Multispectral Texture characterization: Application to Mitotic Count in Breast Cancer Histopathology

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Abstract

Multispectral Imaging (MSI) ...

1. Introduction

In medical image analysis, computer aided detection/diagnosis (CAD) systems are popular for clinical purposes (medical procedures seeking to divulge, diagnose or examine disease) and medical science (including the study of body anatomy and physiology). CAD systems are extensively used in the detection and differential diagnosis of many different types of abnormalities in medical images obtained using different imaging modalities. Medical image analysis in radiology (x-rays, ultrasound, MRI, CT and mammogram) and cytology domains have been major research fields for several decades and numerous systems [32, 10, 33, 14, 2, 16, 29] and software platforms [1, 2, 3, 4, 5, 6] have been developed for these domains. The application of these systems to histopathology is complicated due to radically different imaging modalities and image characteristics. In general, histology images are considerably different from radiology images, having a large amount of objects of interest (like nuclei) widely distributed in the images and surrounded by different neighbouring tissues like blood vessels, muscle, stroma, and fat. In addition, histopathology tissues are generally stained with different colors while radiology images usually contain only gray intensities. Although, cytology images have some similarities to histology images but both images are taken at different magnification level. In case of histology images, cellular structure and function is studied while in histology, whole tissue having cells and architecture like gland formation are studied.

According to World Health Organization, the reference process for breast cancer prognosis is histologic grading that combine tubule formation, nuclei atypia and mitotic counts [3, 9]. This assessment of tissue sample is synthesized into a diagnosis that would help the clinician determine the best course of therapy. We found several CAD systems for tubule formation [28, 27] and nuclei atypia [6, 7, 5, 8], but only few mitotic counts (MC) [17, 18]. One of the most difficult fields in histopathology imagery is spatial analysis, more specifically automated nuclei detection and classification [12]. The objective of nuclei classification is assign label to different type of nuclei as normal, cancer, mitotic, apoptosis, lymphocytes etc that in particular, a challenging problem to address in histopathology. In addition, quantitative characterization is important not only for clinical applications (e.g., to reduce/eliminate inter- and intra-observer variation in diagnosis) but also for research applications (e.g., to understand the biological mechanisms of the disease process [15].

In histopathology, H&E is a well established staining technique that exploits intensity of stains in the tissue images to quantify the nuclei and other structures related to cancer developments. Image processing techniques in this context are devoted to the accurate and objective quantification and localization of such activity in specific regions of the tissue such as cytoplasm, membranes and nuclei. From the chromatic viewpoint, nuclear regions are characterized

[1] 3D Slicer, http://slicer.org/
[2] ImageJ, http://rsb.info.nih.gov/ij/
[3] Mirada Medical, http://www.mirada-medical.com/
[4] Infinite Radiology, http://infiniteradiology.com/
[5] PATHOS-WEB, http://pathos-web.sourceforge.net/
[6] Xebra (medical imaging software), http://en.vionto.com/show/me/Xebra

by non-uniform stain intensity and color, thus preventing a trivial classification based on color separation. In addition, the superposition of tissue layers as well as the diffusion of the dyes on the tissue surface may bring the stains to contaminate the background or other cellular regions which are different from their specific target.Recent work [19, 17, 18] show great potential for CAD of histopathological datasets for breast cancer diagnosis.

Multispectral imaging (MSI) retrieves spectrally resolved information of an image scene at specific frequencies across the electromagnetic spectrum. MSI captures images with accurate spectral content correlated with spatial information and reveals the chemical and anatomic features of histopathology [21, 23]. This is because it provides option to biologists and pathologists to see beyond the RGB image planes that they are accustomed to. Recent publications [11, 24, 34, 20] have begun to explore the use of extra information contained in such spectral data. Specifically, there have been comparisons of spectral unmixing algorithms (to separate constituent dyes) which demonstrate the advantage of multispectral data [22, 13]. The added benefit of MSI for analysis of routine H&E histopathology imagery, however, is still largely unknown, although some promising results are presented in [30, 11, 20, 34].

While nuclei segmentation and classification using MSI in histopathology is new area of research, many researchers used single band of MSI for segmentation of tissue and nuclear region [4, 35, 26] and few used all or selected bands [11, 20]. As far as we know, there is no existing study of the advantage of MSI for automation of mitotic counts in breast cancer histopathology. We proposed here to extend the already successful work of [18] to automation of MC in MSI.

The reminder of the paper is organized as follows. Section 2 reviews the state-of-the-art multispecttral methods, particularly in object or region detection in histopathology, related to this research work. Section 3 describes the proposed framework for mitotic figure detection. Experiment and results are presented in section 4. Finally, the concluding remarks with future work are given in section 5.

2. Literature Review

The main idea of extracting texture from MSI is the use of combined spectral and spatial information for discrimination of region or objects. We found few methods in the MSI literature for texture characterization of histopathological images. Some of them employed single band of MSI and other used multiple selected bands of MSI. Fernandez et al. [11] coupled high-throughput Fourier transform infra-red (FTIR) spectroscopic imaging of tissue microarrays with statistical pattern recognition of spectra indicative of endogenous molecular composition and demonstrate histopathologic characterization of prostatic tissue. They explicitly defined metrics to consist of spectral features that have a physical significance related to tissue biochemistry and facilitated the measurement of cell types. The approach in [**?**] used hyperspectral images of colon biopsy slides whereby the classification algorithm was based on spectral analysis to discriminate between normal and cancerous biopsies of the colon tissue. In this study of hyperspectral cancer analysis, they used Laplacian eigenmaps to take into account the non-linear geometry in the design of learning algorithms and evaluated two approaches for spectral feature selection: Haar wavelet packet best bases (active sensing) and random projections.

Masood et al. [26] proposed a colon biopsy classification method based on spatial analysis of hyperspectral image data from colon biopsy samples. Initially, using circular local binary pattern algorithm, spatial analysis of patterns are represented by a feature vector in selected spectral band. Later, classification is achieved using subspace projection methods like principal component analysis, linear component analysis and support vector machine. Boucheron et al. [4] presented an analysis of the utility of multispectral versus standard RGB imagery for pixel level classification of nuclei in H&E stained histopathological images and found that performance differences between single multispectral image bands and single RGB image bands are not statistically significant.

Khelifi et al. [20] proposed a spatial and spectral gray level dependence method in order to extend the concept of gray level co-occurrence matrix by assuming the presence of texture joint information between spectral bands. Malon et al. [25] demonstrated a segmentation based features with convolutional neural networks using additional focal planes and spectral bands for identification of mitotic nuclei in breast cancer histopathology and achieved best classification accuracy (F-measure = 59%) on multispectral dataset during ICPR context 2013 [31].

Recently, Wu et al. [34] proposed a multilayer conditional random field model using a combination of low-level cues and high-level contextual information for nuclei separation in high dimensional data set obtained through spectral microscopy. In this approach, the multilayer contextual information was extracted by an unsupervised topic discovery process from spectral images of microscopic specimen, which efficiently helps to suppress segmentation errors caused by intensity inhomogeneity and variable chromatin texture.

In the proposed methodology, we address limitation of the shortcomings in previous works, including (1) comprehensive analysis of multispectral spatial feature vector in all bands rather than single band [26, 35, 34] and (2) combining spatial feature with multispectral spatial feature vector in order to discriminate mitotic figures from other nuclei and microscopic objects. The main novel contributions of

proposed work are: (1) a multispectral spatial and morphology feature vector computation which inherit discriminant information from other nuclei and (2) an projection features from multispectral features vector for classification of mitotic figures in breast cancer histopathological images.

3. Proposed Method

3.1. Dataset

We evaluated the proposed methodology on multispectral MITOS dataset [1], a freely available mitosis dataset. The data set is made up of 50 high power fields (HPF) coming from five different slides scanned at 40X magnification using a 10 bands multispectral microscope. There are 10 HPFs per slide and each HPF has a size of $512 \times 512 \mu\text{m}^2$ (that is an area of $0.262 mm^2$). The spectral bands are all in the visible spectrum. In addition, for each spectral band, the digitization has been performed at 17 different focus planes (17 layers Z-stack), each plane being separated from the other by 500 nm. For one HPF, there are 170 gray scale images (10 spectral bands and 17 layers Z-stack for each spectral band). These 50 HPFs contain a total 322 mitotic cells. The training data set consists of 35 HPFs containing 226 mitotic cells and evaluation data set consists of 15 HPFs containing 98 mitotic cells [31]. Figure 1 shows the spectral coverage of each of the 10 spectral bands of the multispectral microscope.

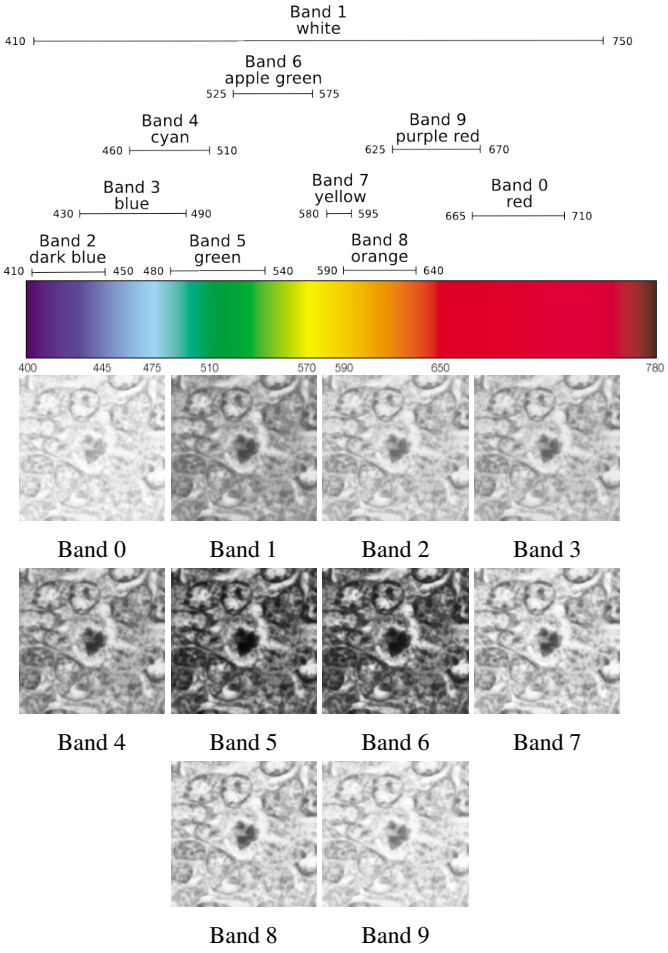

Figure 1: Spectral bands of the multispectral microscope and examples for each band.

3.2. Proposed Method

In this paper, we propose a framework for MC based on spatial analysis of MSI in breast cancer histopathology. Initially, a z-stack plane is selected based on gradient and band is selected based on histogram analysis. Then, candidates for mitotic figures are computed on selected band and z-stack plane. A multispectral feature vector is computed for all detected candidates including intensity and texture features in all bands of multispectral images. In addition, using segmented regions of detected candidates, morphological features are also computed. A feature selection algorithm is employed on this multispectral features vector to save the computation cost and to discard any redundancy in the data in order to improve classification accuracy. Classification is achieved using support vector machine (SVM), Bayesian network (BN) as well as decision tree (DT). A side advantage of performing the spatial analysis on a multiple band is to investigate whether improvement in accuracy can be achieved with carefully selected multispectral features to those methods [26, 35, 34] which use single band data.

3.2.1 Candidate Detection

3.2.2 Multispectral Features Computation

3.2.3 Feature Selection and Classification

4. Experiments and Results

4.1. Experiments

4.2. Results

5. Discussion and Conclusion

References

[1] Mitos contest 2012. http://ipal.cnrs.fr/ICPR2012.

[2] I. Bankman. *Handbook of medical image processing and analysis*. Academic press, 2008.

[3] H. Bloom and W. Richardson. Histological grading and prognosis in breast cancer: a study of 1409 cases of which 359 have been followed for 15 years. *British Journal of Cancer*, 11(3):359, 1957.

[4] L. E. Boucheron, Z. Bi, N. R. Harvey, B. Manjunath, and D. L. Rimm. Utility of multispectral imaging for nuclear classification of routine clinical histopathology imagery. *BMC Cell Biology*, 8(Suppl 1):S8, 2007.

[5] A. R. Chaudhury, K. Iychettira, R. Iyer, and A. Sreedevi. Diagnosis of invasive ductal carcinoma using image processing techniques. In *Image Information Processing (ICIIP), 2011 International Conference on*, pages 1–6. IEEE, 2011.

[6] E. Cosatto, M. Miller, H. P. Graf, and J. S. Meyer. Grading nuclear pleomorphism on histological micrographs. In *Pattern Recognition, 2008. ICPR 2008. 19th International Conference on*, pages 1–4, Dec. 2008.

[7] J.-R. Dalle, H. Li, C.-H. Huang, W. K. Leow, D. Racoceanu, and T. C. Putti. Nuclear pleomorphism scoring by selective cell nuclei detection. In *IEEE Workshop on Applications of Computer Vision*, 2009.

[8] M. Dundar, S. Badve, G. Bilgin, V. C. Raykar, R. K. Jain, O. Sertel, and M. N. Gurcan. Computerized classification of intraductal breast lesions using histopathological images. *Biomedical Engineering, IEEE Transactions on*, 58(7):1977–1984, july 2011.

[9] E. Elston and I. Ellis. Method for grading breast cancer. *Journal of clinical pathology*, 46(2):189, 1993.

[10] B. J. Erickson and B. Bartholmai. Computer-aided detection and diagnosis at the start of the third millennium. *Journal of digital imaging*, 15(2):59–68, 2002.

[11] D. C. Fernandez, R. Bhargava, S. M. Hewitt, and I. W. Levin. Infrared spectroscopic imaging for histopathologic recognition. *Nature biotechnology*, 23(4):469–474, 2005.

[12] T. J. Fuchs and J. M. Buhmann. Computational pathology: Challenges and promises for tissue analysis. *Computerized Medical Imaging and Graphics*, 35(7):515–530, 2011.

[13] S. M. Gentry and R. M. Levenson. Biomedical applications of the information-efficient spectral imaging sensor (isis). In *BiOS'99 International Biomedical Optics Symposium*, pages 129–142. International Society for Optics and Photonics, 1999.

[14] M. L. Giger. Computerized analysis of images in the detection and diagnosis of breast cancer. In *Seminars in Ultrasound, CT, and MRI*, volume 25, pages 411–418. Elsevier, 2004.

[15] M. N. Gurcan, L. E. Boucheron, A. Can, A. Madabhushi, N. M. Rajpoot, and B. Yener. Histopathological image analysis: A review. *Biomedical Engineering, IEEE Reviews in*, 2:147–171, 2009.

[16] L. He. *Towards Image Understanding: Deformable Contour and Graph-based Image Segmentation and Recognition*. LAP Lambert Academic Publishing, 2009.

[17] H. Irshad, S. Jalali, L. Roux, D. Racoceanu, L. Joo-Hwee, G. L. Naour, and F. Capron. Automated mitosis detection using texture, sift features and hmax biologically inspired approach. *Journal of Pathology Informatics*, in press.

[18] H. Irshad, L. Roux, and D. Racoceanu. Automated mitosis detection in histopathology using morphological and multichannel statistics features. *Journal of Pathology Informatics*, in press.

[19] A. M. Khan, H. El-Daly, and N. M. Rajpoot. A gamma-gaussian mixture model for detection of mitotic cells in breast cancer histopathology images. In *Pattern Recognition (ICPR), 2012 21st International Conference on*, pages 149–152. IEEE, 2012.

[20] R. Khelifi, M. Adel, and S. Bourennane. Multispectral texture characterization: application to computer aided diagnosis on prostatic tissue images. *EURASIP Journal on Advances in Signal Processing*, 2012(1):1–13, 2012.

[21] R. M. Levenson. Spectral imaging perspective on cytomics. *Cytometry Part A*, 69(7):592–600, 2006.

[22] R. M. Levenson, P. J. Cronin, and K. K. Pankratov. Spectral imaging for brightfield microscopy. In *Biomedical Optics 2003*, pages 27–33. International Society for Optics and Photonics, 2003.

[23] R. M. Levenson, A. Fornari, and M. Loda. Multispectral imaging and pathology: seeing and doing more. *Expert Opinion on Medical Diagnostics*, 2(9):1067–1081, 2008. PMID: 23495926.

[24] R. M. Levenson and J. R. Mansfield. Multispectral imaging in biology and medicine: slices of life. *Cytometry Part A*, 69(8):748–758, 2006.

[25] M. Malon and E. Cosatto. Classification of mitotic figures with convolutional neural networks and seeded blob features. *Journal of Pathology Informatics*, in press.

[26] K. Masood and N. Rajpoot. Texture based classification of hyperspectral colon biopsy samples using clbp. In *Biomedical Imaging: From Nano to Macro, 2009. ISBI'09. IEEE International Symposium on*, pages 1011–1014. IEEE, 2009.

[27] S. Naik, S. Doyle, S. Agner, A. Madabhushi, M. Feldman, and J. Tomaszewski. Automated gland and nuclei segmentation for grading of prostate and breast cancer histopathology. In *Biomedical Imaging: From Nano to Macro, 2008. ISBI 2008. 5th IEEE International Symposium on*, pages 284–287. IEEE, 2008.

[28] S. Petushi, F. U. Garcia, M. M. Haber, C. Katsinis, and A. Tozeren. Large-scale computations on histology images reveal grade-differentiating parameters for breast cancer. *BMC Medical Imaging*, 6(1):14, 2006.

[29] M. E. Plissiti and C. Nikou. A review of automated techniques for cervical cell image analysis and classification. In *Biomedical Imaging and Computational Modeling in Biomechanics*, pages 1–18. Springer, 2013.

[30] M. Roula, A. Bouridane, F. Kurugollu, and A. Amira. A quadratic classifier based on multispectral texture features for prostate cancer diagnosis. In *Signal Processing and Its Applications, 2003. Proceedings. Seventh International Symposium on*, volume 2, pages 37–40. IEEE, 2003.

[31] L. Roux, D. Racoceanu, N. Lomenie, M. Kulikova, H. Irshad, J. Klossa, F. Capron, C. Genestie, G. L. Naour, and M. N. Gurcan. Mitosis detection in breast cancer histological images an icpr 2012 contest. *Journal of Pathology Informatics*, in press.

[32] M. Sonka. Handbook of medical imaging: medical image processing and analysis. SPIE-International Society for Optical Engineering, 2000.

[33] R. M. Summers. Road maps for advancement of radiologic computer-aided detection in the 21st century1. *Radiology*, 229(1):11–13, 2003.

[34] X. Wu, M. Amrikachi, and S. K. Shah. Embedding topic discovery in conditional random fields model for segmenting nuclei using multispectral data. *Biomedical Engineering, IEEE Transactions on*, 59(6):1539–1549, 2012.

[35] X. Wu and S. K. Shah. A fast band selection method to increase image contrast for multispectral image segmentation. In *Biomedical Imaging: From Nano to Macro, 2009. ISBI'09. IEEE International Symposium on*, pages 1123–1126. IEEE, 2009.