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Cross domain mitotic cell recognition

Tong Hao [a], Ai-Ling Yu [a], Wei Peng [a], Bin Wang [a], Jin-Sheng Sun [a,b,*]

[a] Tianjin Key Laboratory of Animal and Plant Resistance/College of- Life Science, Tianjin Normal University, Tianjin 300387, China
[b] Tianjin Aquatic Animal Infectious Disease Control and Prevention Center, Tianjin 300221, China

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ABSTRACT

Accurate and automated identification of mitosis is essential and challenging to many biomedical applications. To handle this challenge, we propose a novel mitotic cell recognition method by integrating heterogenous data in the framework of cross domain learning. First, we extract the discriminative feature to represent the local structure and textural saliency of individual cell sample. Second, the cell type-dependent classifiers are respectively trained on the target domain and the auxiliary domain and then fused in the framework of adaptive support vector machine for cross-domain learning. The achieved classifier can be implemented for mitotic cell recognition in the cross domain manner. The extensive experiments on two kinds of phase contrast microscopy image sequences (C3H10T1/2& C2C12) show that the proposed method can leverage the datasets from multiple domains to boost the performance by effectively transferring the knowledge from the auxiliary domain to the target domain. Therefore, it can overcome the inconsistence of feature distributions in different domains.

1. Introduction

Recently, researchers are paying increasing attention on applying image analysis and machine learning for various routine clinical pathology tests [1–4]. Results outputted by these advanced techniques can be leveraged for further subjective analysis by scientists, which will make the test results to be more reliable and consistent across laboratories [4]. The related computer-aided methods have been widely used for many medical, especially for breast cancer diagnosis [5]. Among measurable characteristics, the detection and counting of mitotic cells is currently considered as the optimal predictor for long-term prognosis for breast carcinomas [6]. However, the requirement of manual annotation of mitosis is a time-consuming task [7]. Therefore, it is essential to explore the methods for automated mitotic cell recognition.

To our knowledge, most of previous methods work on the learning problem in the same domain [8,9]. Since both training dataset and test dataset are prepared under the same conditions, the classifier learned on the training dataset can be straightforwardly applied to the test dataset for prediction. However, the state-of-the-art public cell image dataset for the classification problem usually contains a limited number of samples. Facing the difficulty caused by the variation of non-rigid cell appearance, irregular motion, the existence of artifacts by the imaging devices, etc., it is essential to take advantage of the classifiers trained in different domains [10,11] and augment the dataset to learn a robust classifier with high generalization ability. However, it is usually expensive for large-scale dataset preparation and manual segmentation and annotation of specific cell regions. Consequently, it is reasonable to explore the method, which can take advantage of different dataset for model learning [12,13].

In this paper, we propose a cross-domain mitosis modeling method for automated mitotic cell recognition. First, the discriminative feature is extracted for individual sample to represent its local structure and textural saliency. Then, the adaptive support vector machine is adapted for this work for cross-domain learning. Two kinds of phase contrast microscopy image sequences (C3H10T1/2& C2C12) are selected for the experiments. The extensive experiments show that the proposed method can leverage the dataset from multiple domains to boost the performance by effectively transferring the knowledge from the auxiliary domain to the target domain. The main contribution lies in two-folds:

1. This method can overcome the inconsistence of feature distributions in different domains.
2. It can reduce the requirement on large-scale manual annotation on the target domain by implicitly augmenting the training data with the existing annotated auxiliary dataset.

The rest of paper is structured as follows. In the 2nd section, we will introduce the related work. Then we will detail the method

* Corresponding author at: Tianjin Key Laboratory of Animal and Plant Resistance/College of- Life Science, Tianjin Normal University, Tianjin 300387, China and Tianjin Aquatic Animal Infectious Disease Control and Prevention Center, Tianjin 300221, China.
E-mail address: jinshsun@163.com (J.-S. Sun).

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for cross-domain mitotic cell modeling. The experimental method and results will be respectively detailed in the 4th section and the 5th section respectively. At last, conclusion is presented.

2. Related work

Automated mitotic cell classification methods usually consist of two essential steps, visual feature representation and mitotic modeling. From the view point of feature representation, various image features have been implemented for this task. Liu et al. [14] extracted the area features (area and convex area), the shape features (eccentricity, major axis length, minor axis length and orientation), and the intensity features (maximum intensity, mean intensity, and minimum intensity), to represent the candidate mitotic region. Perner et al. [15] and Hiemann et al. [4] implemented the textual descriptors for this task. Cordelli and Soda [16] and Strandmark et al. [17] developed specific morphological features to describe the saliency of ROI region. Li et al. [18] extracted the volumetric Haar-like feature to represent the spatiotemporal volume in the image sequence. Moreover, the popular local saliency descriptors, such as GIST [19,20], Scale-Invariant Feature Transform (SIFT) [21–23], and Histogram of Oriented Gradient (HoG) [24], are also applied for this task because of the high discriminative capability and the robustness. To improve the discrimination of feature representation, the strategy of the fusion of multiple image features has been widely evaluated [25,26]. More recently, sparse representation [27] is also implemented to transform the aforementioned low-level visual features into a high-level formulation, which can directly represent the similarity between samples. Liu et al. [28,24] proposed that the sparse representation-based method can benefit discovering discriminative feature comparing to the classic hand-crafted low-level features. Furthermore, Liu et al. [20] extended the traditional sparse representation method to the sequential sparse representation by imposing the temporal context regularization to induce sequential image feature transform. From the view point of model learning, more and more powerful classifiers, including support vector machine, random forest, Adaboost, etc. [29], have been applied on mitotic recognition. Liu et al. [30] originally proposed the clustered multi-task learning-based method to discover the latent relatedness among multiple cell types to boost the performance of cell classification. Recently, the popular deep learning principle [31] is also implemented on this task. Ciresan et al. [32,33] successfully leveraged the Deep Neural Networks on mitosis detection. This approach won the ICPR 2012 and MICCAI 2013 mitosis detection competitions. Another trend for this task is based on the graphical model principle [34–37], which can learn the sequential dynamics within one mitosis event. Gallardo et al. [38] applied the hidden Markov model to train a classifier for mitosis recognition with cell shape and appearance saliency. Liu et al. [39] applied the hidden-state conditional random field to learn the sequential structure of mitosis progression. Recently, Liu et al. [23] originally designed the semi-Markov model for mitosis sequence segmentation. Especially, they proposed the integration of hidden conditional random fields and the semi-markov model for both mitosis identification and localization in the time-lapse microscopy image sequence. Furthermore, they theoretically unify learning both models with the max-margin theory. Extensive experiment and comparison to the competing methods demonstrated that this method can achieve the state-of-the-art performance on mitosis detection. This method has become one of the most representative frameworks for mitosis detection.

3. Cross-domain modeling

This step aims to learn a model which can be implemented for automatic mitotic cell recognition on individual unlabeled images. Different from previous work which simply learned and tested the classifier $f(x)$ on the un-overlapped two parts of one dataset, which captures one type of cell under the same environment (single domain) and the feature representation of individual mitotic candidate regions of both training and test sets belongs to identical distribution, our work will take advantage of the datasets from both target domain and auxiliary domain to augment the generalization ability of the learned model. Specifically, let D^T denote the target domain (e.g. C3H10T1/2 cell in Fig. 1(a)) and let $D^T = D_l^T \bigcup D_u^T$ denote the two parts of the target domain, where D_l^T is the manually labeled part and D_u^T is the unlabeled part. Ideally, the size of D_l^T is smaller compared with the size of D^T. The labeled subset can be represented by $D_l^T = \{(x_i, y_i)\}_{i=1}^N$ where x_i is the visual feature of the ith sample and $y_i \in \{-1, +1\}$ is its binary label. The auxiliary domain capturing the other type of cell under a different environment (e.g. C2C12 cell in Fig. 1(b)) can be represented by D^A. Because D^T and D^A are captured under different conditions, various aspects, including cell types, image resolution, lighting and so on, will have negative influence on direct cross-domain learning and test. Simply concatenating the datasets from both domains might not improve the performance and would even degrade it. To deal with this problem, we well adapt the adaptive support vector machine (ASVM) [40] for cross-domain mitotic learning.

The ultimate goal of our task is to learn a primary classifier $f(x)$ for automatic mitotic cell recognition on the target domain D^T. When there is only limited dataset for primary classifier learning, it is expected to leverage the auxiliary dataset to boost the training dataset and consequently augment the performance. In our work, we can first train the auxiliary classifier $f^A(x)$ by SVM on the auxiliary dataset. Then $f^A(x)$ can be integrated with the primary classifier $f(x)$ for cross-domain learning and test.

To integrate the auxiliary classifier $f^A(x)$ and the primary classifier $f(x)$, the incremental term in the form of $\Delta f(x) = w^\top \phi(x)$ is designed and amended to $f^A(x)$. The proposed cross-domain mitotic modeling method can be formulated as

$$f(x) = f^A(x) + \Delta f(x) = f^A(x) + w^\top \phi(x) \tag{1}$$

Motivated by the max-margin principle, the objective function for learning the parameter w can be formulated as

$$\begin{aligned} &\min_w \quad \frac{1}{2}\|w\|^2 + C\sum_{i=1}^{N}\xi_i \\ &\text{s.t.} \quad \xi_i \geq 0, \quad y_i f^A(x_i) + y_i w^\top \phi(x_i) \geq 1 - \xi_i \end{aligned} \tag{2}$$

The Lagrangian formulation of Eq. (2) is

$$L_P = \frac{1}{2}\|w\|^2 + C\sum_{i=1}^{N}\xi_i - \sum_{i=1}^{N}\mu_i\xi_i - \sum_{i=1}^{N}\alpha_i(y_i f^A(x_i) + y_i w^\top \phi(x_i) - (1-\xi_i)) \tag{3}$$

where $\alpha_i \geq 0$ and $\mu_i \geq 0$ are Lagrange multipliers. Eq. (3) can be optimized by setting its derivative with respect to w and ξ to zero. Consequently, we can achieve

$$\begin{aligned} &w = \sum_{i=1}^{N}\alpha_i y_i \phi(x_i) \\ &\alpha_i = C - \mu_i, \quad \forall i \end{aligned} \tag{4}$$

The Karush–Kuhn–Tucker(KKT) conditions can be formulated as follows to constrain the optimal solution of Eq. (3):

$$\begin{aligned} \alpha_i\{y_i f^A(x_i) + y_i w^\top x_i - (1-\xi_i)\} &= 0 \\ \alpha_i &\geq 0 \end{aligned}$$