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Cell words: Modelling the visual appearance of cells in histopathology images

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ABSTRACT

Detection and classification of cells in histological images is a challenging task because of the large intra-class variation in the visual appearance of various types of biological cells. In this paper, we propose a discriminative dictionary learning paradigm, termed as *Cell Words*, for modelling the visual appearance of cells which includes colour, shape, texture and context in a unified manner. The proposed framework is capable of distinguishing mitotic cells from non-mitotic cells (apoptotic, necrotic, epithelial) in breast histology images with high accuracy.

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1. Introduction

Detection of cells in histopathology images is a subject of interest in a wide range of cell-based studies as it is critical for evaluating the existence of disease and its severity. For example, infiltration of lymphocytes in breast cancer has been shown to be related to patient survival [1]. Similarly, nuclear pleomorphism has diagnostic value for cancer grading [2,3] and mitotic count is an important prognostic parameter in breast cancer grading [4]. Due to diverse variation in the visual appearance of cells, automated systems often require methods that adapt well to different kinds of cells. The difficulty of the problem increases significantly when the cell density of tissue sample is high, resulting in cell overlap and clumping. Moreover, in some applications, the visual appearance of cell types is quite similar to the visual appearance of some other structures present in the same image, posing a great challenge which is often very hard to address with classical image processing techniques.

Traditional approaches to cell detection can be broadly divided into five main categories [5]: intensity based, region based, active contours/level sets, probabilistic and graphical models. (1) Intensity based methods (e.g. thresholding) search for optimal value of intensity such that the intensities that belong to cell are separated from the intensities that belong to background; (2) region based methods (e.g. region growing) normally work on the intensity as well, however they follow the basic principle of merging two neighbouring regions if the regions satisfy some predefined merging criterion; (3) active contour models are deformable splines that can be used to depict the contour of nuclei in an image using gradient information; (4) probabilistic models (e.g. Gaussian mixture models) represent cells in histopathology images as weighted sum of several Gaussian densities or as a mixture of Gaussian and other (e.g. Gamma) densities [6]. The parameters of these models are usually estimated from training data using parameter estimation techniques such as expectation maximisation [7]; (5) graphical models (e.g. graph cuts) conceptualise images as graphs, where each pixel is represented by a node in the graph and the relationship between neighbouring pixels is represented by edges. These methods partition the graph into disjoint subgraphs such that similarity is high within the subgraphs and low across different subgraphs.

In this paper, we propose a model for visual appearance of cells in histopathology images. Rather than using computationally intensive models for cell detection (like active contours and graphical models), we propose a discriminative dictionary learning (DDL) based paradigm to model the visual appearance of cells that intrinsically takes into account various features including colour, shape, texture, and context of cells. The proposed model aims at learning a dictionary (with class-specific atoms) that simultaneously has both good reconstruction and high discrimination ability. Moreover, it exploits some of the attractive properties of sparse methods

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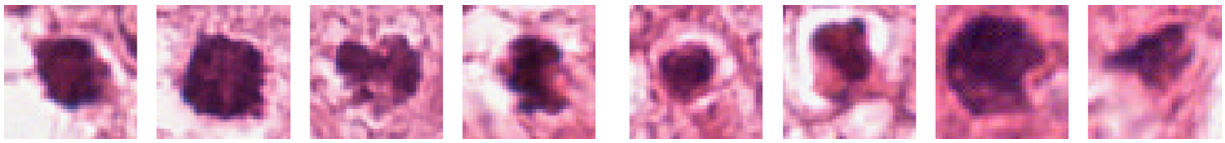

Fig. 1. Visual appearance of different cells in breast histopathological images. First four images (from left) are mitotic cells and last four images are non-mitotic cell images.

(e.g. robustness to noise and succinct representation of the data) in order to learn discriminative representations of complex biological objects.

The proposed model is evaluated on publicly available MITOS dataset [8] for detection of mitotic cells (MCs) in breast histopathology images. Detection and quantification of MCs in histopathology images is an important diagnostic indicator for many cancers including breast cancer. It is a challenging task because of the large intra-class variation in the visual appearance of MCs (see Fig. 1). Additionally, if standard haematoxylin and eosin (H&E) staining is used (which stains chromatin rich structures, such as nucleus, apoptotic cells and MCs in dark blue colour), it becomes extremely challenging to detect the MCs as shown in Fig. 1.

Majority of the previously proposed approaches for MCs detection work by first identifying candidate objects or locations that are then accepted (or rejected) as MCs based on some similarity criterion [9]. The candidate extraction phase often makes use of the colour distinctiveness of MCs by building statistical models [6] or by performing thresholding followed by refining of the detected regions by morphological operations and/or active contours segmentation [10,11]. In the second stage, more specialised features ranging from morphological, geometrical and textural features to more specialised features learnt from deep convolutional neural networks are used to train a classification framework [6,10–13]. The approach proposed in [6] is unique in the sense that it uses tumor segmentation to reduce the search space of mitotic cells [14,15,41].

Our main contributions are as follows: (1) we present a framework for modelling the visual patterns in histopathology images and apply this model to discriminate between different kinds of cells; (2) we present a formulation for DDL that is computationally efficient and yields high accuracy; (3) we present a systematic method for selecting the optimal values for algorithm's parameters; (4) we demonstrate the effectiveness of the proposed model on publicly available MITOS dataset [8] to perform mitotic cell detection.

2. Related work

Recently, some DDL algorithms have been proposed in literature. Discriminative K-SVD [16] uses a linear regression term in a dictionary learning objective function which penalises non-discriminative atoms. The by-product of the learning process is a linear classifier that can be directly applied to the learnt sparse code. Label consistent K-SVD [17] adds a label consistent term into the objective function of the discriminative K-SVD method. The label consistent term encourages the use of atoms with the same label to reconstruct a data point. Structured incoherent dictionary learning [18] integrates a term into the objective function that minimises the covariance between atoms of different classes, so as to circumvent the overlapping of atoms from different classes. Fisher DDL [19], the closest work to the proposed model, employs Fisher discriminant criterion to minimise within-class variation and maximise between-class variation of sparse codes. However, the Fisher term, which makes insignificant improvement in the classification accuracy of the model, is computationally expensive to compute, thus makes the model inefficient for histological images.

The success of these DDL methods is mainly attributed to following two characteristics of sparse models: (1) sparsity, a mechanism for regularising the coefficients that represent the data; and (2) the dictionary, that is learnt directly from the data. These characteristics are controlled by two critical parameters: the desired *sparsity* of the coefficients, and the size (in terms of *number of atoms*) of the dictionary. However, lacking theoretical guidelines to select these parameters, most of the DDL methods require hand-tuning and cross-validation to select optimal parameters, which is often time consuming and ineffective. In this study, we use a more principled approach to select both parameters.

3. The proposed model

Fig. 2 provides an overview of the proposed model, which consists of two phases: (1) dictionary learning; (2) classification. During dictionary learning phase, a dictionary is learnt from the training data by solving an optimisation problem outlined in Section 3.1. During classification, a test sample is first encoded over the learnt dictionary (i.e. represented as a linear combination of few atoms from the learnt dictionary), and then the reconstruction residual based on the code is used to determine the class of the test sample (Section 3.2). Note that, in order to keep the formulation simple, the proposed model uses two class formulation, however, the proposed formulation can be easily extended for more than two classes.

3.1. Dictionary learning

Let $c \in \{\mathrm{C1}, \mathrm{C2}\}$ denotes a class index, where C1 and C2 represent two different classes of cells. Let $\mathbf{X} = [\mathbf{X}_{\mathrm{C1}}, \mathbf{X}_{\mathrm{C2}}] \in \mathbb{R}^{m \times N}$, with $\mathbf{X}_c = [\mathbf{x}_{c,1}, \ldots, \mathbf{x}_{c,n_c}] \in \mathbb{R}^{m \times n_c}$ be a matrix whose columns are patches from class c, m be the number of pixels in a patch, N be the total number of training samples, and n_c be the number of training samples of class c. Let $\mathbf{D} = [\mathbf{D}_{\mathrm{C1}}, \mathbf{D}_{\mathrm{C2}}] \in \mathbb{R}^{m \times K}$, with $\mathbf{D}_c = [\mathbf{d}_{c,1}, \ldots, \mathbf{d}_{c,k_c}] \in \mathbb{R}^{m \times k_c}$ be the dictionary for class c containing k_c atoms, and K be the total number of atoms. Let $\mathbf{A} = [\mathbf{A}_{\mathrm{C1}}, \mathbf{A}_{\mathrm{C2}}] \in \mathbb{R}^{K \times N}$, with $\mathbf{A}_c = [\boldsymbol{\alpha}_{c,1}, \ldots, \boldsymbol{\alpha}_{c,n_c}] \in \mathbb{R}^{K \times n_c}$ be the sparse code matrix corresponding to $\mathbf{X}_c$. Our task is to solve the following optimisation problem:

$$\min_{\mathbf{D},\mathbf{A}} \sum_c \nu(\mathbf{X}_c, \mathbf{D}, \mathbf{A}_c) + \lambda \|\mathbf{A}_c\|_1 \quad \text{subject to } \mathbf{d}_{c,j}^{\mathrm{T}} \mathbf{d}_{c,j} = 1 \quad \forall j = 1, \ldots, k_c, \tag{1}$$

where

$$\nu(\mathbf{X}_c, \mathbf{D}, \mathbf{A}_c) = \|\mathbf{X}_c - \mathbf{D}\mathbf{A}_c\|_F^2 + \|\mathbf{X}_c - \mathbf{D}_c \mathbf{A}_c^{(c)}\|_F^2 + \gamma \sum_{l \neq c} \|\mathbf{D}_l \mathbf{A}_c^{(l)}\|_F^2, \tag{2}$$

$\|\cdot\|_1, \|\cdot\|_F$ denote the l_1 norm, and the Frobenius norm of a matrix, respectively, $\mathbf{A}_c^{(l)}$ denotes a sub-matrix of $\mathbf{A}_c$ that corresponds to $\mathbf{D}_l$, and λ is sparsity regularisation parameter. In Eq. (2), the first term refers to the reconstruction error of $\mathbf{X}_c$ using the whole dictionary, the second term refers to the use of $\mathbf{D}_c$ for reconstructing $\mathbf{X}_c$, while the last term refers to the prevention of reconstructing $\mathbf{X}_c$ using dictionary atoms from other classes, penalised by a parameter γ. Note that the formulation above is simpler and efficient than the one proposed in [19] as we are not calculating any Fisher term, which is computationally very inefficient to compute and yields insignificant improvement.

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