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Automatic classification of Human Epithelial type 2 cell Indirect Immunofluorescence images using Cell Pyramid Matching

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ABSTRACT

This paper describes a novel system for automatic classification of images obtained from Anti-Nuclear Antibody (ANA) pathology tests on Human Epithelial type 2 (HEp-2) cells using the Indirect Immunofluorescence (IIF) protocol. The IIF protocol on HEp-2 cells has been the hallmark method to identify the presence of ANAs, due to its high sensitivity and the large range of antigens that can be detected. However, it suffers from numerous shortcomings, such as being subjective as well as time and labour intensive. Computer Aided Diagnostic (CAD) systems have been developed to address these problems, which automatically classify a HEp-2 cell image into one of its known patterns (e.g., speckled, homogeneous). Most of the existing CAD systems use handpicked features to represent a HEp-2 cell image, which may only work in limited scenarios. We propose a novel automatic cell image classification method termed Cell Pyramid Matching (CPM), which is composed of regional histograms of visual words coupled with the Multiple Kernel Learning framework. We present a study of several variations of generating histograms and show the efficacy of the system on two publicly available datasets: the ICPR HEp-2 cell classification contest dataset and the SNPHEp-2 dataset.

1. Introduction

The Anti-Nuclear Antibody (ANA) test is commonly used by clinicians to identify the existence of Connective Tissue Diseases such as Systemic Lupus Erythematosus, Sjögren's syndrome, and Rheumatoid Arthritis [1]. The hallmark protocol for doing this is through Indirect Immunofluorescence (IIF) on Human Epithelial type 2 (HEp-2) cells [1,2]. This is due to its high sensitivity and the large range expression of antigens. Examples of specimen images are shown in Fig. 1. Despite the advantages, the IIF approach is labour intensive and time consuming [3,4]. Each ANA specimen must be examined under a fluorescence microscope by at least two scientists. This also renders the test result subjective, and thus has low reproducibility and large variabilities across personnel and laboratories [5,6].

In recent years, there has been increasing interest in employing image analysis techniques for various routine clinical pathology tests [5,8,9]. Results produced by these techniques can be used to support the scientists' manual/subjective analysis, leading to test results being more reliable and consistent across laboratories [5]. Thus, in order to address the shortcomings of the manual test procedure, one could use Computer Aided Diagnostic (CAD) systems which automatically determine the pattern in the given HEp-2 cell images of a specimen [5,6,10–15].

Table 1 presents notable CAD systems proposed in the literature over the last 5 years. Most of these systems use carefully handpicked features which may only work in a particular laboratory environment and/or microscope configuration. To address this, several approaches employ a large number of features and apply an automated feature selection process [5]. Another approach uses Multi-Expert Systems to allow the use of a specifically tailored feature set and classifier for each HEp-2 cell pattern class [6]. Nevertheless, the generalisation ability of these systems is still not guaranteed since these systems were only evaluated on a dataset with a specific setup.

One of the most popular approaches for automatic image classification, here called the bag-of-visual-words (BoW) approach, is to represent an image in terms of a set of visual words, selected from a dictionary that has been trained beforehand [24–26]. In order to model an image, the BoW approach

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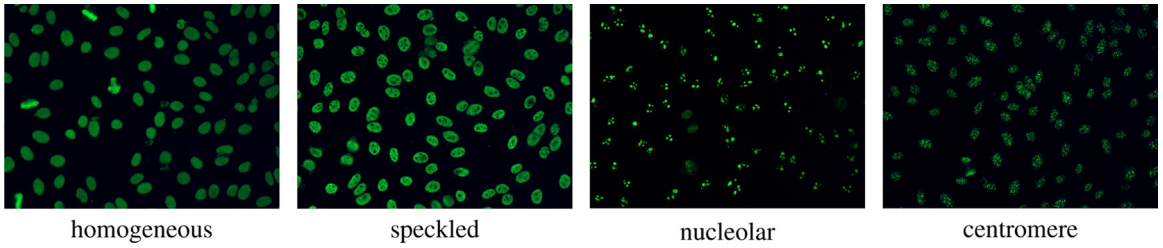

Fig. 1. Examples of strong positive ANA specimens. See Fig. 2 for images of individual cells.

Table 1
Existing CAD systems for HEp-2 cell classification.

Approach	Descriptors	Classifier
Perner et al. [13]	Textural	Decision Tree
Hiemann et al. [5]	Structural; textural	LogisticModel Tree
Elbischger et al. [11]	Image statistics; cell shape; textural	Nearest Neighbour (NN)
Hsieh et al. [12]	Image statistics; textural	Learning Vector Quantisation (LVQ)
Soda et al. [6]	Specific set of features (e.g., textural) for each class	Multi-Expert System
Cordelli et al. [10]	Image statistics; textural; morphological	AdaBoost
Strandmark et al. [14]	Morphological; image statistics; textural	Random Forest
Ali et al. [16]	Biological-inspired descriptor	Boosted k-NN Classifier
Theodorakopoulos et al. [17]	Morphological and texture features	Kernel SVM (KSVM)
Thibault et al. [18]	Morphological and texture features	Linear Regression, Random Forest
Ghosh et al. [19]	Histograms of oriented gradients, image statistics and textural	SVM
Li et al. [20]	Textural and image statistics	SVM
Di Cataldo et al. [21]	GLCM and DCT features	SVM
Snell et al. [22]	Texture and shape	Multistage classifier
Ersoy et al. [23]	Local shape measures, gradient and textural	ShareBoost
Wiliem et al. [15]	Bag of visual words with dual-region structure	Nearest Convex Hull Classifier (NCH)

divides the image into small image patches, followed by patch-level feature extraction. An encoding process is then employed to compute a histogram of occurrences of visual words based on these patches. BoW descriptors often have higher discrimination power compared to the other image descriptors [15,24,26,27]. However, the BoW descriptor has many design options. For example, one needs to determine which patch-level features and encoding technique is most suitable for the task at hand. Our previous study presents an extensive evaluation of popular BoW descriptors in the literature applied to the domain of cell classification [15].

A single histogram of visual words of an image only describes the visual word statistics and does not retain spatial information (i.e. where a visual word appears in the image). Previous studies suggest that location and scale information can provide meaningful discriminative information [24,28]. For example, the locations of visual words describing a wheel could be used to infer the type of vehicle (i.e. whether it is a motorcycle, car, or truck). Spatial Pyramid Matching (SPM) was proposed to exploit this information [24]. Specifically, each image is processed as a pyramid of levels, with each level containing non-overlapping regions. The levels differ from each other through an increasing number of regions. Each region is divided into small image patches, and an average histogram of visual words is computed for each region. The histograms from all regions are then fed into a Support Vector Machine (SVM) classifier [29] that uses a specialised kernel.

Our previous work [15] proposed a Dual-Region (DR) structure within the BoW framework, specifically designed for cell images. Each cell image is divided into two regions: (1) an inner area enclosing inside the cell; and (2) an outer area containing only the cell edge. The use of two regions forces the inner and outer cell content to be modelled and compared separately, leading to higher recognition accuracies than using only one average region (i.e. single histogram) for each cell image. An advantage of this approach is that it has lower dimensionality than SPM (i.e. approximately 90% less), leading to considerably lower storage requirements. However, a mixing coefficient which indicates relative region importance needs to be empirically determined.

The work presented in this paper extends our previous study by proposing a novel approach termed Cell Pyramid Matching (CPM), which incorporates the positive aspects of the SPM and DR approaches, while omitting their negative aspects. Furthermore, we show that combining the CPM approach with a learning framework known as Multiple Kernel Learning [30] (where several variants of CPM are employed concurrently) leads to state-of-the-art performance on the SNPHEp-2 dataset [15], and is comparable to the state-of-the-art on the ICPRContest dataset [7].

We continue this paper as follows. We first delineate the HEp-2 cell classification task in Section 2. In Section 3 we discuss various forms of BoW descriptors and the proposed CPM approach. Section 4 is devoted to experiments and discussions, followed by the main findings in Section 5.

2. HEp-2 cell classification task

Each positive HEp-2 cell image is represented as a three-tuple $(\boldsymbol{I}, \boldsymbol{M}, \delta)$ which consists of (**i**) the Fluorescein Isothiocyanate (FITC) image channel $\boldsymbol{I}$; (**ii**) a binary cell mask image $\boldsymbol{M}$ which can be manually defined, or extracted from the (DAPI) image channel [5]; and (**iii**) the fluorescence intensity $\delta \in \{\text{strong}, \text{weak}\}$ which specifies whether the cell is a strong positive or weak positive. Strong