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Discriminating dysplasia: Optical tomographic texture analysis of colorectal polyps

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ABSTRACT

Optical projection tomography enables 3-D imaging of colorectal polyps at resolutions of 5–10 μm. This paper investigates the ability of image analysis based on 3-D texture features to discriminate diagnostic levels of dysplastic change from such images, specifically, low-grade dysplasia, high-grade dysplasia and invasive cancer. We build a patch-based recognition system and evaluate both multi-class classification and ordinal regression formulations on a 90 polyp dataset. 3-D texture representations computed with a hand-crafted feature extractor, random projection, and unsupervised image filter learning are compared using a bag-of-words framework. We measure performance in terms of error rates, *F*-measures, and ROC surfaces. Results demonstrate that randomly projected features are effective. Discrimination was improved by carefully manipulating various important aspects of the system, including class balancing, output calibration and approximation of non-linear kernels.

1. Introduction

Colorectal cancer is the third most common cancer in men (756k new cases per annum, 10.0%) and the second in women (614 k new cases per annum, 9.2%) worldwide (Ferlay et al., 2013). Colonic polypoid cancers are the earliest detectable form of colorectal cancer and, if completely excised, can offer a potential cure to patients. Screening programmes have played a major role in keeping cancer mortality rates low. As of 2012, 65,535 polyps had been excised and recorded in the UK NHS bowel cancer screening programme (BCSP) database (Majumdar et al., 2012). Histological analysis of polyps is essential for accurate diagnosis. However, the current gold standard method, using Haematoxylin and Eosin (H&E) stained sections, has its limitations. This conventional technique involves taking a thin section of tissue from the centre of the polyp and this will not necessarily be representative of the whole specimen. Much ambiguity exists between experienced pathologists when making diagnoses using H&E sections due to features such as epithelial displacement (EPD) in which surface epithelial cells become misplaced into the stalk of the polyp mimicking true invasive cancer. Over-diagnosis of EPD as cancer has a confounding effect subjecting patients to unnecessary treatments and generating misleading epidemiology reports (Loughrey and Shepherd, 2015; Muto et al., 1973).

Optical projection tomography (OPT) is a relatively new 3-D imaging technique first developed to better our understanding of embryo development (Sharpe, 2009). It is a simple and affordable imaging technology that is well-suited for specimens up to 15 mm in size. OPT of colorectal polyps is non-destructive to the original tissue and enables virtual sectioning of the specimen at any orientation. Fig. 1 shows a comparison between an H&E section and a virtual OPT section of the same polyp. A significant advantage of tomography is the flexibility in viewing virtual sections and manipulating the image to gain more information. By contrast, once the cutting angle has been chosen for the H&E section, it cannot be changed. Histology sections are cut from the tissue once it has been embedded in paraffin wax and subsequently stained. These can be viewed at sub-micron resolutions whereas OPT provides a lower spatial resolution of about 5–10 μm (Sharpe et al., 2002). Near visible wave-length light is used to obtain OPT images and therefore polyps must be optically cleared in advance of scanning using benzyl alcohol benzyl benzoate (BABB).

Inter- and intra-observer variation exists when pathologists diagnose colorectal polyps, notably when grading dysplasia whether from H&E or OPT images (Coats et al., 2012). Reliable and repeatable automatic recognition systems are desirable. As a starting point, this paper proposes and evaluates methods for discrimination of dysplasia in OPT images of colorectal polyps. Specifically, the task addressed is that of differentiating between regions of low-grade dysplasia (LGD), high-grade dysplasia (HGD) and invasive cancer (ICA).

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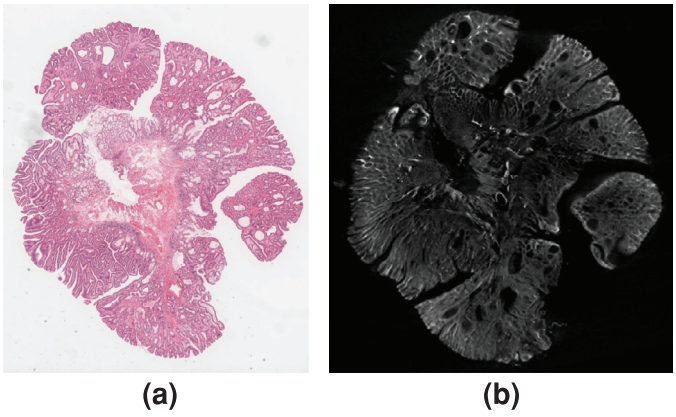

Fig. 1. (a) An H&E-stained whole mount slide. (b) A virtual section from an OPT image of the same polyp with the section chosen to be close to the cut surface that resulted from removal of the physical section shown in (a).

The use of automated image analysis for histopathological grading of colorectal polyps has been studied mainly with stained physical sections imaged using 2D microscopy (e.g., Hamilton et al., 1995; Ficsor et al., 2008; Atlamazoglou et al., 2001; Shuttleworth et al., 2002; Esgiar et al., 2002, 1998; Hamilton et al., 1997; Kalkan et al., 2012; Ozdemir and Gunduz-Demir, 2013). This body of work demonstrates that texture-based analysis is often an important component of lesion detection, segmentation and classification. 3-D texture features have been widely used in medical image analysis more broadly; a comprehensive review of 3-D texture analysis methods is available elsewhere (Depeursinge et al., 2014). Texture representation using local binary patterns (LBPs) and its variants form an important component of many successful 3-D medical image classification systems e.g., for brain white matter lesion classification in MRI (Oppedal et al., 2012), analysis of lung CT (Sorensen et al., 2010), and retinal optical coherence tomography (Liu et al., 2011). Apart from hand-crafted features as exemplified by LBP, two fundamentally different directions for texture analysis have attracted increased attention in recent years. The first is domain-specific descriptors estimated from observations automatically. For example, deep belief networks have been used to learn features for 3-D brain image segmentation (Brosch and Tam, 2013), and independent subspace analysis (ISA) has been used for feature extraction from H&E histology images of Glioblastoma Multiforme (Le et al., 2012), MR images (Liao et al., 2013) and video (Le et al., 2011). The second is random projection (RP), a non-adaptive dimensionality reduction tool motivated by compressive sensing theory, applied directly to image patches. RP compared favourably to state-of-the-art texture descriptors in 2D texture classification experiments (Liu and Fieguth, 2012) and it has been used for image classification (Bingham and Mannila, 2001) and for accelerating feature-based registration of 3-D neural ultrastructure (Akselrod-Ballin et al., 2011), for example. In this paper, for the purpose of discriminating dysplasia, these three contrasting approaches to texture representation are compared. Specifically, we compare RP, LBP (exemplifying hand-crafted features), and ISA (exemplifying unsupervised learning).

The main contribution of this paper is that it provides the first study in the literature on automatically discriminating between invasive cancer, high-grade dysplasia and low-grade dysplasia in optical projection tomography images. It builds on and extends earlier conference papers in which preliminary two-class classification experiments discriminating only between LGD and ICA were reported (Li et al., 2013a, 2013b). While the task of discriminating between LGD, HGD and ICA can be cast as a three-class classification problem, this ignores the ordinal structure of these labels. Here, a classification model and an ordinal regression model, both based on margin maximisation, are compared and contrasted for this task. These raise issues of class imbalance and output calibration which are explored empirically. Two state-of-the-art strategies for fast approximation of non-linear kernels are also evaluated. After describing the methods used, results are reported on a data set of 90 polyps. Although the focus is on OPT images of colorectal polyps, the analysis and evaluation methods used should be applicable to other ordinal regression tasks in other image modalities.

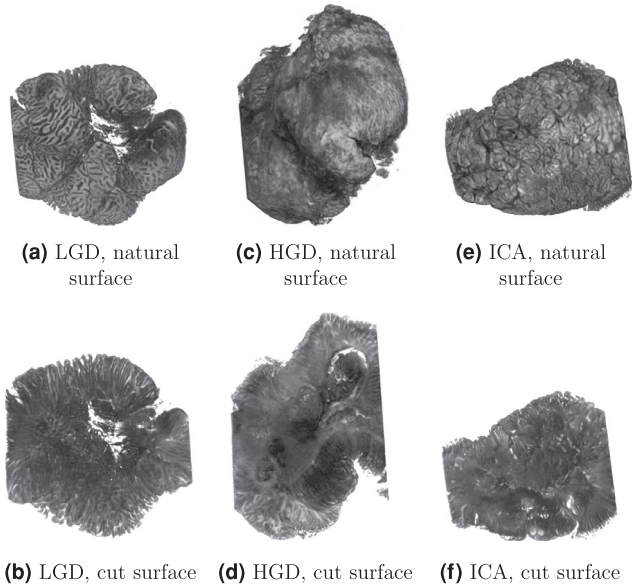

Fig. 2. Direct renderings of OPT polyp images with polyp voxels rendered as opaque: (a) and (b) a low-grade dysplasia (LGD) polyp, (c) and (d) a high-grade dysplasia (HGD) polyp, (e) and (f) an invasive cancer (ICA) polyp. Top row: viewing angles adjusted to view the natural surfaces of the polyps. Bottom row: viewing angles adjusted to view artefactual surfaces due to physical cuts.

2. Materials and methods

2.1. Tissue processing, imaging, and annotation

Ninety colorectal polyps were selected from the NHS Tayside Tissue Bank archive to be representative of the dysplasia subgroups: invasive cancer (ICA), high-grade dysplasia (HGD) and low-grade dysplasia (LGD). Thirty samples were selected for each of these three groups to give a balanced dataset. The H&E stained sections taken from each specimen were re-diagnosed by an experienced gastrointestinal histopathologist according to the NHS BCSP and WHO guidelines to reduce intra-observer bias (Hamilton et al., 2000; NHS BCSP, 2007). Images were acquired using OPT in emission mode under ultraviolet light and Cy3 dye at a voxel resolution of 6.7 μm^3. Each image was of one colorectal polyp and had 1024^3 voxels. Fig. 2 shows renderings of three of these colorectal polyp OPT images.

Each 3-D image was manually annotated with 3-D regions by an individual experienced in interpreting OPT images. Characteristic regions were annotated in each polyp, i.e., regions of ICA were annotated in polyps labelled as ICA, regions of HGD were annotated in polyps labelled as HGD, and regions of LGD were annotated in polyps labelled as LGD. Each region's boundary was delineated such that the annotator had high confidence that all tissues within the region were correctly labelled. The H&E slide corresponding to the cut surface of each polyp was used as guidance for this annotation. Annotations were performed using the software tool ITK-SNAP (Yushkevich et al., 2006) by delineating 2D regions every 4 or 5 slices and then interpolating between them. Fig. 3 shows some examples of annotated slices. Fig. 4 summarises the quantities of voxels annotated per slice.