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Generating region proposals for histopathological whole slide image retrieval

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ABSTRACT

Background and objective: Content-based image retrieval is an effective method for histopathological image analysis. However, given a database of huge whole slide images (WSIs), acquiring appropriate region-of-interests (ROIs) for training is significant and difficult. Moreover, histopathological images can only be annotated by pathologists, resulting in the lack of labeling information. Therefore, it is an important and challenging task to generate ROIs from WSI and retrieve image with few labels.

Methods: This paper presents a novel unsupervised region proposing method for histopathological WSI based on Selective Search. Specifically, the WSI is over-segmented into regions which are hierarchically merged until the WSI becomes a single region. Nucleus-oriented similarity measures for region mergence and Nucleus–Cytoplasm color space for histopathological image are specially defined to generate accurate region proposals. Additionally, we propose a new semi-supervised hashing method for image retrieval. The semantic features of images are extracted with Latent Dirichlet Allocation and transformed into binary hashing codes with Supervised Hashing.

Results: The methods are tested on a large-scale multi-class database of breast histopathological WSIs. The results demonstrate that for one WSI, our region proposing method can generate 7.3 thousand contoured regions which fit well with 95.8% of the ROIs annotated by pathologists. The proposed hashing method can retrieve a query image among 136 thousand images in 0.29 s and reach precision of 91% with only 10% of images labeled.

Conclusions: The unsupervised region proposing method can generate regions as predictions of lesions in histopathological WSI. The region proposals can also serve as the training samples to train machine-learning models for image retrieval. The proposed hashing method can achieve fast and precise image retrieval with small amount of labels. Furthermore, the proposed methods can be potentially applied in online computer-aided-diagnosis systems.

1. Introduction

In the field of pathology, diagnosis with tissue slide is the gold standard of cancer diagnosis [1]. With the rapid development of computer and microscopy technology, pathological slides are usually scanned by microscopes and stored in computers. The digital version of slide is called whole slide image (WSI) and has been widely used in picture archiving and communication systems (PACS). According to American Cancer Society, 1.68 million new cancer cases are predicted to occur in US during 2017 [2], and most of the cases need to be diagnosed with WSIs. Therefore, the amount of WSIs is rapidly increasing and the task of diagnosis with WSIs has become urgent. However, pathological images can only be annotated by pathologists, resulting in the lack of labeling information. To assist pathologists for better accuracy and efficiency, researchers have developed various applications for patho-

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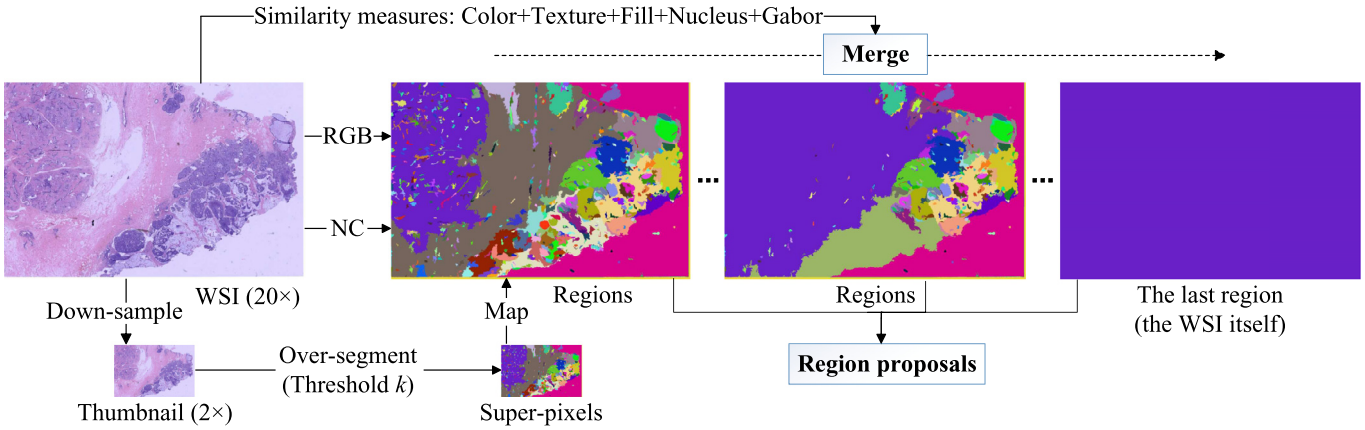

Fig. 1. WSI-SS can efficiently generate region proposals from a huge WSI by utilizing different scales, similarity measures and color spaces.

logical image analysis, such as classification [3,4], segmentation [5] and detection [6]. However, these supervised applications need manual annotation from experts, which is time-consuming and labor-intensive. In contrast, content-based image retrieval (CBIR) [7–10] is particularly effective for pathological WSI because it can search in a huge database with few annotation and return the images similar to the query. If the WSIs in the database have been diagnosed, pathologists can refer to the diagnostic information of the retrieved results.

To build a precise and fast CBIR system, machine learning methods are commonly used. Note that the performance of machine learning depends on the quantity and quality of training samples. In pathological image analysis, the training sample is region-of-interest (ROI) instead of WSI. This is because regions are more accurate in emphasizing lesion and easier to process, and pathological diagnoses are usually based on ROIs. Among unsupervised approaches to generate regions in images, sliding-window is the most simple one by exhaustive search. Although sliding-window has been widely used in pathological image analysis methods [5,6,9], it suffers from severe defects such as dismatch with irregular annotations and numerous invalid windows. It is necessary to propose an unsupervised method that can efficiently generate accurate and effective ROIs.

To solve the problem of generating representative regions from an image, researchers have raised the issue called region proposal (RP), which means the possible objects or ROIs in the image. For a region proposing method, recall is more important than precision because the false RPs can be filtered by subsequent algorithms such as classification and retrieval, but the missed objects cannot be recovered. Different region proposing methods are reviewed in [11]. Through the comparison on output, proposal number, efficiency and recall, we find that Selective Search (SS) [12] is an unsupervised method that can generate accurate RP segments in multiple scale, making it suitable for WSI. Nevertheless, SS is designed for natural image, which is quite different from WSI: 1) WSI is much huger in size; 2) WSI has special structures such as nucleus and cytoplasm; 3) WSI has a unique color distribution determined by stains, e.g., hematoxylin and eosin. In order to improve the performance of SS on WSI, some modifications are necessary.

The key factors for precise and fast retrieval are exact feature and hashing method. Refs. [9] and [8] respectively demonstrated the advantages of Latent Dirichlet Allocation (LDA) feature and supervised hashing (SH) in histopathological image retrieval. The combination of LDA and SH will probably make a better retrieval method.

In this paper, we present a novel unsupervised region proposing method for histopathological WSI called Selective Search for Whole Slide Image (WSI-SS), and the framework is shown in Fig. 1. A preliminary version of this work was reported in a conference paper [13]. Specifically, the WSI is down-sampled into a thumbnail at low magnification, which is sequently over-segmented and the segmentations are mapped back to initial regions in high magnification. More regions are generated by iteratively merging two most similar regions into a new region according to similarity measures of different features, including the proposed nucleus and Gabor feature. As a result, both the initial regions and the merged regions are output as RPs. In addition to common RGB color space, different staining channels corresponding to nuclei and cytoplasm in WSI are considered through the above procedure to generate complementary RPs. Afterwards the RPs are utilized for training the retrieval method in [9]. Furthermore, we address Supervised Hashing with Latent Dirichlet Allocation (LDA-SH) in image retrieval. This is achieved by comprehending the latent semantic feature from LDA and small amount of label information from SH, improving both speed and accuracy.

The methods are tested on a large-scale multi-class database of breast histopathological WSIs. The results demonstrate that our region proposing method can generate 7.3 thousand region segments from one WSI, fitting well with 95.8% of the ROIs annotated by pathologists. The proposed hashing method can retrieve a query image among 136 thousand images in 0.29 s and reach precision of 91% with only 10% of training images labeled.

We conclude our contributions as two-fold. On one hand, the task of region proposing in WSI is introduced and WSI-SS is proposed based on SS and the features of WSI. The generated RPs can accurately predict ROIs. Moreover, the RPs can also serve as the training samples to construct better models for WSI retrieval. On the other hand, by combining the latent semantic feature of LDA and the supervised information of SH, fast and accurate retrieval is achieved with small percentage of labels. The method is capable to practical applications with mass data but scarce annotations.

The remainder of this paper is organized as follows. Section 2 reviews related works on region proposing and hashing methods for pathological images. Section 3 presents the procedures of WSI-SS in details. Section 4 introduces the idea of LDA-SH. Section 5 demonstrates the experimental results and analysis. Section 7 summarizes our conclusions and future work.

2. Related works

In some pathological image analysis methods [3], the training directly starts with regions which are manually selected from WSI. For other approaches where WSI is the input of training [9] or in-