Web based Mitosis Detection on Breast Cancer Whole Slide Images using Faster R-CNN and YOLOv5

Mitosis Detection on Breast Cancer WSI using Faster R-CNN and YOLOv5

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***Abstract*—Histological grading quantifies the tumor architecture and the cytology deviation of breast cancer against normal tissue. Nottingham Grading System grades the breast cancer classification and allots tumor scores. Mitotic detection is one of the major components in the Nottingham Grading System. Using a conventional microscope is time-consuming, semi-quantitative and has limited histological parameters. Digital scanners scan the tissue slice into high-resolution virtual images called whole slide images. Deep learning models on whole slide images provide a fast and accurate quantitative diagnosis. This paper proposes two deep learning models namely Faster R-CNN and YOLOv5 to detect mitosis on WSI. The proposed Deep Learning models uses 56258 annotated tiles for training/testing and provide F1 score as 84%. The proposed model uses a web-based imaging analysis and diagnosis platform called CADD4MBC for image uploading, Annotation and visualization. This paper proposes an end-to-end web based Deep Learning detection for Breast Cancer Mitosis.**

***Keywords*—Nottingham grading system; breast cancer biomarker; whole slide image; mitosis; faster R-CNN; YOLOv5**

I. Introduction

Histological grading system is used to evaluate the behavior and prognosis of breast cancer on Hematoxylin and Eosin (H&E) stained images which quantifies the tumor architecture and the cytology deviation of the breast cancer tissue against the normal tissue. The grading also provides a degree of differentiation in the morphological assessment of breast cancer. As clinical stages are unable to provide early as well as developed lymph-blood meta stages information, Bloom and Richardson defined a histological grading system. This system allotted tumor scores between 1-3 based on individual components such as mitotic nuclei, nuclear pleomorphism, and tubule formation [1]. Their grading system was not accepted as a routine procedure for breast cancer grading classification due to the inconsistent issue in grading [2].

Elston-Ellis modified the Bloom and Richardson system and called their grading system as Nottingham grading system (NGS). NGS is accepted globally as a guide for grading breast cancer classification due to its semi-quantitative assessment of three morphological components such as a number of mitotic figures in the most active area called a high-power field, the size and shape of nuclear variation in tumor tissue against small regular uniform cells (Nuclear Pleomorphism) and the percentage of tumor tubule formation [3]. Hence the detection of mitosis is the major component of NGS. Mitosis is a cell duplication process that divides the cell into two cells which are genetically identical. The rapid and irregular mitosis cell count decides the tumor grading and the selection of tumor treatment options.

Histological grading on glass tissues using conventional microscopes is time-consuming which also has a limited evaluation of histological Parameters and semi-quantitative properties which is subject to high inter-observer variability. These limitations are overcome by the advent of digital pathology and Whole Slide Image (WSI) technology. WSI technology uses digital scanners to create high-resolution virtual images of the glass slide. The digitized images are stored as pyramid structures to view and analyze WSI at various Zoom levels (5x - 40x) [4]. Deep learning models performed over WSI virtual images provide fast and accurate diagnoses [5].

This paper proposes 1) Creation of digitized WSI Breast Cancer dataset; 2) performs mitosis annotations on the created dataset by pathologists; 3) develop two deep learning models, namely, Faster R-CNN and YOLOv5 to detect mitosis on WSI. This proposal reduces the difficulties of pathologists such as time consuming and inter-observer variability. The proposed models produce quantitative results. The paper is organized as follows: Section 2 lists the existing works, Section 3 proposes Faster R-CNN and YOLOv5 models and describes the dataset and preprocessing methods used by the deep learning models, Section 4 discusses the implementation/results and Section 5 conclude the summary of the proposed work.

II. Literature Survey

MP-Mitdet [6] used a multiphase CNN framework to detect mitosis using the public dataset, namely MITOS 12 [7], MITOS 14, AMIDA 13 [8] and TUPAC 16 [9] with the evaluation parameters as F1 Score 0.74 and precision 0.71. The model performs Mean-Standard normalization as the pre-processing procedure on the different public datasets which are captured by different scanners. Model Mask-RCNN is used for automatic labelling and detection of mitosis. Resnet is used for cell-level classification. The model also proved that deep CNN's performance is better than conventional classifiers such as SVM, Logistic Regression, XGBoost, Random Forest and Navies Bayes.

The Deep Mitosis model [10] adopts three components to detect mitosis using a deep detection model on 205 weakly annotated mitosis. The first component DeepDet produces all possible detection of mitosis, the second component DeepVer removes false positives, and the final component DeepSeg uses RPN to segment the mitosis. They conclude that the model DeepVer reduces the performance and other models produce an F1 Score of 0.38.

Meriem Sebai et al [11] use two datasets ICPR12 & ICPR14 for the localization, classification and segmentation of mitosis. The weakly annotated mitosis dataset i.e. ICPR 14 which has labels only the centroid of mitosis is trained by Mask-RCNN Model [12]. The model segments the mitosis by using the pixel-level annotated mitosis dataset called ICPR12. The model Mask-RCNN is used as a two-stage deep learning framework in which the first stage identifies the centroid of the mitosis and in the subsequent stage detects the instance segmentation of mitosis. This model produces an F1 Score of 0.863 on the 2012 ICPR and achieves an F1 Score of 0.475 on the 2014 ICPR datasets.

De Cai et al. [13] segments mitotic cells by using the deep learning model called Faster R-CNN [14]. This two-stage object detector model first identifies the possible mitotic cells and then the second stage detects the target mitotic cells from the result of the first stage which produces higher accuracy than the single-stage detectors and also reduces the computation time. This model achieved a 0.76 recall value and 0.736 F1 Score on Miccai and TUPAC datasets.

Dan C Cireșan et al. [15] proposed a supervised model called Deep Neural network to detect mitosis on H&E images. This model uses Max Pooling layers as a subsampling layer to classify whether a cell is a mitosis or not. The model is trained and tested by two public datasets namely ICPR12 and ICPR14. In the training datasets, the cells in the H&E images are labelled as mitosis or non-mitosis based on the number of pixels which are closer to mitosis. The training dataset also uses bounding boxes to label mitosis. This model achieved an F1 Score of 0.782.

The research done by Gabriel Jiménez et al [16] suggests two deep learning architectures namely CNN and U-net [17] for mitosis classification and detection in histopathological tissue samples. The images used to evaluate the proposed approaches were obtained from two public datasets from the ICPR-2012 competition and the MITOS-ATYPIA-2014 challenge. Convolutional Neural Network is used for binary classification to classify mitotic and non-mitotic cells. The model got 95% testing accuracy with an F1 score of 94.35%. The model U-net is used for the semantic segmentation of mitosis and produces 0.9 F1 score accuracy.

MiNuGAN [18] automatically segments mitoses and nuclei using conditional generative adversarial networks [19] on the public datasets namely TUPAC16, ICPR14, and ICPR12 Datasets. The model uses 618 annotation files for training and 200 file images for testing with an F1 Score of 0.824.

The limitations in the existing literature are most of the researchers applied deep learning models only on the three public datasets namely ICPR 12, ICPR14 and Tupac in which, ICPR14 and Tupac are weakly annotated (only the mitotic centroids are labelled) and ICPR 12 is a strongly annotated dataset (all the pixels of mitotic cells are labelled). The combined data size of the three datasets is around 7000 only. The less data in deep learning training may produce less accuracy. Another main problem in mitosis detection is to differentiate normal cells from mitotic figures. If the pathologist missed this differentiation causes wrong annotations. The existing works are not providing information about the data collection /annotation of the mitosis dataset.

The above-mentioned limitations are overcome by the proposed system by training the deep learning models on both public datasets and private KMIT datasets. KMIT dataset is a private dataset contains breast cancer WSI, tile images with their respective mitotic figure annotations. CADD4MBC is a web-based deep learning platform developed internally by the authors which is used for uploading WSI/tiles, creating annotations, JSON downloading and visualization of WSI. Thus, the proposed system provides a web-based end-to-end AI mitosis detection which connects pathologists, technicians and hospitals.

III. Proposed System

A. Dataset Description

*1) Public dataset:*The proposed Deep learning models use three public datasets namely ICPR12, ICPR14, and TUPAC. Mitos Dataset is a public dataset of the mitosis competition held by ICPR in 2012. In each slide, the pathologists selected 10 high-power fields at 40X magnification. This dataset consists of 2994 files of size 512 x 512. After applying augmentation methods such as horizontal flipping and vertical flipping increase the files to 4367. The ICPR 2014 dataset was presented in the MITOS-ATYPIA-14 grand challenge and comprises 2400 files of size 512 x 512 at 40x magnification. Pathologists annotated a total of 1502 centroid pixels of mitosis (weakly labelled).

The TUPAC mitosis dataset contains 73 cases collected from the department of pathology at the university medical Centre in Utrecht, The Netherlands. Each case was represented by one WSI region with an area of 2mm x 2mm. The annotated mitotic figures are accepted by two pathologists and the dataset contains 1552 weakly annotated mitotic figures of the size 512 x 512.

2) KMIT dataset: KMIT dataset contains 75 WSI which are collected from Basavatarakam Indo-American Hospital and scanned by Tapadia diagnostics Centre using a Morphile scanner at 40x magnification for the last two years. The dataset contains around 56,000 mitotic figures annotated by pathologists from both hospitals using the CADD4MBC platform and each WSI varies from 8 - 12 GB. The 40X level magnification WSI is divided into several tiles (around 30,000 - 50,000) of size 500 x 500. Each uploaded WSI is divided into several (minimum 100) batches and each batch consist of 150 tiles as shown in Fig. 1.

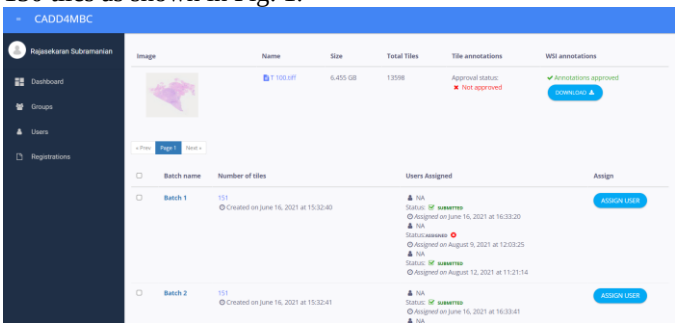

Fig. 1. Uploaded WSI and the batches of tiles

Each tile is annotated by the pathologists using the drawing tools in the CADD4MBC as shown in Fig. 2.

Fig. 2. Mitosis annotations on tiles

Basavatarakam Indo-American Hospital and Tapadia diagnostics centre annotate around 42,000 tiles for mitotic figures using CADD4MBC platform. This Dataset is increased to 56,258 after applying augmentation methods such as horizontal and vertical flipping. The proposed Deep learning (DL) models use both private and public datasets for training. The summary of the dataset used by the proposed deep learning models is shown in Table I.

TABLE I. DATASET SUMMARY

Dataset Name	Size of Dataset	Image Size	Number of Tiles after Augmentation	Labels	Annotation Type
ICPR 12	2994	512 x 512	4367	Strongly Labelled	CSV
ICPR 14	2400	512 x 512	-	Weakly Labelled	CSV
TUPAC	2650	512 x 512	-	Weakly Labelled	CSV
KMIT Dataset	42,000	512 x 512	56,258	Strongly Labelled	JSON

B. KMIT Dataset Preprocessing

1) Color normalization: Hematoxylin and Eosin staining provide a detailed view of the cells in the tissue. Color variations may occur in the image due to the H&E staining affects deep learning predictions and can result in an incorrect diagnosis.

Color normalization provides a uniform standardized staining effect on tissue images. Reinhard color normalization method [20] adjusts the color variations of the input image by comparing the mean color variations between the input image and the standard reference image. After color variation adjustment the input image will be converted back to RGB color space.

2) Mask generation: The input files and the respective annotated JSON files are gathered from the CADD4MBC platform and the mask is created by using the ellipse function in the OpenCV library as shown in Fig. 3.

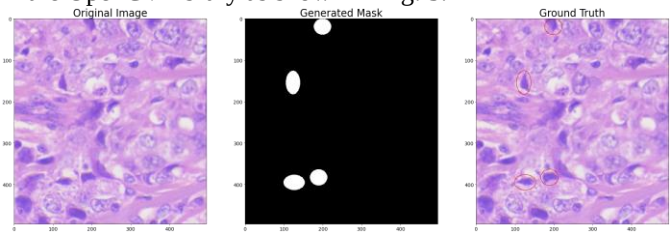

Fig. 3. Generated mask and the respective mitotic figure annotations

The generated mask is used to calculate the area of the ellipse and the semantic segmented points of the mitosis. If the area of the ellipse is very small then the respective annotations are removed as they won't produce good accuracy in deep learning training.

3) Annotation formats: The JSON format of the annotations is downloaded from CADD4MBC and are converted into a COCO dataset format and .txt for Faster R-CNN and YOLOv5 model respectively. The COCO annotation format [21] is used and understood by the most popular advanced neural network libraries such as Facebook Detectron-2. The COCO format can be used for object detection for both binary and multiclass detection. COCO dataset format is a combined file of all the annotations (JSON formats). Hence as shown in the Fig 4, all training image annotations are presented in a single file instead of individual JSON files for each annotation and similarly, testing requires only one COCO dataset JSON file.

The YOLOv5 model requires the annotations in a .txt file format. Each line in the .txt file represents one annotation and has [Class, X-center, Y-center, Width, Height] format, where the class number is used for mitosis and the remaining are the bounding box coordinates of the annotations which is shown as [0, 0.221, 0.579, 0.058, 0.058].

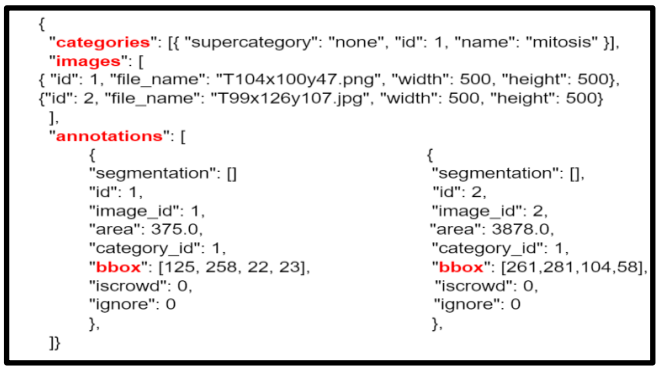

Fig. 4. Sample mitotic figure COCO format annotation

C. Proposed DL Models Description

1) Faster R-CNN: Object detection networks primarily depend on algorithms which propose regions. The Proposed work uses Faster R-CNN to detect mitotic figures which is the most popular and advanced CNN-based object detection model. Faster R-CNN consists of three components such as backbone network, region proposal network and region of interest pooling.

a) Backbone network: In this proposed method, the Resnet-FPN [22] model is used as the backbone for automatic mitosis detection which is a combined model of Residual networks (Resnet) [23] and Feature Pyramid Network (FPN). As the input image is given to the first convolution block of the model then the features are extracted till the last convolution block. This layer-by-layer feature extraction sometimes leads to a gradient vanishing problem which makes it to lose the important features of the original image. The gradient vanishing problem is handled by Resnet by using its skip connections property and by FPN. The main objective of FPN is up sampling the low-resolution features with high-level feature maps (feature maps generated from the previous layers).

b) Region proposal network (RPN): Region Proposal network takes feature maps generated by FPN as input. RPN generates anchor boxes by using two parameters such as scales and aspect ratio. After generating anchor boxes there will be a possibility of many boxes which do not contain any object inside them. Region proposal network is mainly used for localizing and classification of the anchor box which are performed by the bounding box regression layer (anchor deltas convolution) and the bounding box classifier layer. These layers produce four regression parameters such as (x, y, w, h) where (x, y) is the centre, and w and h are the width and height of the anchor box.

c) Region of interest (ROI) pooling: The main issue in object detection is each proposal of RPN will be in a different shape. As per the Faster R-CNN architecture after ROI pooling there is a Fully Connected layer which generates a fixed-size feature map from the non-uniform size of input feature maps.

2) YOLOv5: YOLOv5 [24] is a single-stage object detector which requires only a single pass to the neural network and predicts all the bounding boxes. This feature makes YOLOv5 faster than any other traditional detection algorithm.

a) YOLOv5 consists of three important components: Cross Stage Partial Network (CSP) [25] is used as a backbone to extract informative features from an input image. CSPNet is used to achieve a good gradient combination and reduce the amount of computation which is achieved by partitioning the feature map of the base layer into two parts and then merging them through a proposed cross-stage hierarchy. PANnet [26] is used as a model neck which generates feature pyramids and scaled up the features.

The YOLOv5 model uses the YOLO layer as the head layer for the final detection of the objects. This layer generates 3 different sizes (18 × 18, 36 × 36, 72 × 72) of feature maps (bounding boxes) to achieve optimal prediction. This layer enables the model to handle small, medium, and big objects depending on the size of the objects.

IV. Results and Discussions

The proposed system initially uses three public datasets namely ICPR 12, ICPR 14 and TUPAC to detect mitosis. ICPR 12 contains semantic segmentation of mitosis whereas ICPR 14 and TUPAC contain the centroid of the mitosis. The proposed system uses the Faster R-CNN model to detect mitosis by using the ICPR 12 dataset for training and testing around 2994 tiles and produces an F1 score of 82.1. Subsequently, ICPR 14 and TUPAC datasets are tested by the Faster R-CNN model which is tested on around 900 tiles to detect mitosis. From tested results, the false positives are removed by comparing the centroid annotations of mitosis in ICPR 14 and TUPAC. The model produces Fl Score as 75% and 84% for ICPR 14 and TUPAC, respectively.

KMIT dataset is created by scanning 75 breast cancer WSI using a Morphle scanner at 40X magnification. The breast cancer tissue slides are collected from Basavatarakam Indo-American hospital, Hyderabad and Tapadia diagnostic centre Hyderabad. After digitizing WSI, each WSI is divided into tiles and on each tile the preprocessing methods such as normalization and resizing are applied. The tiles are annotated on the CADD4MBC platform by the pathologist of both the hospitals. Then masks are generated for the annotated tiles as well as JSON format of the annotations are downloaded from the platform. The JSON annotations are converted into COCO annotation format which is applicable to Faster R-CNN. The model is trained by 45,006 tiles and tested by 11,251 tiles. The model got an F1 score of 77% and the time taken for training is 10 hours 46 minutes

To improve accuracy the proposed system uses the YOLOv5 model which is the fastest object detection model on the KMIT dataset. YOLOv5 model accepts .txt annotations format. After converting JSON format into .txt format, YOLOv5 is trained by 45,006 tiles and tested by 11,250 files. The model produces an F1 score of 84%, and the time duration for training is around 9 hours 12 minutes.

To improve training and testing time YOLOv5 distributed model is applied to the KMIT dataset. This model used 45,006 files for training and 11,251 for testing and produced an F1

score of 84% within 5 hours and 28 minutes. Table II shows the performance of the proposed models, size of training and testing dataset, Evaluation metrics, and the training time of the proposed deep learning models.

TABLE II. PERFORMANCE OF THE PROPOSED MODEL

Dataset Name	Training	Testing	Model	F1-Score	Recall	Precision	Training Duration
ICPR12	3304	1063	Faster R-CNN	85.48	88.91	82.15	49 mins
ICPR14	-	547	Faster R-CNN	81.46	87.89	76.52	-
TUPAC	-	321	Faster R-CNN	82.15	81.56	81.69	-
KMIT Dataset	45006	11251	Faster R-CNN	75.86	73.83	76.86	10 Hrs 46 mins
KMIT Dataset	45006	11251	YOLOv5 (CPU)	84.23	81.62	86.76	9 Hrs 12 Min
KMIT Dataset	45006	11251	YOLOv5 (Distributed GPU)	84.58	82.31	86.42	5 Hrs 28 mins

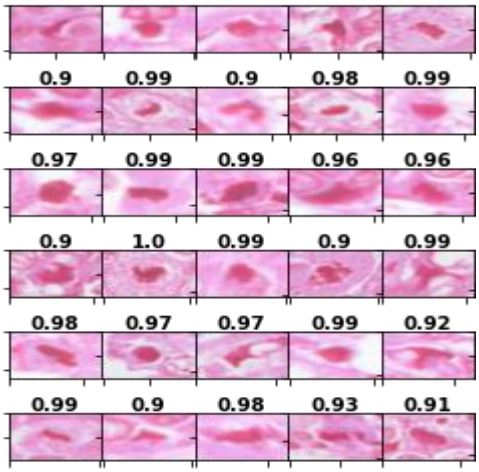

Fig. 5. Single mitosis detection by faster R-CNN

Single Mitosis Detection using Faster R-CNN model is demonstrated in Fig. 5.

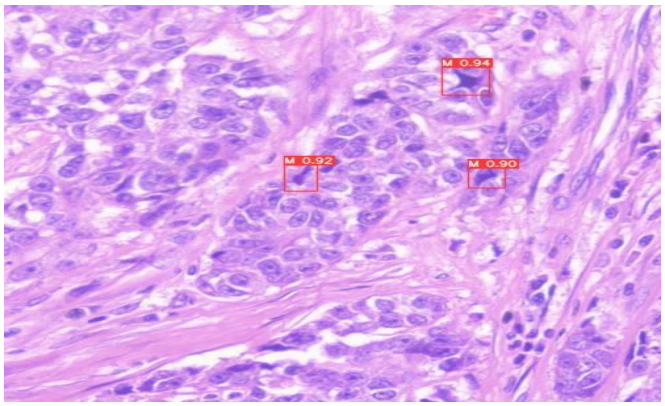

Fig. 6. Mitosis cell detection on tiles by Faster R-CNN

Mitosis cell detection on WSI tiles using Faster R-CNN model is demonstrated in Fig. 6.

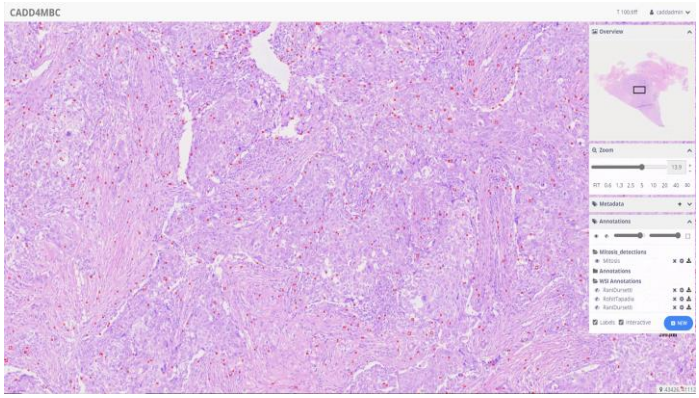

Fig. 7. Mitosis detection by YOLOv5 on WSI image

A number of mitoses (as red dots) detection on WSI image through YOLOv5 model is demonstrated in Fig. 7. The Results shows that the proposed deep learning models Faster RCNN and YOLOv5 produces good accuracy than the other models which are mentioned under the literature survey section. The other models use only the public dataset having 8000 tiles with strong/weak annotation and produce an F1 score between 0.3 and 0.7, whereas the proposed system produces an F1 score of 0.84 by trained and tested around 56,000 mitotic annotated tiles.

V. CONCLUSION

Nottingham grading system is a globally accepted system for breast cancer classification and grading the tumor. Detection of mitosis is the major component of NGS. Conventional microscopic mitosis detection is time-consuming, semi-quantitative and subject to inter observability. Digital pathology digitizes the tumor slides as WSI and applying deep learning models on WSI reduces the workload of the pathologist and assists them for quick accurate report generation. The deep learning models Faster R-CNN and YOLO v5 are learned from both the public datasets and KMIT dataset which has 56,258 tiles with annotated mitosis figures. The proposed web-based deep learning models detect mitosis with an F1 score of 0.84. The accuracy can be improved by increasing the size of the Breast Cancer WSI Mitosis dataset and Mitosis annotations to the models.

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