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Segmenting renal whole slide images virtually without training data

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ABSTRACT

Digital pathology is a field of increasing interest and requires automated systems for processing huge amounts of digital data. The development of supervised-learning based automated systems is aggravated by the fact that image properties can change from slide to slide. In this work, the focus is on the segmentation of the glomeruli constituting the most important regions-of-interest in renal histopathology. We propose and investigate a two-stage pipeline consisting of a weakly supervised patch-based detection and a precise segmentation. The proposed methods do not need any previously obtained training data. For adapting and optimizing this model, a kernel two-sample test is applied. For the segmentation stage, unsupervised segmentation methods including level-set and polygon-fitting approaches are adapted, combined and evaluated. Overall, with the best performing polygon-fitting segmentation method, 51% of glomeruli were segmented with sufficient accuracy (DSC > 0.8). 42% of the detections were false positives. Due to the difficult application scenario in combination with the small required training corpus, the obtained performance is assessed as good. Strategies for increasing the segmentation performance even further are discussed in detail.

1. Introduction

Research in pathology often requires large numbers of annotated whole slide images (WSIs) where an image has a typical resolution of about one giga pixel. Here, we focus on an application scenario from kidney pathology where the objects of interest are the so-called glomeruli (Fig. 1, right, for details see Sect. 1.1). Automated detection and segmentation of the glomeruli would extremely facilitate the work of pathologists who currently count and segment these structures manually for research purposes. Variations, such as different staining intensity and thickness of the histological slices, lead to qualitative differences between WSIs, even if all of them show kidneys stained with the same dye and originating from the same whole slide scanner. As these variations have effects on color, texture and morphology [1], they can reduce the generalization ability of a classifier trained on a set of images showing different properties than the data to be evaluated, which is commonly referred to as domain shift [2].

A potential domain shift between training and evaluation data exhibits a distinct burden for methods relying on supervised classification. To tackle this problem, either large amounts of training data need to be collected showing all possible variations or separate training data sets for each ”characteristic” need to be available [3]. A further solution could be to rely on domain adaptation methods [1] to compensate the occurring changes.

1.1. Medical background

Kidneys have a complex anatomy and virtually all kidney diseases lead to structural changes which are currently much more specific than any other biomarker. For a precise diagnosis and hence a correct therapy of patients with renal diseases, a histological evaluation of kidney biopsies is therefore essential. Histological analyses of kidneys are also crucial and are broadly used in basic and translational research, in drug development as well as in drug toxicity testing. Morphological and ultrastructural alterations give information on the pathomechanisms of renal injury, location (which compartment or which cells of the kidney are injured), distribution (is the damage focal or diffuse within the whole kidney or segmental or global within a glomerulus) and severity of damage. Glomeruli (Fig. 2), the blood-filtration units of the kidney, are one of the most important kidney compartments which are affected in a large number of kidney diseases. Analysis of glomeruli is therefore one of the most important steps in histological evaluation of kidney biopsies in

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both clinical and experimental nephropathology. To obtain morphological information of specific structures, different histological stainings are applied. The most important staining in renal histopathology is PAS (periodic acid schiff) providing important information for diagnosis. Fig. 2 shows an example glomerulus as well as the ground-truth segmentation stained with PAS.

1.2. Related work

The problem of glomerulus segmentation has only been addressed by very few approaches so far. A supervised classification based approach was proposed by Kato et al. [4]. The authors introduced a separate detection and segmentation stage, both based on training a supervised classification model (linear support vector machine (SVM)). For detection, the method relies on the rectangular histogram of oriented gradients descriptor (RHOG), which is applied in a patch-wise manner. Based on the trained model, a patch-wise score is computed and finally, after non-maxima-suppression, the center points of the glomeruli are obtained. In a second stage, the segmentation is obtained by means of a polygon-fitting method utilizing another HOG derivative, specifically the spherical-HOG descriptor (SHOG) [5]. For this purpose, the classification model is trained with patches on the contour as well as other patches located inside or outside of the glomeruli. The polygon-fitting method aims at producing a relatively circular segmentation while keeping the classifier's score (for the contour-class) high. The drawback of this method is given by the high dependency on precise label data. Whereas the detection stage requires some roughly located objects only, the segmentation stage needs precisely annotated regions-of-interest. Additionally, this method was developed for a specific staining (desmin) which highlights cells in glomeruli, facilitating a detection and segmentation.

To circumvent the need for a significant amount of reliable training data, Samsi et al. [6] proposed a segmentation algorithm for glomeruli in mouse kidney biopsies. Specifically, the authors aim at segmenting the white sickle-shaped Bowman's capsule surrounding the glomerulus by performing color-based segmentation. This segmentation method consists of thresholding the image followed by k-means clustering and morphological operations. However, the inherent problem of this approach is, that the Bowman's capsule is not always visible, depending on the straining protocol as well as the position of the glomerulus relative to the cutting plane (Fig. 1). Since the Bowman's capsule is not always present, in general, this method is not capable to generate a reliably precise segmentation.

All futher studies do not focus on a segmentation, but on a detection only or on patch-wise tissue classification. In Ref. [7], different image representations have been investigated to determine whether they are appropriate for distinguishing between regions in renal pathology, with a focus on patch-wise classification. The authors found that color as well as texture representations can be utilized for distinguishing between the texture classes.

Similarly, in Ref. [1] domain adaptation methods were investigated for patch-wise classification of renal tissue. The authors showed that domain adaptation can help to improve the fit of trained models for image data showing changed properties. However, the investigated semi-supervised domain adaptation method still requires annotated target domain data (i.e. data from the image to be evaluated) and a larger set of (arbitrary) source domain training data.

A review of state-of-the-art literature in this field as well as related fields, such as automated diagnosis in endoscopy [8–10], reveals a major problem preventing automated systems from being widely deployed in research as well as clinical practice: depending on intra- and inter-class variability in image data sets, for effective training of classification models large amounts of annotated training data have to be acquired in order to accurately estimate the classifier's decision boundaries [9]. For unchanging problem definitions, the acquisition and annotation of large training data is time consuming, but acceptable. However, issues with large training data arise if variations lead to distinct changes in the image and consequently to changes in the computed image representation. The inflexibility of supervised-learning-based systems constitutes a severe obstacle for many real-world application scenarios.

In general literature on machine learning, several strategies to deal with high variability in the image domain were identified. Specific variations can be compensated by means of image normalization methods. The proposed techniques reach from simple contrast normalization to more sophisticated and problem specific methods such as stain normalization [11]. Another approach to compensate variability such as scale-, rotation- and illumination-variations is given by invariant image descriptors [10]. Finally, variations can be modeled and compensated by learning a transformation between training and test data which is referred to as domain adaptation [2]. Since these domain adaptation methods are developed to deal with slight domain shifts only, methods claimed to be invariant not necessarily outperform conventional ones in real-world applications [10]. Normalization is only sensibly applicable for some specific kinds of variations such as changes in color intensity.

Recently, instead of improving the image representation, the focus has been on augmenting the data set to ’learn’ the variability as far as possible by taking advantage of deep learning architectures [12,13]. Architectures such as fully convolutional networks (FCNs) [14], however, require a significant amount of annotated data for training these models in the first place.

Unsupervised segmentation approaches have been applied for the segmentation of histopathological tissue as well. Whereas there is limited literature on unsupervised segmentation of higher level objects (such as renal glomeruli [6]), a significant amount of research has been performed

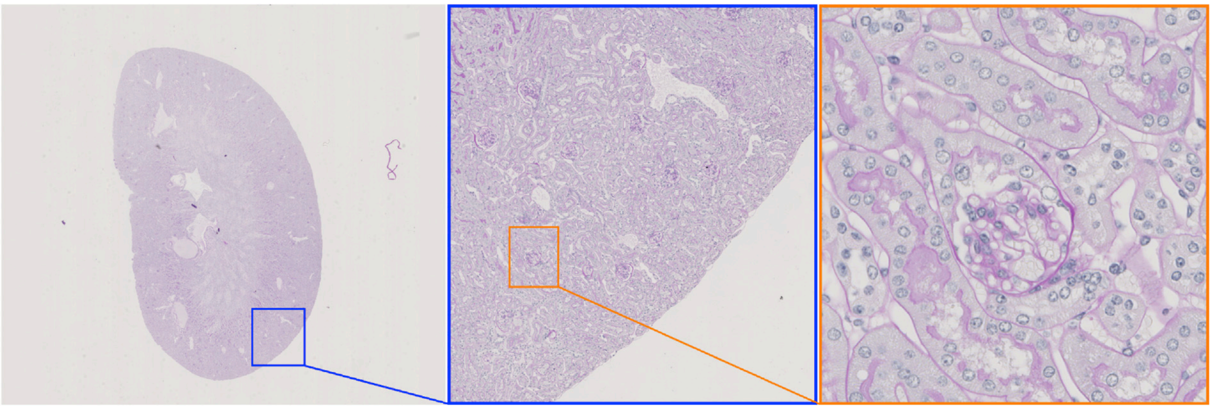

Fig. 1. An example WSI showing mouse kidney (left), and zoomed versions of a certain patch based on two zoom-levels exhibiting the high detail degree of pathological image data. The right patch clearly shows a renal glomerulus.