Computerized Medical Imaging and Graphics 35 (2011) 579–591

Contents lists available at ScienceDirect

Computerized Medical Imaging and Graphics

journal homepage: www.elsevier.com/locate/compmedimag

Time-efficient sparse analysis of histopathological whole slide images

Chao-Hui Huang[b,c], Antoine Veillard[b,c], Ludovic Roux[b,e], Nicolas Loménie[a,b,*], Daniel Racoceanu[a,b,c,d]

[a] Centre National de la Recherche Scientifique (CNRS), Paris, France
[b] IPAL (Image & Pervasive Access Lab), International Mixed Research Unit, UMI CNRS 2955 (CNRS, NUS, I2R/A*STAR, UJF), Singapore
[c] National University of Singapore, Singapore
[d] University of Franche-Comté, Besançon, France
[e] University Joseph Fourier, Grenoble, France

ARTICLE INFO

Article history:
Received 9 June 2010
Received in revised form 25 October 2010
Accepted 18 November 2010

Keywords:
Digitized histopathology
Breast cancer grading
Whole slide image
Multi-scale analysis
Dynamic sampling
Virtual microscopy
Graphics processing unit

ABSTRACT

Histopathological examination is a powerful standard for the prognosis of critical diseases. But, despite significant advances in high-speed and high-resolution scanning devices or in virtual exploration capabilities, the clinical analysis of whole slide images (WSI) largely remains the work of human experts. We propose an innovative platform in which multi-scale computer vision algorithms perform fast analysis of a histopathological WSI. It relies on application-driven for high-resolution and generic for low-resolution image analysis algorithms embedded in a multi-scale framework to rapidly identify the high power fields of interest used by the pathologist to assess a global grading. GPU technologies as well speed up the global time-efficiency of the system. Sparse coding and dynamic sampling constitute the keystone of our approach. These methods are implemented within a computer-aided breast biopsy analysis application based on histopathology images and designed in collaboration with a pathology department. The current ground truth slides correspond to about 36,000 high magnification (40×) high power fields. The processing time to achieve automatic WSI analysis is on a par with the pathologist's performance (about ten minutes a WSI), which constitutes by itself a major contribution of the proposed methodology.

1. Introduction

Histopathology is widely accepted as a powerful gold standard for prognosis in critical diseases such as breast, prostate, kidney and lung cancers, allowing to narrow borderline diagnosis issued from standard macroscopic non-invasive analysis such as mammography and ultrasonography. At the molecular/genetic scale as well, challenging methods recently emerged for clinical diagnosis purposes. However, histomorphology as operated in hospitals is and will remain the basis for most cancer classification [1].

The histopathological image analysis process has largely remained the work of human experts so far: the pathologist's task for grading consists in the daily examination of hundreds of slides with a microscope, directly impacting critical diagnosis and treatment decisions. According to pathologists' opinion [2], such a tedious manual work is often inconsistent and subjective, lacking traceability and computer assisted analysis/annotation/grading support tools. In addition, hospitals will have to manage a shortage of expert pathologists keen at doing this kind of unrewarding tasks.

The study of fully fledged digitized histopathology system including image processing capabilities is quite a recent topic due to the late uptake of acquisition devices as competitive as in the radiological field. However significant works in the field of automatic image analysis have been carried on sample histopathological images for the overview of which a good state-of-the-art can be found in [3]. For the specific issue of WSI based Computer Assisted Diagnosis very few works emerged [4,5]. A few image analysis algorithms and automated grading systems dedicated to breast histopathology images have already been studied. Estévez et al. [6] and Schnorrenberg et al. [7,8] worked on Fine Needle Aspiration (FNA) biopsies. FNA images are relatively easier to analyze than WSIs since such an examination has limited diagnostic options and produces mostly well separated cells over a well-contrasted background. Petushi et al. [9,10] introduced a system able to label several histological and cytological microstructures in high resolution frames, including different grades of epithelial cells, fat cells and stroma. Doyle et al. [11,12] proposed a method based on geometrical features, to distinguish between healthy tissue, low grade and high grade cancer. Tutac et al. [13] initiated an innovative knowledge guided approach relying on the prior modeling of medical knowledge using ontology designed according to the clinical standard called Nottingham Grading System [14]. In that work, a formalization of the clinical and biological knowledge used for the grading like the nuclear pleomorphism scoring is proposed. This

* Corresponding author at: IPAL (Image & Pervasive Access Lab), International Mixed Research Unit, UMI CNRS 2955 (CNRS, NUS, I2R/A*STAR, UJF), Singapore. Tel.: +65 64082548.
E-mail address: Nicolas.Lomenie@mi.parisdescartes.fr (N. Loménie).
URL: http://ipal.i2r.a-star.edu.sg/ (N. Loménie).

0895-6111/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.compmedimag.2010.11.009

score assesses the variability in shape, color and texture of the cell nuclei and is a common indicator for the prognosis of breast cancer. More theoretical work about a cognitive approach to perform spatial reasoning over a WSI was also put forward in [15]. An extension to this work involving multi-scale approaches was proposed by Dalle et al. [16].

In close collaboration with a histopathology department, we built up a high-speed WSI analysis platform able to detect scale-dependent meaningful regions of interest in microscopic biopsy images. This platform is dedicated to the grading of breast cancer for prognosis purposes but the methodology we present here is quite generic. We use a standard optical microscope that can be found in most of the analysis laboratories in pathology or bacteriology (in our case, an optical microscope Olympus BX51, with 4×/10×/40×/60×/100× possible magnifications, Prior H101A ProScanII motorized X/Y stage and Z focus with a travel range of 114 mm × 75 mm and a minimum step size of 0.02 μm, and a 1280 × 1024 pixels digital camera MediaCybernetics "EvolutionLC color" IEEE1394 MegaPixel). We use a MediaCybernetics controller connected to the microscope to perform an acquisition of high power fields/frames (at 40× magnification according to the request of the pathologist for the high resolution analysis). The acquired 40× high power fields are stitched together in order to obtain the WSI.

To the best of our knowledge, most previous research works focused on the analysis of individual high resolution frames [17] and/or proposed solutions computationally too expensive to be applied at the WSI level [18]. A few notable exceptions [19] rely on the analysis of lower resolution images for the selection of regions of interest. Unfortunately, there is little correlation between low resolution images and the actual levels of nuclear pleomorphism observable at high resolution for instance. Therefore, even such methods proved to be inefficient for the particular issue of nuclear pleomorphism assessment on full biopsy slides. As a consequence, the time-efficiency problem posed by the extremely large scale of biopsy images (several thousands of frames) still lacks a practical solution.

In this work, we propose solutions to improve the efficiency of such a microscopy digital platform both in terms of speed and precision, in particular with a multi-scale dynamic sampling approach and the use of graphics processing unit (GPU) programming. The processing of a WSI starts by the detection of invasive regions of interest (ROI) at low resolution level (1.2×). This method relies on a bio-inspired visual information paradigm related to sparse coding and GPU implementation to dramatically speed-up the processing line. This part will be detailed in Section 2. Once the ROIs are detected, a map of local cancer grades is established using a new generic multi-scale, computational geometry-based dynamic sampling method combined with high-resolution application-specific image analysis algorithms. Then, this map is used to analyze the WSI within an operational time frame compatible with the pathology department needs and on a par with the processing time of an experienced pathologist. This part will be detailed in Section 3. The overall process is sum up in Fig. 1: within a clinical perspective, that is an operational one, we state that the general idea of sparse analysis is the only scientific strategy for processing such amount of data as afforded now by digitized WSI and subsequently we put it forward as the key module of any WSI exploration system in the global workflow. GPU/cloud computing is a major current available tool but remains just a technological means to achieve much faster results. A global strategy at the signal processing level is definitely required and can be translated to various fields of microscopic imaging but also to issues about very high resolution satellite imaging. Finally, Section 4 elaborates on the results and validation issues and Section 5 is dedicated to conclusions and future research directions.

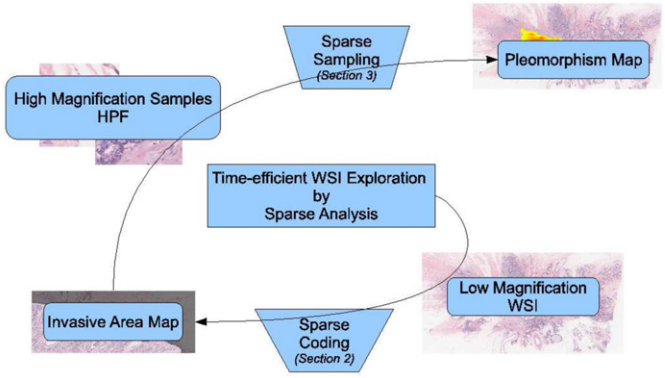

Fig. 1. Overall sparse analysis process for time-efficient exploration of WSIs.

2. Low resolution analysis and sparse coding

As a fundamental phase for breast cancer grading based on histopathological images, pathologists identify regions of interest (ROI) to efficiently select the most important invasive areas in order to speed up the grading process. Since neither the pathologist nor the computer is able to explore every detail at high magnification within a reasonable time, the effective and efficient choice of these ROIs is a critical step.

In this study, ROI detection is casted as a classification problem. The low magnification analysis will determine if a given region is an invasive area in a similar manner as a pathologist would do when evaluating a biopsy. In order to mimic this behavior, we exploit the relationship between human vision and neurosciences [20].

In this study, we extracted the first- and second-order visual features from the given input. Based on these features, we designed a classification algorithm to distinguish between invasive area and normal tissue based on these low-level visual information. In order to speed up this task, we make use of GPU technology and leverage the parallelization capabilities to provide a time-efficient pre-attentive vision module over the WSI for the final application.

GPU is a specialized processor that offloads graphics rendering from the microprocessor. The highly parallel structure of the GPU makes the computation more efficient than general-purpose CPUs for a range of complex algorithms. In a personal computer, a GPU can be related to a video card. Currently, most of the new desktop and notebook computers have integrated GPUs, which are usually far less powerful than those on a dedicated video cards.

2.1. Color representation

In this section, we aim at discovering the relationship between the content of a breast biopsy image when displayed on a screen (as opposed to the optical mainstream microscope the pathologists are still commonly using so far) and the decision-making procedure which is performed when a pathologist is analyzing the image on the screen.

It is important to understand that digitized pathology is at a significant turning. Up to now, pathologists are still working with the microscope unlike radiologists that have long past been working with digitized images. So not only the greater amount of data to process in digitized pathology is an original issue but also the staining and cut procedures that yield to changing color images (again unlike radiology) that the pathologist learns to read all along his/her career. Pathologists read their slides, according to their own terms. So the ergonomic, cognitive aspect of visualization and, based on this display, making a decision is as challenging for the device provider as the efficiency of the processing that have been set up in the system. This is the reason why we chose to detect invasive