally, we plan to release a publicly available dataset for mitosis detection, facilitating further research and advancements in this field.

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