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A two-layer structure prediction framework for microscopy cell detection

Yan Xu[a,b], Weiying Wu[a], Eric I-Chao Chang[b], Danny Chen[c], Jian Mu[c], Peter P. Lee[d], Kim R.M. Blenman[d], Zhuowen Tu[e,f,*]

[a] State Key Laboratory of Software Development Environment, Key Laboratory of Biomechanics and Mechanobiology of Ministry of Education, Beihang University, China
[b] Microsoft Research, Beijing, China
[c] Department of Computer Science and Engineering, University of Notre Dame, Notre Dame, USA
[d] Cancer Immunotherapeutics and Tumor Immunology (CITI), Duarte, CA, USA
[e] Department of Cognitive Science, University of California, San Diego, CA, USA
[f] Department of Computer and Engineering, University of California, San Diego, CA, USA

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ABSTRACT

The task of microscopy cell detection is of great biological and clinical importance. However, existing algorithms for microscopy cell detection usually ignore the large variations of cells and only focus on the shape feature/descriptor design. Here we propose a new two-layer model for cell centre detection by a two-layer structure prediction framework, which is respectively built on classification for the cell centres implicitly using rich appearances and contextual information and explicit structural information for the cells. Experimental results demonstrate the efficiency and effectiveness of the proposed method over competing state-of-the-art methods, providing a viable alternative for microscopy cell detection.

1. Introduction

With the development of bioimage informatics, there has been an increasing focus on the cell detection studies, which come over the problem of the traditional microscopy studies that only a few cells are detected, providing a more powerful statistical tool for experiments and medical diagnosis [1,2]. Studying the amount, types, morphological shape, and configuration of the cells in microscopic images has significant biological and clinical significance in e.g. cancer diagnosis and cancer treatment [3–7]. Performing cell segmentation is mostly based on certain families of morphological descriptors, which can also be viewed as a structural prediction problem. For example, the auto-context algorithm was adopted to perform membrane segmentation with supervised (machine learning) method, see [8]. One could also follow the procedure for object detection as in the recent computer vision literature to perform cell detection by a layout processing step [9]. However, as we will see later in the experiment results, adopting the state-of-the-art vision approaches does not provide satisfactory results in the task of microscopic cell centre detection. Since the Conditional Random Fields (CRFs) [10] model can only detect the structure of cells from one layer, thus may not satisfactorily grasp the full knowledge representation and achieve the requested detection accuracy due to the ignorance of complex information of the cell with much subtle and variable structure. The examples like derivative formulas of the CRFs model, or auto-context, can not achieve the approving performance of the serious demanding for complicated cell detection goal with the ignorance of various size, colour, deformation, and structural dependence more or less. Here, we study the problem from a structured learning perspective and emphasize on the representation issue.

Existing approaches for microscopy cell detection consist of the segmentation and detection steps, which are usually based on geodesic active contour, watershed, gradient vector diffusion or Hessian matrix [5–7,11,12]. In many cases, some of the above-mentioned methods are combined for a better performance of microscopic cell detection. One of the typical examples is using the

* Corresponding author at: State Key Laboratory of Software Development Environment, Key Laboratory of Biomechanics and Mechanobiology of Ministry of Education, Beihang University, Microsoft Research, Beijing, China.
Tel.: +86 10 82338755; fax: +86 10 82338755.
E-mail addresses: xuyan04@gmail.com (Y. Xu), wuweiying18@gmail.com (W. Wu), echang@microsoft.com (E.I.-C. Chang), dchen@cse.nd.edu (D. Chen), jmu@nd.edu (J. Mu), plee@coh.org (P.P. Lee), kblenman@cinci.rr.com (K.R.M. Blenman), zhuowen.tu@gmail.com (Z. Tu).

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ridge measures for cell shape detection, which is widely applied more or less in the field of image segmentation. Ersoy et al. combined the shape feature of cells with the curve evolution model exploiting the halo effect to perform the human cancer cell image detection, which was based on Hessian matrix and directional derivatives [7]. Yeo developed automated image segmentation and classification for separation of clusters of cell nuclei into individual objects, mixing the adaptive two pass threshold-based segmentation, clustered nuclei using segmentation (including operations of the fill hole, noise removal, distance, adaptive *h*-minima transform incorporated with edge information and watershed transform) and the supervised process with the labelling ground truth for shape descriptors, emphasizing the accuracy of cell nuclei counts from the supervised process [11]. The evaluation of the performance by Smal et al. for the purpose of quantitative analysis of biological image data gave a detailed comparison utilizing seven unsupervised methods and two supervised methods with the same ground truth given by the experts, effectively emphasizing the high accuracy of the machine learning methods [5].

Typically, structured labelling studies the problem of predicting a vector output from an input vector, which is common since structured inputs and outputs are in a wide range of applications. There are many different approaches in which such kind of application with structured labelling has been applied. For example, Markov Random Field (MRF) and Conditional Random Fields (CRFs) [10] have been widely used to model the correlations of the structured labels. However, due to the heavy computational burdens in their training and testing (inference) stages, MRF and CRFs are usually limited to capturing a few neighbourhood interactions only, which will thus limit their modelling capabilities. Structural support vector machine (SVM) [13–15] models the correlation in a way similar to the CRFs but tries to specifically maximize the prediction margin. Nevertheless, the high computational demand just makes it firmly rely on the range of contexts.

Considering of the limitations of the above approaches, we propose a new two-layer structural prediction framework for detecting microscopic image cells, which focuses on the representation issue to propose a model to effectively capture the rich contextual information. The contribution of the approach includes: (1) we tackle the problem of microscopic image cell detection from structure learning perspective; (2) the second layer takes the output of the first layer as knowledge abstraction and propagation.

2. Related work

With the wide application of the biomedical cell detection, various methods have been applied for cell segmentation, which is aiming to segment the objects into their constituent objects and a background [12,6,16–23]. Therefore, the cell segmentation problem can be very difficult, depended by the type of the given specimen. For example, in [18], the aim of segmentation was to distinguish the cell nuclei with a positive staining reaction and other cell nuclei in the field of immunohistochemistry, with a robust classifier and built-in metric corresponding to the colour space. Except the cell nuclei segmentation, there have also been many segmentation algorithms for other cell structures. The paper [24] by Nguyen et al. proposed a rapid cell detection algorithm, providing the Adaptive Boosting baseline as cell candidate rules, optimizing the global parameters from the input image by integration, which had highly accelerated the training process of machine learning for cell detection. Yang et al. [21] utilized the level set methods to acquire the extended-time live cell image, which performed the cell cluster separation and mitotic cell detection steps after identifying the cell trajectories, providing a method to solve the cell analysis problem, including the detection of numbers, locations, borders, areas and states of cells. In [6], the hierarchical model was combined with three operators of edge detection (Sobel, Prewitt and Laplace) to perform the multiple cell image segmentation, in addition, the false removal algorithm was used to increase the accuracy of the cell detection.

In our task, the first layer takes the auto-context algorithm, basing on the detection of the contextual information from the whole image, which is in widespread use in the object recognition [8,25–28]. Jurrus et al. [8] adopted the idea of structural labelling with a neuro-network implementation to perform membrane segmentation, which meant the ignorance of the complex information of the cells with only one layer of cell. The system developed by Yang et al. [28] aimed to perform multi-class segmentation to define shape priors from the output of object detectors.

There have been various graphical models for image segmentation. The Markov Random Field (MRF) is a typical one with a set of random variables including a Markov property [29]. Following the Markov property, the Conditional Random Fields (CRFs) directly generates the posteriori probability distribution model of the random variables from the given observation image input [30–33], which has been widely used in many image segmentation problems. For example, in [32], Bauer et al. combined the powerful SVM based on the features of multispectral intensities and textures with subsequent hierarchical CRFs regularization to delineate the brain tumour boundaries. The CRFs model was also used for the prostate cancer localization in the multispectral MRI image segmentation when combined with a cost-sensitive framework in [33], which boosted the performance significantly. Our algorithm utilizes a probability model Event Detection Conditional Random Field (EDCRF), which is related to the work of mitosis detection [34] with the use of phase-contrast time-lapse microscopy. However, the input for the second layer they use is a hidden layer in the model whereas our second layer also looks back at the original data.

The jump-diffusion process provides an optional method for our second layer algorithm, which has been an effective method for a range image segmentation [35–37]. The paper [35] focused on the segmentation of the objects of various types and sizes in the complex-real world scenes, which jumped between the parameter subspaces of differing dimensionality, providing a good performance for the object segmentation.

3. Method

This section attempts to give the details of our two-layer model for cell centre detection/segmentation in microscopic images.

We describe cell detection as a structural prediction problem [38–40], which tries to introduce a two-layer structural framework for detecting microscopy cells, with the two probability models to approximate the true cell locations. In the first layer, the auto-context model is performed to capture the structural information of the cells, passing on the results combined with the original cell images as the input for the second layer for segmentation. In addition, some related algorithms are briefly discussed for comparison.

3.1. A Conditional Random Fields approach for the problem

The Conditional Random Fields (CRFs) have been applied a lot in machine learning, with a classifier trained from the given sets X and Y, which are respectively the observed and output variables, to predict a classifier from a given sample for structured prediction [10]. The conditional distribution is an undirected graphical model related to X and Y, which is denoted by $p(Y|X)$ and modelled from them.

We derive the cell centre classification results from the first layer using the seminal CRFs models (such as auto-context [41]), whereas