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# Mitotic Cell Detection in Breast Histopathology Image: A Review

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**Abstract.** Mitotic assessment is one of the critical features in the Nottingham Histological Grading (NHG) system for breast cancer grading. In recent years, rapid development in the performance of mounted camera, computer processing power, and data processing speed have fostered the research interest in detection of mitotic cells using image processing techniques. This paper is meant as an introduction of the recent methods and approaches specifically in detection of mitotic cells for the non-experts. It starts with overview of the grading system, online dataset, and the recent proposed methods in each step (i.e., color normalization, nuclei detection, feature extraction, and classification) of the mitotic cell assessment procedure. A brief discussion and the open problems pertinent to the established works were presented at the end of this paper.

## 1. Introduction

Over the past decade, tremendous growth in image processing algorithms and computational technology have foster the development of computer-aided analytical approaches such as computer-aided diagnosis (CAD) and computer-aided prognosis (CAP) in the medical domain. The recent advent of Whole Slide Imaging (WSI) scanner allows analogue histopathology slides to be converted into digital slides. This scanner demonstrates a significant impact to relieve the pressing need for CAD to reduce the workload among pathologist [1]. Furthermore, the emergence of WSI images allows image analysis and processing approaches to be incorporated to reduce inter- and intra-observer variation in grading [1, 2].

In this paper, we provide an overview for methods that have been published in the field of mitotic cell detection in breast histopathology images. The organization of the paper is as follows: Section 2, Nottingham Histological Grading (NHG) system, Section 3, Assessment of mitotic cell; and Section 4, discussion and conclusion. For a broader overview in breast histopathology images analysis, we refer the recent review in [1, 2, 3].

## 2. Nottingham Histological Grading (NHG) System

A patient that confined with breast carcinoma is required to perform the grading procedure. Grading of breast carcinoma provides a strong prognosis value and is well recognized as one of the key components of clinical decision-making-tools [4]. The grading assessment was proposed by Patey and Scarff [5] and



Bloom and Richardson [6]. The grading system was modified by Elston and Ellis [7] and becoming more semi-quantitative when compared to the previous methods. The modified grading system by Elston and Ellis is known as the Nottingham Histopathological Grading (NHG) system [4]. The NHG system is nowadays accepted worldwide and is used as a gold standard in performing grading procedure [4, 8]. The overall output grade obtained from the NHG system is dependent on the total score obtained from three important features. The features are glandular formation, nucleus pleomorphism, and mitotic count. Table 1 shows details explanation for each feature.

**Table 1.** The semi-quantitative histology grading system: NHG system.

Feature	Remark	Score
Glandular formation	Majority of tumor (>75.0%)	1
	Moderate degree (10.0%-75.0%)	2
	Little or none (<10.0%)	3
Nucleus pleomorphism	Small nuclei with little increase in size respect to normal breast epithelial cells, regular outlines, uniform nuclear chromatin and low degree of variation in size	1
	Increase in cell size with open vesicular nuclei, visible nucleoli, and moderate variability in term of shape and size	2
	Vesicular nuclei, often with prominent nucleoli, present significant variation in shape and size, occasionally with very large and eccentric forms	3
Mitotic counts (field diameter: 0.40mm)	$\leq 4$	1
	5 - 9	2
	$\geq 10$	3
Final grading	Grade 1	Total score: 3-5
	Grade 2	Total score: 6 or 7
	Grade 3	Total score: 8 or 9

Note: Score 1: Low, score 2: moderate, and score 3: high.

The assessment of mitotic count is the most prognostically significant [9]. Assessment of mitotic count is time consuming, tedious, required intensive care and experience [10, 11, 12]. The assessment depends on tissue fixation and slide preparation procedures. The observers must only include clear and definite mitotic cell. Karyorrhectic and apoptotic nuclei that shared similar appearance with the mitotic cells should be neglected. To perform mitotic count, the observers should first delimit the area with the highest mitotic activity. The total number of mitotic cells in the 10 consecutive high power field (HPF) is then recorded. The cut off threshold of the mitotic count is dependent on the field diameter. Thus, it is important to control the calibration of the microscope or the magnification level (40x magnification) during the mitotic count.

### 3. Assessment of Mitotic Cell

#### 3.1 Online Dataset

There are publicly assessable online datasets which provide a platform for the researchers to compare their proposed methods. The online datasets contain breast carcinoma biopsy slides which were stained with hematoxylin and eosin (H&E) dyes to enhance the contrast between different tissue components. MITOS-ATIPIA2014 [13] dataset consists of breast carcinoma slides with magnification of x20 and x40. These slides were scanned using two scanners: Aperio Scanscope XT and Hamamatsu Nanozoomer 2.0-HT. AMIDA2013 [14] dataset consists of breast carcinoma slides with magnification of 40x. These slides were scanned using Aperio Scanscope XT scanner. Similar to AMIDA2013, the Mitosis-ICPR2012 [15] dataset contains slides at 40x magnification and were scanned using Aperio Scanscope XT and Hamamatsu Nanozoomer 2.0-HT scanners. A summary of the online datasets is shown in Table 2.

**Table 2.** Summary of the online datasets.

Datasets	Number of frame	Number of mitotic cells	Resolution
MITOS-ATIPIA2014 [13]	1200	749	1539 × 1376
AMIDA2013 [14]	311	550	2000 × 2000
Mitosis-ICPR2012 [15]	50	327	2084 × 2084

In recent year, a new online available dataset, namely TUPAC16 [16] was released to the public. The dataset consists of 500 training and 321 testing data (WSI slides). Only the ground truth of the training dataset was provided to the public to ensure an independent and fair evaluation on the dataset. Overall, there are 383 mitotic cases with score 1, 194 cases with score 2 and 244 cases with score 3. The TUPAC16 [16] provides two tasks to the participants: (1) to predict the mitotic scores and (2) to reproduce the most common method of assessing tumor proliferation (to predict the gene expression based on PAM50 proliferation scores).

### 3.2 Color Normalization

Color normalization is one of the essential steps in the assessment of mitotic cell, typically in histopathology images. The main purpose of color normalization is to reduce the color inconsistency across different histopathology slides. The heterogeneity properties of the disease, different manufactures, timing of stain absorption, concentration of the reagent, thickness of the biopsy section, and the differences in fixation and staining protocol are some of the main contributions to this problem [2, 17]. Histogram matching [18], color transfer [2], color swapping [19], spectral matching [20], illuminant normalization [21] and color deconvolution [22] are examples of techniques used in color normalization. It is important to emphasize that the selection of color normalization method is closely related to the object of interest. For instance, histogram matching technique is fast and simple method as compared to color deconvolution method. Histogram matching involves in simple mathematic computation but requires careful selection of reference image.

### 3.3 Nuclei Detection

Nuclei segmentation remains as a challenging task albeit numerous attempts have established to address this problem. Irshad implemented Laplacian of Gaussian (LoG) together with thresholding, morphological and active contour model methods to segment the mitotic cells [23]. Irshad et al. proposed a novel mitotic cell detection based on texture, Scale-Invariant Feature Transform (SIFT) feature and Hierarchical Model and X (HMAX) biologically inspired approach [24]. Wang and Cruz-Roa combined LoG and local dynamic thresholding on a blue ratio space of RGB input images [25]. Maximum Likelihood Estimation (MLE) was used to segment the true mitotic cells [26]. Lu and Mandal implemented Bayesian Modelling and local-region thresholding in the mitotic cells segmentation [27]. Logambal and Saravanan also used local-region thresholding [28]. They performed Otsu method to calculate the local-region thresholding. In recent year, Jian et al. proposed a color thresholding method on color decorrelation stretched image [12]

and a K-Mean with guided initialization [11] to segment the nuclei cells. Several studies extended their study by implementing false positive reduction to reduce the number of non-mitotic candidates [29, 30, 31, 32].

### 3.4 Feature Extraction

The extracted features from the mitotic cells could be characterized into three domains: color, texture, and shape domains. In color domain, color moment (e.g., min, max, mean, median, variance, skewness, kurtosis) and color histogram can be extracted whereas in texture domain, Gray Level Co-occurrence Matrix (GLCM) [33] and Complete Local Binary Pattern (CLBP) [34] can be extracted. In GLCM, 14 textural features can be measured from the probability matrix: energy, entropy, contrast, variance, homogeneity, correlation, sum average, sum entropy, sum variance, difference variance, different entropy, maximum correlation coefficient, information measures of correlation 1, and information measures of correlation 2 [35]. Eccentricity, solidity, area, perimeter, form factor, ratio of minor and major axis, extent, length, roundness, compactness, minor, and major axis are parameters that can be extracted from shape domain. To the best of our knowledge, there is lack of evidence showing which features are best to describe the mitotic cell.

### 3.5 Classification

Support Vector Machine (SVM) is a widely used classifier. SVM has shown effective classification in mitotic detection [26, 29]. Other classifiers are decision tree [36], nearest neighborhood tree [36], discriminant analysis [36] and ensemble classifier [36]. Some studies used neural network [25, 37] and Model Explanation System (MES) classifier [27] in mitotic cell classification.

## 4. Discussion and Conclusion

The introduction of WSI scanner has fostered the development of medical image processing specifically in histopathology images. Several leading journals are focused in the publication of works pertinent to automated analysis in medical images. However, there is a need to provide evidence in clinical applicability to further evaluate the established works. It is important for the established works to demonstrate tangible and clear effect in the clinical domain in order to benefit the pathologist in the standard routine procedure.

By far, the publicly available online datasets are limited. Due to the limited clinical annotation and time constraint, the histopathology data are anticipated to undergo a bottleneck in the near future. Comparison across different literature is difficult. Researchers tend to evaluate their results using different metrics and some researchers evaluate their detection system using self-collected data which is confidential. Implementation of CAD and CAP in routine procedure is cost effective. For instance, image-based detection can be used to predict disease occurrence and recurrence [1] as a high mitotic count is correlated with high speed of tumor cells replication and/ or high proliferative activity in tumor cells. Hence, the expensive molecular assays may not be required for the same purpose. It is important to maintain a constant collaboration between researchers from biomedical, computer, and electronic engineering background with the clinical pathologists as the pathologists could provide knowledge in histopathology which may eventually lead to new research ideas.

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