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Automated mitosis detection using texture, SIFT features and HMAX biologically inspired approach

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Abstract

Context: According to Nottingham grading system, mitosis count in breast cancer histopathology is one of three components required for cancer grading and prognosis. Manual counting of mitosis is tedious and subject to considerable inter- and intra-reader variations. **Aims:** The aim is to investigate the various texture features and Hierarchical Model and X (HMAX) biologically inspired approach for mitosis detection using machine-learning techniques. **Materials and Methods:** We propose an approach that assists pathologists in automated mitosis detection and counting. The proposed method, which is based on the most favorable texture features combination, examines the separability between different channels of color space. Blue-ratio channel provides more discriminative information for mitosis detection in histopathological images. Co-occurrence features, run-length features, and Scale-invariant feature transform (SIFT) features were extracted and used in the classification of mitosis. Finally, a classification is performed to put the candidate patch either in the mitosis class or in the non-mitosis class. Three different classifiers have been evaluated: Decision tree, linear kernel Support Vector Machine (SVM), and non-linear kernel SVM. We also evaluate the performance of the proposed framework using the modified biologically inspired model of HMAX and compare the results with other feature extraction methods such as dense SIFT. **Results:** The proposed method has been tested on Mitosis detection in breast cancer histological images (MITOS) dataset provided for an International Conference on Pattern Recognition (ICPR) 2012 contest. The proposed framework achieved 76% recall, 75% precision and 76% F-measure. **Conclusions:** Different frameworks for classification have been evaluated for mitosis detection. In future work, instead of regions, we intend to compute features on the results of mitosis contour segmentation and use them to improve detection and classification rate.

Key words: Classification, histopathology, Hierarchical Model and X, mitosis detection, Scale-invariant feature transform, texture analysis

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INTRODUCTION

Researchers in histopathology have been familiar with the importance of qualitative analysis of histopathological images. These analyses are used to confirm the presence or the absence of disease and also to help in the evaluation of disease progression. Being important in diagnostic pathology, this qualitative assessment is also used to understand the ground realities for specific diagnostic being rendered like specific chromatin texture in the cancerous nuclei, which may indicate certain genetic abnormalities. In addition, quantitative characterization of pathology imagery is important not only for clinical applications (e.g., to reduce/eliminate inter- and intra-observer variations in diagnosis) but also for research applications (e.g., to understand the biological mechanisms of the disease process).^[1]

Nottingham Grading System is an international grading system for breast cancer recommended by the World Health Organization.^[2] It is derived from the assessment of three morphological features: Tubule formation, nuclear pleomorphism, and mitotic count. Several studies on automatic tools to process digitized slides have been reported focusing mainly on nuclei or tubule detection. Mitosis detection is a challenging problem and has not been addressed well in the literature.

Mitosis detection has diagnostic significance for some cancerous conditions. Indeed, mitotic count provides clues to estimate the proliferation and the aggressiveness of the tumor and is a critical step in histological grading of several types of cancer.^[3] In clinical practice, the pathologists examine proliferated area and determine mitotic count after a tedious microscopic examination of hematoxylin and eosin (H and E) stained tissue slides at high magnification, usually $\times 40$. The area visible under the microscope under a $\times 40$ magnification lens is called a high power field (HPF). This mitotic counting process is cumbersome and often subject to sampling bias due to massive histological images. This results in considerable inter- and intra-reader variation of up to 20% between central and institutional reviewers in tumor prognosis.^[4]

In histopathological image analysis, the accuracy of mitosis detection is crucial to identify the severity of the disease. Mitosis detection is a difficult task having to cope with several challenges such as irregular shaped object, artifacts, and unwanted objects because of slide preparation and acquisition. Mitosis has four main phases and each phase has different shape and texture. It is also observed that artifacts produce objects, which look similar to mitosis. As a result, there is no simple way to detect mitosis based on shape and pixels values. However, the major problem is the very low density of mitosis in a single HPF. It is not unusual to have an HPF without any mitosis.

The remaining paper is organized as follows. Section 2 presents an overview for mitosis detection and counting in histopathology. Section 3 describes the proposed framework for mitosis detection. Experimental results to demonstrate the effectiveness of our mitosis detection method with different classifiers are presented in section 4. Finally, the concluding remarks with future work are given in section 5.

Review of Previous Work

A number of research studies have been applied to nuclei detection in H and E images but to the best of our knowledge there are very few research studies specifically dedicated to automated mitosis detection. Sertel *et al.*, developed a computer-aided system based on pixel-level likelihood functions and two-step component-based thresholding for automatic detection and counting of mitosis nuclei in digitized images of neuroblastoma tissue slides.^[5] This approach resulted in 81% of detection rate and 12% false positive rate. Anari *et al.*, proposed fuzzy c-mean clustering algorithm along with ultra-erosion operation in CIE Lab (Commission Internationale de l'Eclairage; L = luminance, a = red-green axis, and b = blue-yellow) color space for detection of proliferative nuclei and mitosis index in immunohistochemistry (IHC) images of meningioma.^[6] Recently, Roullier *et al.*, proposed a graph based multi-resolution segmentation for mitosis detection.^[7] This approach performed unsupervised clustering at each resolution level driven by domain specific knowledge and refined the associated segmentation in the specific areas as the resolution increases. The whole strategy was based on graph formalism that enabled to perform segmentation adaptation at each resolution. They performed mitosis detection at higher resolution and resulted in more than 70% sensitivity and 80% specificity. These methods, mainly based on clustering, thresholding and morphological operations and using only pixel level information, achieve mitosis detection with low true positive rate and high false positive rate.

Mitosis nuclei have large variations in shape, size and pixel intensity values. In the proposed framework, we address the limitations and weaknesses of previous works: (1) By including comprehensive analysis of texture features (second order statistics features such as co-occurrence and run-length features) in RGB color space and blue-ratio image and (2) by exploring other feature models like SIFT and HMAX model to achieve a better discrimination of mitosis from other objects.

MATERIALS AND METHODS

We propose a color image processing-based strategy for mitosis detection in H and E images. The aim is to improve the accuracy of mitosis detection by integrating the color channels that better capture the

texture features, which discriminate mitosis from other objects. Two main stages are involved in the proposed method as shown in Figure 1. In the first stage, we perform detection of candidate mitosis. The input RGB images are transformed into blue-ratio images.^[8] We perform Laplacian of Gaussian (LoG), thresholding and morphological operations on blue-ratio images to generate candidate mitosis regions. Later, we selected candidate regions using morphological rules; we calculate center point for each region as seed points for mitosis and extract a patch of size 80 × 80 pixels from blue-ratio image and red and blue channel of RGB color space. In the second stage, we compute co-occurrence features, run-length features and SIFT features for each candidate patch, and select those features having better discrimination of mitosis regions from others. Finally, a classification is performed to put the candidate patch either in the mitosis class or in the non-mitosis class. Three different classifiers have been evaluated: Decision tree, linear kernel SVM, and non-linear kernel SVM. We also evaluate the performance of the proposed framework using the modified biologically inspired model of HMAX and compare the results.

Candidate Detection

In H and E stained color images, nuclear and cytoplasm regions appear as hues of blue and purple while extracellular material have hues of pink. To reduce the complexities for integrating LoG responses, the RGB images are transformed to accentuate the nuclear dye. We first convert RGB images into blue-ratio images for computing LoG responses, which discriminate the nuclei region from the background, hence, assisting in classification of mitosis from other objects. In a blue-ratio image, a pixel with a high blue intensity relatively to its red and green components is given a high value, whereas, a pixel with a low blue intensity or a low blue intensity

as compared to its red and green components is given a low value. As we are interested in nuclei, which appear as blue-purple areas, a blue-ratio image is an efficient tool to have a first clue on the position of nuclei in the image. An example of blue-ratio image is shown in Figure 2b. Then, we perform binary thresholding and morphological operations to eliminate too small regions and fill hole. Finally we use morphological rules to select the candidate regions and take a patch of window size 80 × 80 from blue ratio image and red and blue channels of RGB color space. An example of candidate detection is shown in Figure 2.

Candidate Classification

We proposed three different methods for classification of candidates that have been detected in candidate detection stage.

Method 1: Texture Based Classification

We extracted the following second order statistics features using co-occurrence matrices and run-length matrices.

Co-occurrence Matrices

The grey level co-occurrence matrix (CM) describes the joint probability of certain sets of pixels having certain grey-level values. A co-occurrence matrix C is defined over an image I, and parameterized by an offset (Δx, Δy), as

$$C_{\Delta x, \Delta y}(i, j) = \sum_{p=1}^n \sum_{q=1}^m \begin{cases} 1 & \text{if } I(p, q) = i \text{ and } I(p + \Delta x, q + \Delta y) = j \\ 0 & \text{otherwise,} \end{cases}$$

It calculates how many times a pixel with grey-level *i* occurs jointly with another pixel having a grey value *j*. By varying the displacement vector between each pair of pixels many CMs with different directions can be generated. For each image segment, four CMs having direction (0°, 45°, 90°, 135°) were generated with a displacement vector.

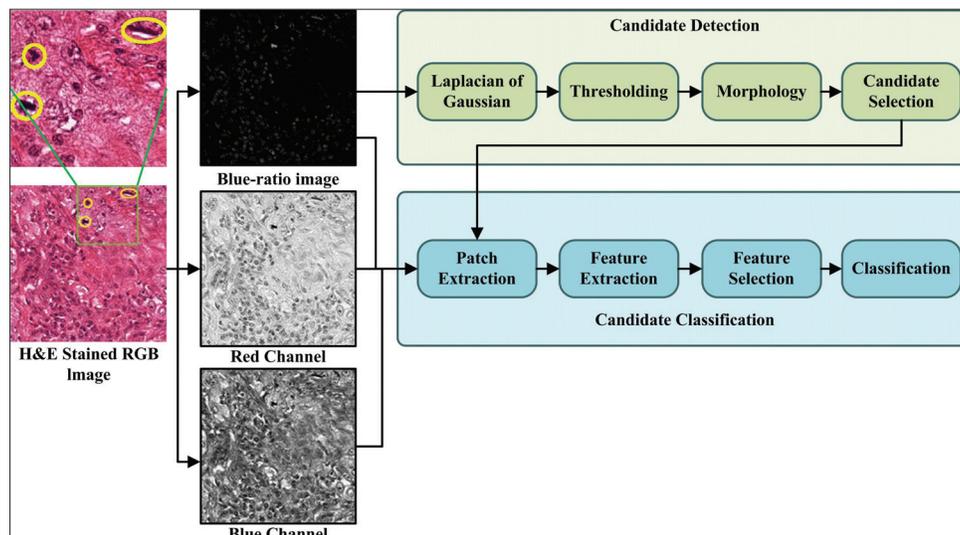


Figure 1: Framework for mitosis detection

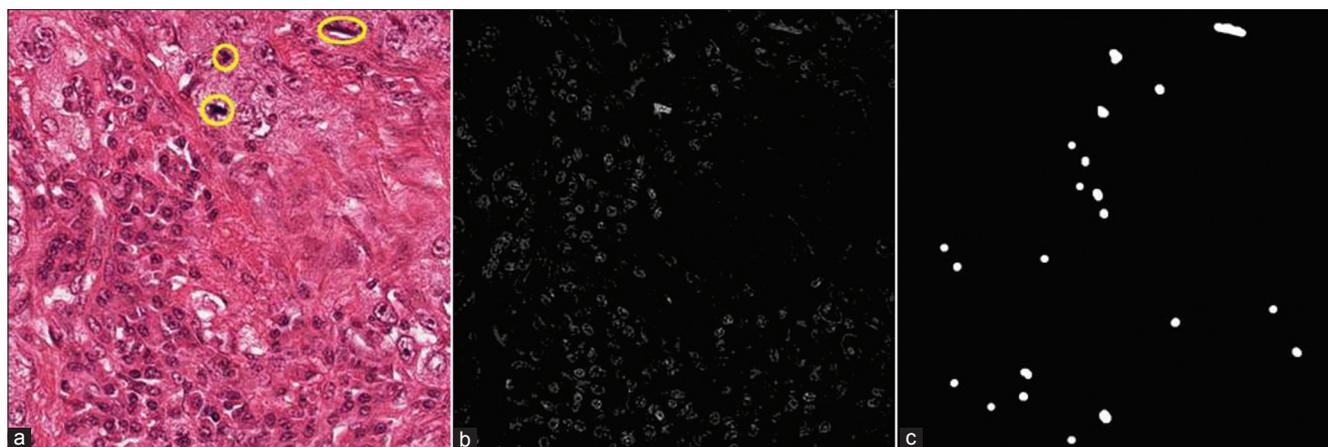


Figure 2: Example of candidate detection; (a) RGB image, (b) Blue-ratio image, (c) Detected candidates

We extracted eight second order statistics features for each direction of a swatch, which are also known as Haralick features.^[9] These eight features are: Correlation, cluster shade, cluster prominence, energy, entropy, inertia, Haralick correlation, and Inverse Difference Momentum (IDM).

Run-Length Matrices

The set A of consecutive pixels, with same grey level, collinear in a given direction, constitute a grey level run. The run length is the number of pixels in the run and the run length value is the number of times such a run occurs in an image. The grey level run length matrix (RLM) is a two dimensional matrix in which each element $P(i,j|\theta)$, gives the total number of occurrences of runs of length j at grey level i , in a given direction θ .^[10] RLM were generated for each candidate region having directions ($0^\circ, 45^\circ, 90^\circ, 135^\circ$), then the following ten second order statistics features are derived: Short run emphasis (SRE), long run emphasis (LRE), grey-level non-uniformity (GLN), run length non-uniformity (RLN), low grey level runs emphasis (LGLRE), high grey level runs emphasis (HGLRE), short run low grey level emphasis (SRLGLE), short run high grey level emphasis (SRHGLE), long run low grey level emphasis (LRLGLE), and long run high grey level emphasis (LRHGLE).

The eight CM features and ten RL features are computed for each candidate in blue ratio image and blue and red channels of RGB color space, which resulted in a total of 54 features. When we used all the extracted features for classification of mitosis and non-mitosis region, the classification performance was poor. Some features are irrelevant for classification and some features are redundant that represents duplication of features, degrading the classification performance. All extracted features in the combined measures have been investigated for possibly highly correlated features that helped in eliminating bias towards certain features, which might afterwards affect the classification procedure. The relevant features are isolated

from both texture feature sets based on their ability to distinguish candidate with mitosis and non-mitosis nuclei. We used principal component analysis (PCA) to select a subset of features that maximize the variance of data. We selected all the features having an eigenvalue greater than 1, which is a total of eight features. All together, these eight features cover 95.82% of the variance of the original 54 features. We used these eight features to train different classifiers like decision tree, linear kernel SVM and non-linear kernel SVM.

Method 2: Scale Invariant Feature Transform

Scale Invariant Feature Transform (SIFT) feature extraction method is a well-known method which has produced promising results in classification tasks.^[11] Here we investigate its application in classification of mitosis patch. In SIFT methods, a series of features are calculated using difference of Gaussian (DoG) methods over different scales. Once a set of features is selected, features from new images are compared with these candidate regions using their Euclidean distance and from the full set of matches. A subset of key point features, which agree on the object, its scale, orientation and location in the new image, are identified to filter out good matches. Finally, a histogram of features is calculated and the final histograms are sent to a SVM classifier. In this experiment we use Pyramid histogram of visual words (PHOW) features (dense multi-scale SIFT descriptors), Elkan k-means for fast visual word dictionary construction, spatial histograms as image descriptors, a homogeneous kernel map to transform a Chi2 support vector machine (SVM) into a linear one and finally an internal SVM for classification using VLFeat toolbox.^[12]

Method 3: Modified Biologically Inspired Approach of Hmax

In order to compare with other feature extraction and classification methods, we use HMAX (Hierarchical MAX) model, a biologically inspired model of image classification,^[13] which shows promising results on general

classification tasks such as Caltech101 dataset.^[14]

Our biologically inspired model of image classification is similar to the one in.^[15] In the first three layers (S1, C1, and S2) as in illustrated in Figure 3. However, our approach is different in the creation of dictionary of features and in the way C2 layer is created. In the first layer of the hierarchy, the normalized dot products of Gabor filters of different orientations are calculated over all ten scales of the image pyramid (S1 layer). In the C1 layer, a local max on neighboring positions and scales is taken on the Gabor filter responses on all image pyramid levels for pooling in order to provide invariance to scale and position of features. A dictionary of features is sampled from C1 layer pyramid using frequency and spatial information of features. Once the dictionary of features is created, the response of each feature in the dictionary to each candidate region is calculated (S2) and a max is taken over all candidate regions and over all dictionary features (C2) and fed to a linear support vector machine for classification.

In order to learn the features for the HMAX model, we use candidate patches, which include mitosis and non-mitosis. Features are extracted from these patches using multiple scale Gaussian filters on different layers of the hierarchy of the patches. A max operator is used in C layers to provide invariance to translation and scale variations.

RESULTS AND DISCUSSION

We evaluated the proposed framework on MITOS dataset,^[16] a freely available mitosis dataset. This dataset consists of 35 HPF images at $\times 40$ magnification. A HPF has a size of $512 \times 512 \mu\text{m}^2$ (that is an area of 0.262 mm^2), which is the equivalent of a microscope field diameter of 0.58 mm. Each HPF has a digital resolution of 2084×2084 pixels. These 35 HPFs contain a total of 226 mitosis. The pathologists have annotated mitosis manually in each HPF images. We select 25 HPFs containing 154 mitosis and 12,446 non-mitosis as training set, the remaining 10 HPFs containing 72 mitosis being used for testing.

On testing dataset, the candidate detection phase identified 2,182 mitosis candidates, containing 66 mitosis

from a total of 72 ground truth mitosis. Therefore, among the entire candidate detection set, there is 2116 non-mitosis in testing dataset. The candidate detection phase generated a large number of non-mitosis and missed six ground truth mitosis.

In classification phase, we compared the results of these classification methods with ground truth information provided along with the dataset. The metrics used to evaluate the mitosis detection of each method include: Number of true positive (TP), number of false positive (FP), number of false negative (FN), sensitivity or true positive rate (TPR), precision or positive predictive value (PPV) and F-measure. A comparison of all different classification methods is presented in Table 1. One of the parameters that affect our experiments is the existence of no balance between the number of mitosis and non-mitosis candidates. When we used this dataset for training the classifier, then most of the classifiers are biased toward non-mitosis, which resulted in high number of false positives. When we used all textures features with decision tree classifier, we get very few false positive but also not so many true positive resulting in 58% F-measure as shown in Table 1.

In first method, we used linear and non-linear SVM and decision tree classifier on eight selected texture features. As compared with linear kernel, the experiments with non-linear kernel resulted in better performances in terms of less false positives but less true positives as well resulting in 49% F-measure. When we used selected texture features with random forest, an ensemble classifier consisting of many decision trees, we achieved classification with low false positives and highest PPV and F-measure. The random forest classifier has better results as compared to other classifiers because of balancing error in class population unbalanced datasets. Figure 4 shows an example of a detected, undetected, and mistakenly detected mitosis using texture features with random forest method. Figure 5 shows the results of mitosis detection in testing set images.

SIFT features are also examined in this study, but due to the lack of balance between number of mitosis and non-mitosis regions, the SIFT method does not perform as good as

Table 1: Results of different classifiers (ground truth = 72)

Methods	TP	FP	FN	TPR %	PPV %	F-Measure %
All features with Decision Tree	34	12	38	47	74	58
Selected features with Decision Tree	55	18	17	76	75	76
Selected features with L-SVM	43	71	29	60	38	46
Selected features with NL-SVM	41	53	31	57	44	49
SIFT with SVM	59	78	13	82	43	56
HMAX model	61	41	11	85	60	70
HMAX model (generative features)	63	43	9	88	60	71

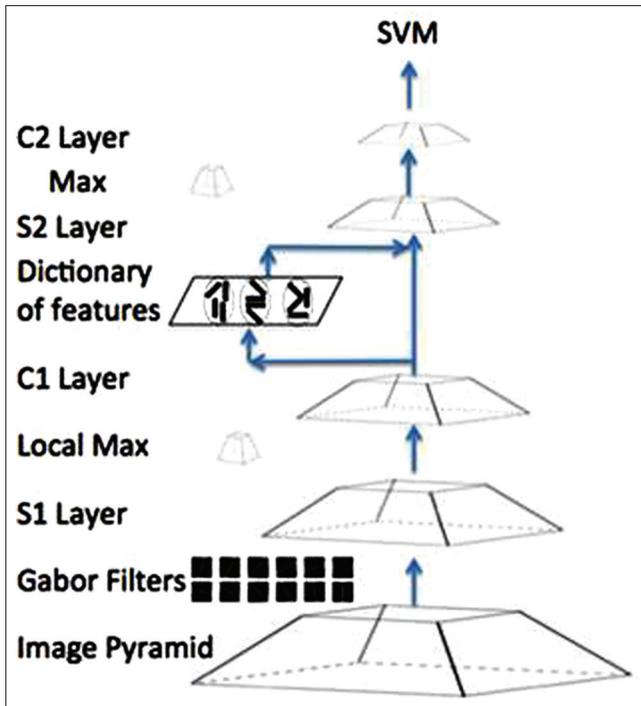


Figure 3: Global architecture of the HMAX model^[15]

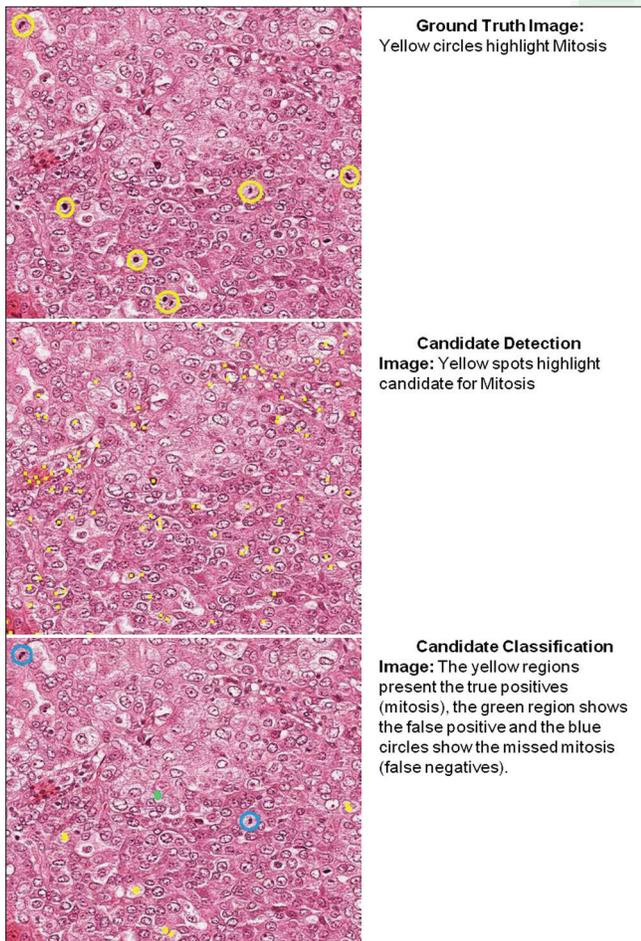


Figure 4: Mitosis detection framework results

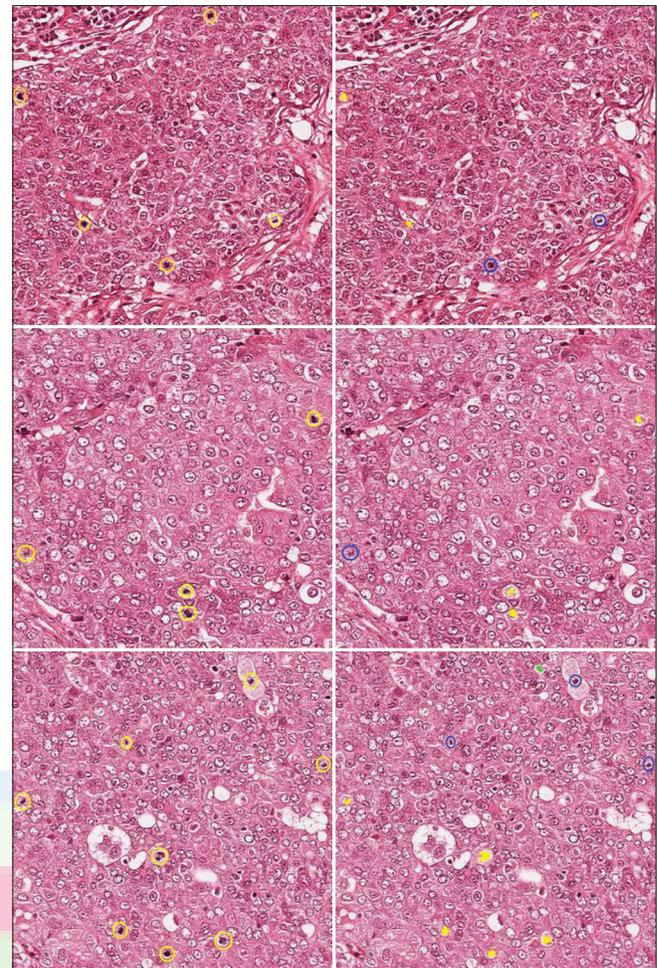


Figure 5: Visual results of mitosis detection in a testing set images

other methods. As can be seen in Table 1, we have also used HMAX model to train a dictionary of features from local max on Gabor filter responses over 12 orientations as described in Section 3, which resulted in high true positives but high false positives as well. The dimensionality of features in HMAX model is directly related to the size of the dictionary of features and we evaluated different sizes over several runs and used the optimum numbers. A global dictionary of features from generative images (Caltech 101) was also used in another experiment to evaluate the performance of different dictionaries on these images and achieved almost the same results. It is because of the nature of this model in which the statistics of natural images are encoded. However, using a non-linear kernel for SIFT and HMAX, in which the features' dimensions are high, (order of 10,000) results in over-fitting, which resulted in lower classification accuracies.

CONCLUSION AND FUTURE WORK

An automated mitosis detection framework for H and E images based on different features and classifiers has

been proposed in this study. The candidate detection stage represents detection of candidate regions for mitosis using thresholding and morphological processing in blue-ratio space. Different frameworks for classification have been evaluated on candidate regions. In future work, instead of regions, we intend to compute features on the results of mitosis contour segmentation and use them to improve detection and classification rate. One future modification is to tune different parameters of HMAX model to achieve the best performance for mitosis detection rather than using general settings for natural images. Furthermore, we also plan to investigate other model-based features for mitosis detection.

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