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# Automated analysis and diagnosis of skin melanoma on whole slide histopathological images



<sup>a</sup> College of Computer Science, Shaanxi Normal University, Xi'an, Shaanxi Province 710119, China
<sup>b</sup> Department of Electrical and Computer Engineering, University of Alberta, Edmonton, Alberta, Canada T6G 2V4

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#### ABSTRACT

Melanoma is the most aggressive type of skin cancer, and the pathological examination remains the gold standard for the final diagnosis. Traditionally, the histopathology slides are examined under a microscope by pathologists which typically leads to inter- and intra-observer variations. In addition, it is time consuming and tedious to analyze a whole glass slide manually. In this paper, we propose an efficient technique for automated analysis and diagnosis of the skin whole slide image. The proposed technique consists of five modules: epidermis segmentation, keratinocytes segmentation, melanocytes detection, feature construction and classification. Since the epidermis, keratinocytes and melanocytes are important cues for the pathologists, these regions are first segmented. Based on the segmented regions of interest, the spatial distribution and morphological features are constructed. These features, representing a skin tissue, are classified by a multi-class support vector machine classifier. Experimental results show that the proposed technique is able to provide a satisfactory performance (with about 90% classification accuracy) and is able to assist the pathologist for the skin tissue analysis and diagnosis.

#### 1. Introduction

Cancer is a major cause of death all over the world. It is caused by the uncontrolled growth of abnormal cells in the body. Skin cancer is one of the most frequent types of cancer, and melanoma is the most aggressive type of skin cancer [17]. According to a recent article, approximately 70,000 people are diagnosed with melanoma skin cancer, and about 9000 die from it in the United States alone every year [1]. The malignant melanoma is curable, if it is diagnosed at early stages [17]. Therefore, an early detection and accurate prognosis of malignant melanoma will definitely help us to lower the mortality from this cancer. Approaches to melanoma diagnosis have dynamically evolved during the past 25 years [22]. Although there are many new emerging techniques, e.g., dermatoscopy [29], that could provide initial diagnosis, the pathological examination remains the gold standard for the final diagnosis. In addition, useful prognostic information in the clinical management of the patient can also be provided by the histological examination.

The histopathology slides provide a cellular level view of the diseased cell and tissue and is considered the "gold standard" in the diagnosis of diseases for almost all kinds of cancer [12]. Traditionally,

mmandal@ualberta.ca (M. Mandal).

http://dx.doi.org/10.1016/j.patcog.2015.02.023 0031-3203/© 2015 Elsevier Ltd. All rights reserved. the histopathology slides are examined under a microscope by pathologists. With the help of the whole slide histology digital scanners, glass slides of tissue specimen can now be digitized at high magnification to create the whole slide image (WSI) [23,32]. Such high resolution images are similar to what a pathologist observes under a microscope to diagnose the biopsy. The pathologists can now do the examination via the WSI instead of using the microscope. Note that the WSI takes a large storage space and huge computing power for processing. For example, a 20 mm<sup>2</sup> glass slide tissue scanned with a resolution of 0.11625  $\mu$ m/pixel (at 40 × magnification) will consist of about 2.96 × 10<sup>10</sup> pixels, and will approximately require 80 GB of storage space in uncompressed color format (24 bits/pixel). Therefore, it is time consuming and difficult to analyze a WSI manually. In addition, the manual diagnosis is subjective and often leads to intraobserver and inter-observer variability [9].

In order to address the above-mentioned problems, automated computational tools/technique which can provide reliable and reproducible objective results for quantitative analysis is needed. Recently, many researchers have applied sophisticated digital image analysis techniques to extract objective and accurate prognostic clues throughout the WSI. These computer-aided systems have shown promising initial results in the case of breast cancer [21,8], prostate cancer [4], head and neck cancer [18], cervical cancer [30], neuroblastoma [25,10], and ovarian cancer [26].

In this work, we propose an automatic analysis and diagnosis technique for the whole slide skin pathological image. The goal of







<sup>\*</sup> Corresponding author. Tel./fax: +86 29 85310161. E-mail addresses: chenglu@snnu.edu.cn (C. Lu),

the proposed technique is to provide quantitative measures which will help the pathologist for their diagnosis and classify the melanoma, melanotic nevus and normal skin biopsy automatically.

This paper is organized as follows. Section 2 presents the related works on the automatic WSI analysis and skin tissue analysis. Section 3 describes the image data used in this paper. Section 4 presents the proposed technique that consists of five modules. Experimental results are presented in Section 4, followed by the conclusion in Section 5.

#### 2. Related works

#### 2.1. WSI analysis techniques

The whole slide histopathological image analysis has become an attractive research topic in recent years [25,10,4]. The WSI is able to provide global information of a tissue specimen for quantitative image analysis. However, the automated WSI analysis is challenging since it has high computational complexity. Several techniques based on the multi-resolution framework have been proposed. Table 1 shows the state-of-the-art literature on the WSI analysis techniques.

Petushi et al. [21] employed gray scale conversion, adaptive thresholding and morphological operations to segment the nuclei and identify the high nuclei density regions in the invasive breast carcinoma WSIs. Classification of the tissue type is then performed based on the features extracted from pre-segmented areas using different classifiers. A classification accuracy of 68% has been reported on a database of 24 WSIs.

Mete et al. [18] proposed a block-based supervised technique for detection of malignant regions in histopathological head and neck slides. With the pre-defined training subimages ( $128 \times 128$  pixels), this technique first extracts the most prominent colors that are present in the positive and negative training samples. These colors are then clustered into several groups that are used to train the SVM. For malignancy detection in a candidate image, the color information is extracted and is classified by the pre-trained SVM. The technique provides a good performance. However, the performance may suffer from the staining color variations of the WSIs.

Wang et al. [30] developed an automated computer-aided technique for the diagnosis of cervical intraepithelial neoplasia. This technique first segments the epithelium using prior knowledge of the tissue distribution. Based on the measurements and features obtained from the squamous epithelium, the SVM is employed to perform the classification. This CAD technique has been reported to achieve 94.25% accuracy for four classes tissue classification on 31 digital whole slides.

Sertel et al. [25] developed a multi-scale CAD technique for classification of stromal development for neuroblastoma. This technique uses texture features extracted using co-occurrence statistics and local binary patterns. A modified *K*-NN classifier was employed to determine the confidence resolution for the classification. The experimental results showed an overall classification accuracy of 88.4%. Kong et al. [10] developed a similar CAD technique for classification of the

#### Table 1

Related works on the whole s	ide histopatholog	y image analysis.
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Tissue type	Reference	Dataset info.
Breast	Petushi et al. [21]	24H&E stained, $20 \times$
Head and neck	Mete et al. [18]	7H&E stained, $20 \times$
Cervical	Wang et al. [30]	31H&E stained, $40 \times$
Neuroblastoma	Sertel et al. [25]	43H&E stained, $40 \times$
Neuroblastoma	Kong et al. [10]	33H&E stained, $40 \times$
Breast	Roullier et al. [24]	H&E stained, $20 \times$
Skin	Smolle and Gerger [28]	H&E stained, $10 \times$

grades of neuroblastic differentiation. This technique first segments a WSI into multiple cytological components (e.g., nuclei, cytoplasm, RBCs) at each resolution level using an Expectation-maximization approach. The cytological and statistical features derived from the presegmented results are then fed to a multi-classifier combiner for the training. The trained classification technique is tested on 33 WSI with 87.88% accuracy.

Roullier et al. [24] proposed a multi-resolution graph-based analysis framework for the WSI analysis of breast cancer. The 2-means clustering is applied on the histogram of the regularized image to cluster the region of interest and background. Spatial refinement based on the discrete label regularization are used to achieve accurate segmentation around the boundary. The above steps are repeated at four different resolution images (from lower to higher). Finally, the mitosis are identified in the labeled region of interest with the domain knowledge that the mitosis are visually recognized by the red-cyan color difference.

#### 2.2. Skin tissue analysis techniques

Since different tissue types have different specific diagnostic features considered by the pathologists, the techniques mentioned in Section 2.1 could not be applied in the skin tissue analysis and diagnosis.

Unlike other types of tissue specimen, a typical skin tissue slide consists of three main parts: epidermis, dermis and sebaceous tissues. The anatomy of a typical skin tissue is shown in Fig. 1, where the lower image shows the manually labeled contour of the epidermis.

The epidermis area is an important observation area in skin melanoma diagnosis. The morphological features and distribution of the interested objects are most useful in diagnosis. Two examples of skin WSI are shown in Fig. 2. Fig. 2(a) shows an example of melanocytic nevus, where melanocytes are invading into the dermis area (the invading melanocytes appear as the dark blue area in dermis). Fig. 2(b) shows an example of superficial spreading melanoma, where the image looks like normal skin tissue unless the epidermis area is examined carefully. For automated diagnosis of the skin tissue, the existing techniques mentioned in Section 2.1 are not expected to get satisfied results since most of the existing techniques focus on color or texture features at pixel-level [18,25,10,30].



Fig. 1. The anatomy of a skin tissue.

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