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Discrimination between tumour epithelium and stroma via perception-based features

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ABSTRACT

In this work we propose the use of image features based on visual perception for discriminating epithelium and stroma in histological images. In particular, we assess the capability of the following five visual features to correctly discriminate epithelium from stroma in digitised tissue micro-arrays of colorectal cancer: coarseness, contrast, directionality, line-likeliness and roughness. The use of features directly related to human perception makes it possible to evaluate the tissue's appearance on the basis of a set of meaningful parameters; moreover, the number of features used to discriminate epithelium from stroma is very small. In the experiments we used histologically-verified, well-defined images of epithelium and stroma to train three classifiers based on Support Vector Machines (SVM), Nearest Neighbour rule (1-NN) and Naïve Bayes rule (NB). We optimised SVM's parameters on a validation set, and estimated the accuracy of the three classifiers on a independent test set. The experiments demonstrate that the proposed features can correctly discriminate epithelium from stroma with state-of-the-art accuracy.

1. Introduction

Tumour-stroma ratio (TSR) has been recognised as an independent prognostic factor for a number of oncologic diseases. In patients with invasive breast cancer, a high tumor-stroma ratio was shown to correlate with increased hazard for disease relapse [1]. In early cervical carcinoma, the disease-free and overall survival were found significantly better in the stroma-poor than in the stroma-rich group [2]. Similar findings have been described in oesophageal squamous cell carcinoma, where stroma-rich tumors were associated with poor prognosis and an increased risk of relapse [3]. Likewise, in non-small cell lung cancer, survival analysis showed that tumour-stroma ratio was significantly correlated with survival [4]. Reliable assessment of tumor-stroma ratio is therefore a key-point to patient stratification and follow-up. Courrech Staal et al. [5] investigated the intra- and inter-observer reproducibility of TSR assesment from oesophageal adenocarcinoma biopsies using optical microscopy. In their study they found inter-observer agreement ranging from 81% to 98% when TSR was quantised in two classes ($<50\%$ or $\geq 50\%$), but the figures dropped drastically (agreement from 51% to 72%) when TSR was quantised into four classes ($<25\%$, $\geq 25\%$ to $<25\%$, $\geq 50\%$ to $<75\%$ or ≥ 75).

Computer-assisted classification of tumour epithelium and stroma through digital image processing could be a real possibility to eliminate – or at least reduce – the variability observed among human experts. During the last years, computer-assisted analysis of tissue images has benefited from the steady improvement in imaging technologies as well as from the development of new image descriptors [6–8]. Among them, Local Binary Patterns (LBP) and variants have received a great deal of attention due to their high discrimination capability, ease of implementation and low computational cost [9–11]. Linder et al. [12] recently proposed a combination of Local Binary Patterns + Contrast measure (LBP/C) and linear support vector machine (SVM) for automated identification of tumour epithelium and stroma obtaining strong agreement ($\approx 97\%$) between the human observer and the computerised approach. A potential drawback of the method, however, is that LBP features are quite difficult to interpret in terms of high-level visual cues, and rather unrelated to the way pathologists perceive and interpret human tissue. Though local binary patterns were originally believed to be related to image micro-structures such as edges, corners, and spots [13], other studies suggested that this link could be rather weak [14]. As a consequence, LBP-based classification works, to the eye of the physician, as a 'black-box' approach.

In this paper we propose an alternative strategy based on a compact set of perception-based features: *coarseness*, *contrast*,

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directionality, *line-likeliness* and *roughness*. Our approach is inspired on the work of Tamura et al. [15], but also represents a significant improvement on their contribution, for we solve some substantial implementation and normalisation issues that are not addressed in the original reference. In addition, we investigate the discrimination power of each feature and the degree of correlation between couples of features. The advantages of the perceptual feature space proposed here are basically two: first, the use of features directly related to human perception makes it possible to assess the tissue's appearance on the basis of a set of values which the pathologist can interpret in a meaningful way; second, the number of required features is very small – we show that state-of-the-art accuracy can be obtained with as few as five features. Consequently, the resulting model provides a very compact description of the phenomenon, reduces the computational complexity of the whole procedure, avoids any potential problems related to the 'curse of dimensionality' [16] and helps the user understand how the model behaves and which features are important (see, for example, Ref. [17] for a discussion on this topic).

In the remainder of the paper we first present the materials used in the study (Section 2) then provide a detailed description of the methods for feature extraction and classification (Section 3). The experimental activity is discussed in Section 4, followed by the results (Section 5) and some concluding considerations (Section 6).

2. Materials

This study is based on an image database including 1376 images of tissue samples from patients with colorectal cancer. The dataset is available within the WebMicroscope virtual platform [18] and its use for research, scientific and/or information purposes is expressly permitted.[1]

The whole dataset is composed of three groups: train, validation and test. Each contains images representing regions of interest belonging either to tumour epithelium or stroma (see Fig. 1). The proportion of epithelium/stroma samples is 41/39, 395/217 and 425/295 in each of the train, validation and test group, respectively. Image resolution varies from 162×161 to 2372×2373 pixels (see Table 1). The tissue samples come from a series of 643 patients with histologically-verified colorectal cancer; further information on the clinico-pathological features of the patients, as well as details about the preparation and digitisation of the tissue microarrays are available in Ref. [19].

3. Methods

3.1. Features

The use of image features corresponding to visual perception was originally proposed by Tamura et al. [15]. Based on a set of psychological experiments, they came to define, in their seminal study, six basic textural features, namely: *coarseness*, *contrast*, *directionality*, *line-likeness*, *regularity* and *roughness*. The practical computation of these features, however, is not completely straightforward: Ref. [15] in fact provides just an outline of how to implement the perceptual features, but leaves many important details to the user. Nor is the matter solved in posterior works [21,22]. Moreover, in the definitions given in Ref. [15] the output range differs from one feature to another, a condition that is likely to impair the results of any classification strategy based on such features. In the following subsections we discuss our approach to the calculation of each feature. In some cases our implementation departs significantly from the original one. In all cases – and differently from the original definition – our algorithms guarantee that each perceptual feature is represented by a real number in the [0,1] interval. As a result, all the features have the same weight in the classification phase. In the remainder we assume that the origin of the image coordinate system is the upper-left pixel with the x and y axes pointing downwards and rightwards, respectively.

3.1.1. Coarseness

The concept of coarseness is related to the intrinsic size of the texture elements: the higher the size, the coarser the texture and vice versa. The computation of this features proceeds as follows. We first apply a set of mean filters to the input image, each filter being defined by a square window of dimension $2^k \times 2^k$, where $k \in \{1, \ldots, K\}$. Values outside the bounds of the image are circularly repeated by implicitly assuming that the input is periodic (circular scanning). The selection of a suitable value of K is left to the user – herein we set $K=4$. Let $\mathbf{A}_k$ indicate the k-th transformed image resulting from this step.

In the second step we apply, to each $\mathbf{A}_k$, a vertical and a horizontal difference mask which assign, to each pixel, the difference between the values of the two symmetric pixels that lie vertically or horizontally at distance $2^{(k-1)}$ from the given one. Let the resulting matrices corresponding to the horizontal and vertical directions for each value of k be $\mathbf{E}_{k,h}$ and $\mathbf{E}_{k,v}$, respectively. We now search the value of k that minimises, in each point, the value of $\mathbf{E}(x,y)$ in either directions, i.e.:

$$\bar{k}(x,y) = \arg\max_{k \in \{1,\ldots,K\}} \{\mathbf{E}(x,y)_{k,h}, \mathbf{E}(x,y)_{k,v}\} \tag{1}$$

Finally, we take as coarseness the average windows size that in each point maximises the value of $\mathbf{E}(x,y)$ in either directions:

$$F_{\mathrm{crs}} = \frac{1}{2^K} \frac{1}{WH} \sum_{x=1}^{H} \sum_{y=1}^{W} 2^{\bar{k}(x,y)} \tag{2}$$

where W and H are the dimensions of the input image. Factor $1/2^K$ in Eq. (2) normalises the output in [0,1].

3.1.2. Contrast

According to Tamura et al. the concept of 'contrast' depends on the distribution (histogram) of grey-levels, the sharpness of edges and the period of repeating patterns [15]. Following the approach proposed in the cited reference, we estimated this parameter through the following expression:

$$F_{\mathrm{con}} = 2\frac{\sigma}{\alpha_4^n} \tag{3}$$

where σ and α_4, are, respectively, the standard deviation and the kurtosis of the distribution of the grey levels. The first reflects the 'dispersion' of the distribution; the second, for many distributions encountered in practice, their 'peakedness' (see Ref. [23, p. 53]). Parameter n is a positive number which we set to $1/4$ as suggested in Ref. [15]; factor 2 normalises the output in [0,1].

3.1.3. Directionality

Directionality is related to the probability that the variation of the pixels' intensities occurs along certain predefined orientations. An image mainly composed by parallel lines will have 'strong' directionality; one made up of almost randomly scattered points will have 'weak' directionality. To estimate this parameter, we first apply a vertical and horizontal 3×3 Sobel filter to compute the image gradient at each point; let us indicate these as $\mathbf{G}_x$ and $\mathbf{G}_y$. Then we compute the gradient orientation at each pixel $\theta(x,y)$ through Eq. (4), discarding those pixels where the magnitude of

[1] http://www.webmicroscope.net/about/disclaimer.asp.