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Incorporating local and global context for better automated analysis of colorectal cancer on digital pathology slides

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Abstract

Phenotypic information derived from visual characteristics of colorectal cancer (CRC) is routinely used for diagnosis and recommendations for treatment. Previously published studies show that the ratio of tissue types within CRC is prognostic. Such studies generate large amounts of data, combining expert classifications with x-y coordinates, which has previously been used to train image analysis algorithms. This paper describes extensions to algorithms employed in previously published work, using pixel clustering as a pre-processing step before normalised cuts in order to reduce the size of the graph for unsupervised segmentation. Image segments are processed for features and given a candidate classification which is weighted by neighbouring segment classes. Global slide features are incorporated to mitigate inconsistencies in overall appearance caused by histological and biological differences. The proposed algorithm increases agreement with the ground truth from 75% to 79% on a dataset of 7,159 images across 157 digital slides.

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Keywords: digital pathology; colorectal cancer; automated analysis; unsupervised segmentation; contextual analysis;

1. Introduction

With over 40,000 new cases and 16,000 deaths per year, colorectal cancer (CRC) is currently the second highest cause of cancer mortality in the UK[1]. Histopathological examination of cancer tissue provides pathologists with phenotypic information from visual characteristics of the disease[2] which is used to predict response to therapies.

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These predictions facilitate the provision of appropriate treatments for individual patients, possibly avoiding exposure to toxic radiotherapies and expensive drugs. This visual information is traditionally acquired via a glass slide tissue sample and microscope, but the rise of high resolution digital pathology scanners allows pathologists to inspect tissue using standard computer screens and software tools for more consistent and quantifiable manual analysis. The RandomSpot stereology tool[3] is used routinely at a number of institutions and has been used by pathologists to help identify the prognostic capabilities of the ratio of tumour to stroma within a patient's cancer (T:S)[4]. This is a time consuming and laborious task which requires pathologists to classify several hundred points on a single slide in order to obtain an appropriate sample size, and therefore automation of the task is highly desirable.
Previous work used existing clinical data to extract regular sized image patches at specific co-ordinates, with the associated pathologist-classified ground truth label[5]. Results showed that the automated analysis of the images was more accurate on smaller patches (64x64px), which was inconsistent with pathologist scoring, yielding significantly higher human agreement on larger images (≥256x256px). The following conclusions were drawn:

1) Algorithm accuracy was lower on larger image patches because they were more likely to contain multiple classes of tissue within them
2) Pathologist accuracy was lower on smaller images because the visual information surrounding the patch (context) is important for making decisions

This paper reports on work undertaken in order to compensate for these two issues by applying unsupervised segmentation in larger image patches, and including contextual information to assist with machine learning. Normalised cuts[6] is a graph based segmentation algorithm which uses both similarity and dissimilarity metrics to partition a graph into two or more sub-graphs. Images are treated as regular graphs which can be segmented with globally optimised clustering, but requires computationally expensive per-pixel, pairwise comparisons. Tao et al[7] propose a weighted mean-shift algorithm to reduce the colourspace of images before the application of normalised cuts. By clustering the image into similar coloured areas, the size of the graph (and complexity of the affinity matrix) is greatly reduced, facilitating the application of the algorithm to complex histological slide images[8]. This work has been extended further by its application to a hierarchical pyramid for the analysis of ovarian cancer tissue microarrays[9]. The normalised cuts algorithm has also been modified for use in this field by include adding extra features to improve accuracy of segmentation on gastroeneterology images[10]. Other approaches to segmentation in colorectal histology images include weakly supervised algorithms for learning gland or nuclear shape[11] and sparse dictionary based representations of structures[12]. In most cases, approaches involve either pixel level clustering or model fitting[13]. Due to the ground truth data relating to single x-y coordinates rather than objects and structures, there is a need for unsupervised segmentation so that these co-ordinates can be expanded into tissue regions before analysis of features.

Contextual information can be incorporated at different resolutions in order to provide a more complete description of the visual space. In histopathology, local context typically relates to neighbouring tissue classes and the pattern that the tissue forms (or lack thereof). Global context describes the overall condition of the tissue and/or slide, the level of staining and the type of cancer being analysed, which helps the pathologist to understand the visual information at a microscopic level. These relationships between resolutions have previously been mapped in automated solutions using Bayesian networks[14], label regularisation[15], rotationally invariant contextual analysis (spin-context)[16], or simply providing a 'context vector' as a set of features in order to pre-analyse images[17].

2. Methods

2.1 Data

The experiments reported in this paper use a subset of an existing dataset from one colorectal cancer trial[18]. The dataset contains image data from 2,214 cases, which comprises of mostly of stage II cancer patients, with the remaining cases being stage III. Half of the patients received chemotherapy and the other half did not. Most cases had only one glass slide digitally scanned, using an Aperio AT scanner at 20x magnification (0.5 µm per pixel), stained with haematoxylin and eosin stains (H&E). For this study, the subset was comprised of 157 cases, which had been preselected by a pathologist in order to provide a dataset representative of typical workload), and each case had been analysed using the RandomSpot stereology tool, using a target number of 50 spots per digital slide (with a