

Survey Paper

Title: Detection and Segmentation of Cell Nuclei in Virtual Microscopy Images: A Minimum-Model Approach

The earliest attempt to use technology for automated nuclei detection and analysis of microscopy images date back a few decades. The goal of this paper is to illustrate the accuracy of using a minimum-model approach to automate nucleus detection in microscopy images. This approach uses minimal a priori information about cellular/nuclear feature and it detects the contours independent of the shape of the cell. There are currently numerous model-based approaches to cellular detection that can assist pathologists to increase diagnostic precision and inter-observer reliability. Using a priori information to generate a generic cellular model for detection and segmentation can perform well if cell populations are relatively homogeneous in term of shape and size. However, in recent cases this approach has proven to be a challenging since using a generic model of contour features has high risk of introducing a segmentation bias.

The paper presents a workaround to this issue by using minimal a priori information and finds contours independent of their shape by combining a global contour search with local gradient information. This study involves the use of a gold-standard data set using randomly-selected images containing 7931 cells manually labels by a pathologist. The pool of images includes various breast cancer samples representing a broad morphological variety including normal tissue components, normal liver tissue, kidney tissue, and as well as bone marrow with normal and pathological altered cells. The result of analyzing the predicted data using the proposed approach yielded an overall precision of 0.908.

Wienert, Stephan et al. "Detection and Segmentation of Cell Nuclei in Virtual Microscopy Images: A Minimum-Model Approach." *Scientific Reports* 2012. Web. 11 July. 2012

Title: Robust Nucleus/Cell Detection and Segmentation in Digital Pathology and Microscopy Images: A Comprehensive Review

This article is a comprehensive review of nucleus/cell detection and segmentation. There are numerous methods out there and this article helps identify and classify these different algorithms. The classified groups are distance transform, morphology operation, H-minima/maxima transform, Laplacian of Gaussian (LoG) filtering, maximally stable extremal region (MSER) detection, Hough transform, radial symmetry-based voting, and supervised learning. This paper introduces each group of method and their underlying algorithms, and then the variants and applications on specific types of images. For comparison of these methods, there is a section in the paper with tables of the detection and segmentation accuracy for each method and their data set.

Xing, Fuyong, and Lin Yang. "Robust Nucleus/Cell Detection and Segmentation in Digital Pathology and Microscopy Images: A Comprehensive Review." *IEEE reviews in biomedical engineering* 9 (2016): 234–263. *PMC*. Web. 28 Apr. 2018.

Title: Automatic cell nuclei segmentation and classification of breast cancer histopathology images

Breast cancer remains the leading types of malignant tumor observed in women and it depends on early diagnosis in order to effectively treat this. Histopathological images are the “gold standard” data set that pathologists use for diagnosis. However, the complexity of these breast cancer histopathological (BCH) images makes reliable segmentation and classification very difficult. This paper proposes an automatic quantitative image analysis technique of BCH images with numerous models and algorithms for feature detection and image modification. Due to the complexity of these BCH images and how clustered the images can get, a top-bottom hat transform is applied to the images in order to enhance the quality so that nuclei segmentation can be performed easier. For improvement with precision localization, Wavelet decomposition and multi-scale region-growing (WDMR) are used to obtain regions of interest (ROIs). For classification of cell nuclei, 4 shape-based features and 138 textual features based on color spaces are extracted. Other methods used in this paper include Curvature Scale Space (CSS) for corner detection in order to split overlapped cells for better accuracy and robustness. This proposed method was applied on 68 BCH images containing more than 3600 cells. The result shows that the mean segmentation sensitivity is 91.53% and 96.19% for accuracy of classification of normal and malignant cell images.

P. Wang, X. Hu, Y. Li, Q. Liu, and X. Zhu. “Automatic cell nuclei segmentation and classification of breast cancer histopathology images.” Signal Processing: Elsevier, May 2016.

Title: Cell Detection in Microscopy Images with Deep Convolutional Neural Network and Compressed Sensing

Given that cell detection has been a popular researching field, there has been numerous methods and proposals to solve this issue. The cell detection methods have evolved from employing hand-craft features to deep learning-based technique. The importance of all of these methods is that their classifier and detectors are trained in the pixel space. However, this paper proposes a convolutional neural network (CNN)-based cell detection method that uses encoding of outer pixel space instead. This method includes random projection to encode the outer space to a compressed vector to fixed dimension. This proposed method is the first successful use of CNN with compressed sensing-based output space encoding.

Y. Xue, N. Ray. “Cell Detection in Microscopy Images with Deep Convolutional Neural Network and Compressed Sensing.” Alberta, Canada: University of Alberta, 21 Feb. 2018.

Title: Automatic Detection of Cervical Cancer Cells by a Two-Level Cascade Classification System

According to the statistics of World Health Organization (WHO), there were 530,000 new cervical cancer cases in the world in 2012. Cervical cancer remains the second highest mortality rate in cancers of female patients with 270,000 female patients dying every year in the world. Cervical cancer is typically diagnosed by pathologist reviewing the liquid-based cytology (LBC) slides. This paper proposes a method for automatic detection of cervical cancer cells using a two-level cascade integration system of two classifiers to classify the cervical cells into normal and abnormal epithelial cells. Based on the characteristics of each cell type, there were 28 features proposed, including 20 morphologic features and 8 texture features. The result of this study concluded that with the integration of both C4.5 and LR (Logical Regression) classifiers, the recognition rate was significantly higher (95.642%) compared to (92.7% and 93.2%) when applied the classifier individually.

Su, Jie et al. "Automatic Detection of Cervical Cancer Cells by a Two-Level Cascade Classification System." *Analytical Cellular Pathology (Amsterdam)* 2016 (2016): 9535027. *PMC*. Web. 28 Apr. 2018.

Title: Automated detection of cell nuclei in pap smear images using morphological reconstruction and clustering

This paper proposed a method for improvement in automated cell nuclei detection in pap smear images using morphological reconstruction and clustering. The first step of the refinement is to locate the candidate nuclei centroids in the pap smear images with morphological analysis and the second step is to incorporate a priori knowledge about the circumstance of each nucleus to the image. The two steps that eliminated the undesirable artifacts are the application of a distance-dependent rule on the resulted centroids and the application of classification algorithms. These refined images are then run through an unsupervised (fuzzy C-mean) and a supervised (support vector machines) classification technique. The dataset that was used in this study includes 38 cytological images of conventional Pap smears containing 5617 recognized squamous epithelial cells. The results of both technique show an improvement to the performance of the clustering algorithm.

Plissiti Me, Nikou C, and Charchanti A. "Automated detection of cell nuclei in pap smear images using morphological reconstruction and clustering." *IEEE Trans Inf Technol Biomed*. Web. Oct 14. 2010.

Title: A Deep Learning Algorithm for One-Step Contour Aware Nuclei Segmentation of Histopathological Images

This paper addresses an approach of nuclei segmentation in high-resolution histopathological images with an automatic end-to-end deep neural network algorithm. The purpose of nuclei segmentation does not only count the number of nuclei in an image, it obtains the detailed information of each nucleus by outputting the contour of each nucleus instead of just position of their central points. To perform the detection of the nuclei, a nuclei-boundary model is used to detect the boundaries of each nucleus in the histopathology images. Detecting the boundary helps improve the accuracy of nuclei detection and helps split any overlapping or touching nuclei. In order to work with extra-large high-resolution images that most U-net cannot handle due to the limitation on the GPU memory, a seamless path-wise segmentation approach is used to segment the images. There is also an extensive study on the effects of a variety of data augmentation methods for nuclei segmentation. Data augmentation is very important with deep learning models since they often have millions of parameters which is why a large-scale sample dataset is usually required for training deep learning models. Without a large sample of dataset, the issue with overfitting may occur. In this study, the dataset that they are using only contain tens of images, but they are 1000x1000 images which contain hundreds of nuclei. There are also four evaluation criteria for more accurate nuclei segmentation performance evaluation: missing detection rate, false detection rate, under-segmentation rate, and over-segmentation rate.

In this experiment they are working with raw H&E stained images. There are some data preprocessing that have to be done before the images are ready for training and testing. The data preprocessing includes color normalization using the H&E stain normalization methods which helps to eliminate the negative interference caused by color variation. In other studies, pure Haematoxylin-channel grayscale image would be much easier than RGB images since it would be easier to distinguish between the foreground (nuclei) and the background (cytoplasm). However, it was found that this proposed method extracts the nuclei more efficiently with RGB images. The reason is that the H-channel grayscale images might miss some information that might be helpful for distinguishing nuclei and the cytoplasm.

The dataset they used to train their model contains 12000 randomly extracted patches from 12 training images. The result of the method outperformed the state-of-the-art method CNN3 in terms of both F1 score and Dice's coefficient. The method is not only more accurate but also much faster. It takes about 5 seconds to predict a 1000x1000 image by one Nvidia Titan X GPU and the time it took for post-processing took less than 0.1 seconds. In conclusion, this method and technique of data augmentation outperforms CNN3 breast cancer nuclei segmentation method by a large margin in terms of precision, recall and F1 score.

Y. Cui, G. Zhang, Z. Liu, Z. Xiong, J. Hu. "A deep learning algorithm for one-step contour aware nuclei segmentation of histopathological images." Columbia, SC: University of South Carolina, Mar 7, 2018.

Title: Nuclei Recognition Using Convolutional Neural Network and Hough Transform

In this paper, a method was proposed for nuclei segmentation on cytological images based on the Convolutional Neural Network (CNN) and modified Hough Transform method. The approach for approximating the nuclei is by fitting ellipses to nuclei regions that have been segmented by CNN. The dataset used contains 50 cytological RGB images which got divided into training set and testing set. Training set for CNN includes patches of size 28 x 28 pixels which were created based on images from training set and corresponding ground-truth labels. The reason for choosing CNN for segmentation is because of its ability for better accuracy in separating overlapping nuclei than conventional methods such as Otsu thresholding. Lastly, the modified Hough Transform was applied to these patches by fitting ellipses for nuclei segmentation.

Żejmo M., Kowal M., Korbicz J., Monczak R. (2018) Nuclei Recognition Using Convolutional Neural Network and Hough Transform. In: Kościelny J., Syfert M., Szyber A. (eds) *Advanced Solutions in Diagnostics and Fault Tolerant Control*. DPS 2017. *Advances in Intelligent Systems and Computing*, vol 635. Springer, Cham.

Title: Cell Nucleus Segmentation in Color Histopathological Imagery Using Convolutional Networks

Convolutional networks have proven to achieve great success in high-level vision problems such as object recognition and image segmentation. In this paper, the convolutional networks are trained using gradient descent techniques to segment the cell nuclei from the background in the histopathology images. The convolution networks encode enough high-level domain knowledge into the model by learning the training data. The dataset that was used in this experiment includes 58 H&E stained breast cancer biopsy images. The result found that the convolutional networks, with 3 hidden layers and 8 feature maps per hidden layer, outperformed other pixel classification methods such as FLDA and SVM.

B. Pang, Y. Zhang, Q. Chen, Z. Gao, Q. Peng, and X. You. "Cell nucleus segmentation in color histopathological imagery using convolutional networks". in *Chinese Conference on Pattern Recognition (CCPR)*, Wuhan 430074, China, Oct 23, 2015.

Title: Automated Training of Deep Convolutional Neural Networks for Cell Segmentation

The proposed method for cell segmentation in this paper is to use deep convolutional neural networks (DCNN) since it has emerged as one of the top superior tasks for image segmentation. Despite the fact that methods that are based on Deep Convolutional Neural Networks solve very complex segmentation problems, the performance of DCNN still depends heavily on having a large amount of problem-specific training samples. One main difference between DCNN and traditional image segmentation approaches is that those traditional image segmentation approaches require experiment-specific parameter tuning while DCNNs require training data. This experiment also works with bright-field images of cultured cells based on end-point fluorescent staining. Bright-field imaging is currently the least invasive microscopy imaging approach allowing long time-lapse studies and it is usually a cheaper approach since it is available in all microscopes. However, automated segmentation of unstained cell images by bright-field microscopy is very challenging. There were some data augmentations that were done to the training data such as flipping and translations. The evaluation of running 58 test images through the training model was that 81% of the cells have an F-score greater than or equal to 0.6 on average.

S. Sadanandan, P. Ranefall, S. Guyader, and C. Wählby. "Automated training of deep convolutional neural networks for cell segmentation". in *Scientific Reports* 7, Article number: 7860, June 29, 2017.