SEGMENTING CERVICAL EPITHELIAL NUCLEI FROM CONFOCAL IMAGES USING GAUSSIAN MARKOV RANDOM FIELDS

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ABSTRACT

Cervical cancer is always preceded by epithelial lesions which have larger and more densely spaced nuclei than normal tissue. Detecting and removing these lesions prevents the development of cervical cancer. A proposed method to detect precancerous lesion *in vivo* is to use the nuclear size and density information from fiber optic confocal images of the cervical epithelial tissue to classify the tissue as normal or precancerous. Automatically segmenting nuclei is challenging because they are hard to decipher from the noise in the confocal images. This paper outlines an algorithm to automatically segment cervical epithelial nuclei from fiber optic confocal videos using Gaussian Markov random fields. Gaussian Markov random fields segment images with additive Gaussian noise by modeling the underlying structure of the image. The algorithm described in this paper detects 90% of the nuclei in each frame with a 14% error rate.

1. INTRODUCTION

Cervical cancer is the second most common cancer among women of all ages. In 2001, 12,900 women were diagnosed with cervical cancer and 4,400 women died from cervical cancer in the United States [1]. Although a third of women diagnosed with cervical cancer will die from it, cervical cancer is entirely preventable. Lesions with larger and more densely spaced nuclei in the cervical epithelium (outer-most layer of tissue) precede cervical cancer. Detecting and removing these precancerous lesions prevents the development of cervical cancer [2].

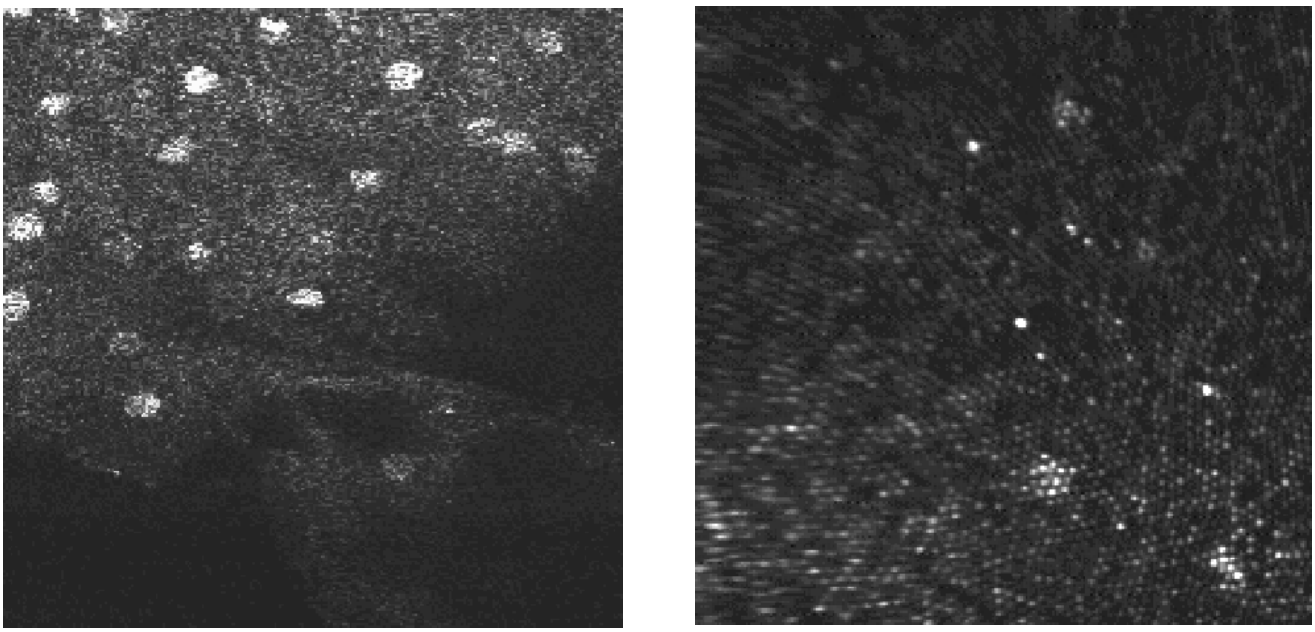
The current method for finding cervical precancer is cytology followed by histology. This cervical precancer detection processes, which requires up to four office visits, is time consuming for the patient, especially if she does not live near a gynecologist. Other disadvantages of this diagnostic method are that it is expensive, costing $6 billion annually in the United States [3], and it depends on the accuracy of Pap smears, which have a high false positive rate [4].

A proposed alternative method to detect precancerous lesions is an automated system that uses nuclear size and density information extracted from *in vivo* confocal videos to classify cervical tissue as normal or precancerous [5]. The advantages of this diagnostic method are that it can be used to find cervical precancer in one office visit, making detection less time consuming and less expensive for the patient, and it does not depend on the accuracy of pap smears. However, this method relies on accurately extracting nuclear size and density information from confocal videos. Confocal microscopes optically section cervical tissue throughout the depth of the epithelium by using a pinhole to remove out of focus light. In confocal videos, nuclei appear bright against a dark background. Thus, confocal videos show similar information as biopsies without removing, staining and slicing cervical tissue. Figure 1(a) shows a frame from a video of a cervical epithelium biopsy taken *ex vivo* by a non-fiber optic, confocal microscope [6] and figure 1(b) shows a frame from a video of cervical epithelium taken *in vivo* by a fiber optic, confocal probe [6]. Since the *ex vivo* microscope's user has more control over the tissue's environment, the nuclei in figure 1(a) are easier to identify than the nuclei in figure 1(b). Additionally, the fiber optic sampling causes spaces between the groups of bright pixels as shown in figure 1(b). Figure 2(a) shows the nuclei in the frame from the fiber optic, *in vivo* system circled in white.

This paper outlines an algorithm to automatically segment cervical epithelial nuclei from fiber optic confocal videos using Gaussian Markov random fields. The algorithm described in this paper detects 90% of the nuclei in each frame with a 14% error rate.

2. MARKOV RANDOM FIELD MODEL

The number and size of nuclei change throughout the cervical epithelium. In other words, no prior knowledge of nuclear size or location exists. However, it is known that the nuclei will manifest in the images as groups of bright pixels. Markov random fields can capture these



a b

Figure 1: Comparison between *ex vivo* and *in vivo* images of cervical tissue. (a) A non-fiber optic, *ex vivo* confocal video frame of cervical tissue. (b) A fiber-optic, *in vivo*, confocal video frame of cervical tissue.

local dependencies of the image information to extract nuclei from the confocal videos, because they model the underlying structure of an image by estimating the grayscale value of a pixel using its neighbors [7]. The general conditional probabilistic model of Markov random fields is:

$$P(b_{i,j} = r_k \mid B) = P(b_{ij} = r_k \mid b_{i-1,j}, b_{i+1,j}, b_{i,j-1}, b_{i,j+1}) \quad (1)$$

where B is an image, r_k is a grayscale, b_{ij} is a pixel with immediate north, south, east and west neighbors of $b_{i-1,j}$, $b_{i+1,j}$, $b_{i,j-1}$ and $b_{i,j+1}$. This model relates a pixel to its neighbors. Thus, it can segment cervical epithelial nuclei which are random but have local dependences.

Markov Random fields were first used to segment images with noise by Hanson and Elliot [8]. Their model assumes additive Gaussian noise with zero mean and a known standard deviation and uses a pixel's noisy neighbors to find its actual grayscale set. This work directly applies to segmenting cervical epithelial nuclei from fiber optic, confocal videos because the fiber optic confocal videos have additive noise.

3. NUCLEI SEGMENTATION ALGORITHMN

3.1. Pre-processing

The faces of some optical fibers reflect light back even when nothing is present. Subtracting the optical fibers' face reflections from each frame will remove the offsets that the reflections cause. An empty frame (frame with no nuclei) will contain each optical fiber's face reflection, but it will also contain random noise. Assuming that the noise is zero mean ergodic, averaging several empty frames together will reduce the noise and find each optical fiber's face reflection offset. Figure 2(b) shows the optical fiber bundle's face reflection for the video containing figure 2(a), and figure 2(c) shows the frame in figure 2(a) with the optical fibers' face reflections removed.

3.2. Markov Random Field Segmentation

The Markov random field model described in [8] estimates the actual grayscale of a pixel using only the pixel and its north neighbor. The following is a brief overview of this algorithm. The first step is to create D(*i,j,k*), which has dimensions number of pixel rows by number of pixel columns by number of grayscales and represents the log of the probability that each original grayscale value at pixel *i,j* is r_k. Specifically:

$$D(i,j,k) = -(g_{ij} - r_k)^2 / 2\sigma^2 \quad (3)$$

where g_{ij} is the input grayscale value, r_k is the grayscale value at depth k, and σ is the standard deviation. For the images in this paper, 16 grayscales evenly spaced between the image's minimum and maximum grayscales were used. Using additional grayscales did not improve segmentation. The standard deviation was found by averaging the standard deviation from all of empty frames after subtracting the optical fiber face reflection. Next, the Markov random field algorithm uses D(*i,j,k*) to find the log-likelihood that a pixel belongs to the same grayscale set as the pixel directly above it. The log-

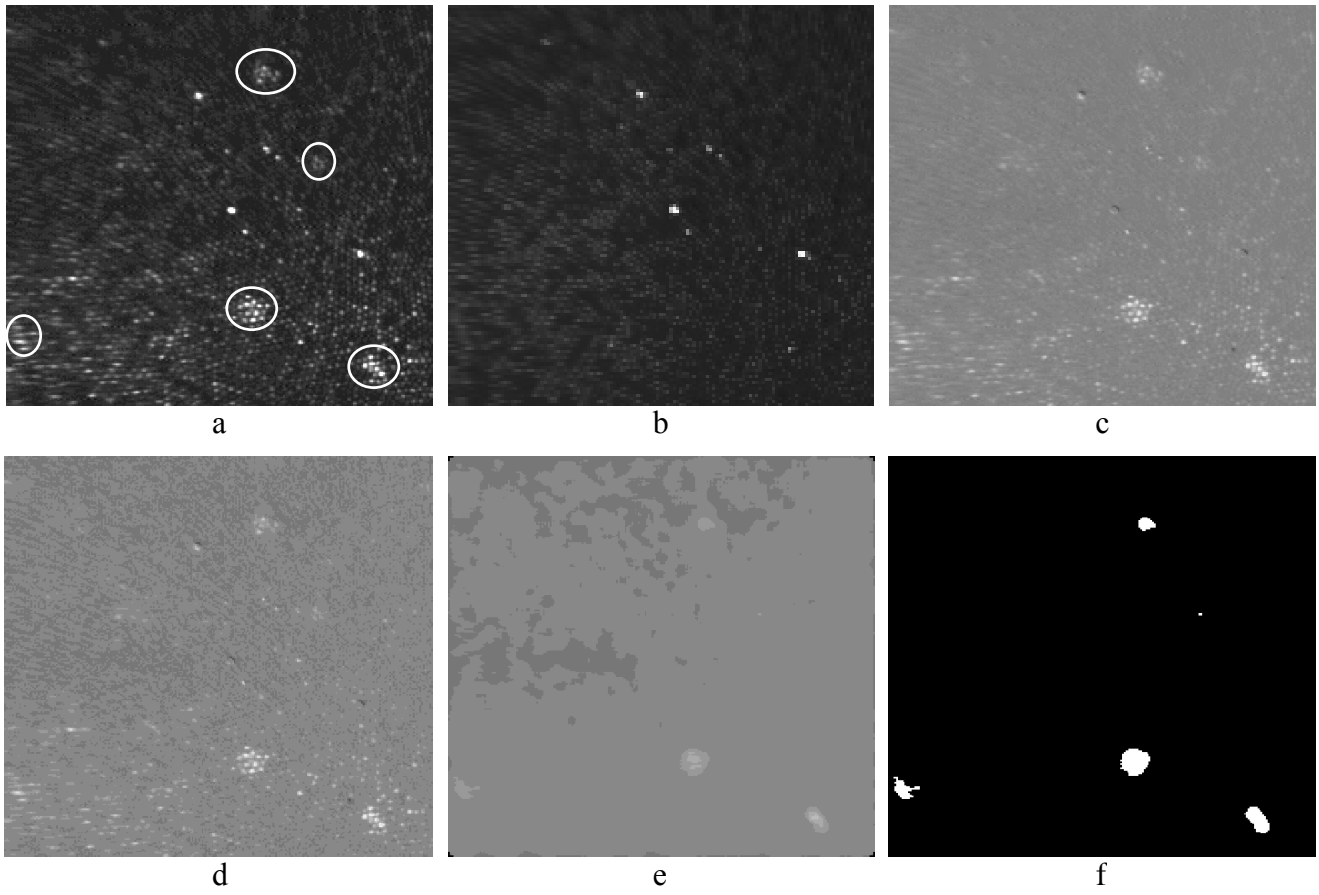


Figure 2: A frame from a fiber optic confocal video of cervical epithelium at different points in the segmentation process. (a) Original frame with nuclei circled in white. (b) Optical fiber bundle's face reflection for video containing the original frame. (c) Original frame with optical fibers' face reflections subtracted. (d) Optical fiber face reflection subtracted frame segmented using Gaussian Markov random fields. (e) Segmented frame median filtered. (f) Median filtered frame after applying a threshold.

likelihood function, $L(i,j,k)$, is found by indexing through each row. The first row is initialized to $D(1,j,k)$, then

$$L(c,j,k) = \max_{1 \le j \le k} (L(c-1,j,k) + D_{kc} + \pi_{kj}) \qquad (4)$$

where $\pi_{kj} = \ln(T)$ if $k = j$, and $\pi_{kj} = \ln(1-T)$ otherwise. T is the transition probability. Thus, the log- likelihood function compares the current pixel probability plus the probability of its northern neighbor at each grayscale value, weighting the same grayscale value by T. For the figures shown throughout this paper, the transition probability was 0.95, making each pixel's grayscale value highly dependent on the one above it. Finally, each pixel was assigned to the grayscale r_k where k is the maximizing k for $L(i,j,k)$. Figure 2(d) shows the optical fiber face reflection subtracted frame (figure 2(c)) segmented using this Markov random field model.

3.3. Post-processing

The final steps of nuclei detection are median filtering the frames to remove the fiber pattern and applying a threshold to separate the nuclei from the background. Figure 2(e) shows the segmented nuclei in figure 2(d) median filtered with a 7 by 7 window and figure (f) shows the median filtered frame after applying a threshold. The next step in creating an automated, precancer detecting system is to extract nuclear information from these segmented images.

4. RESULTS

As figure 2(f) shows, the Gaussian Markov random field model described in this paper can be used to segment cervical epithelial nuclei from *in vivo*, fiber optic confocal videos. Overall, the algorithm detects most of the nuclei in each frame. To determine the accuracy of detection, a human viewer hand segmented 100 frames from a fiber optic *in vivo* confocal video of cervical

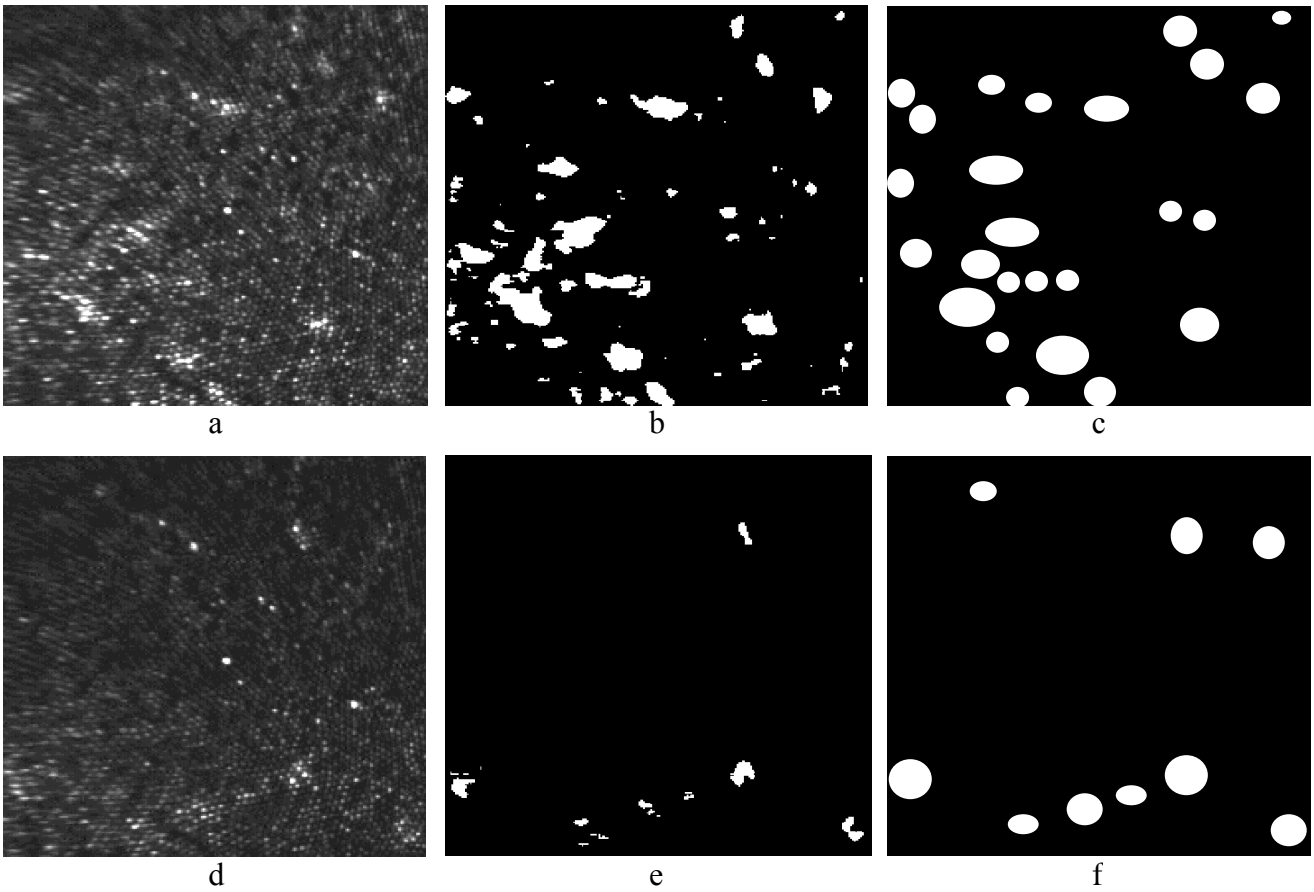


Figure 3: Two frames from a fiber optic confocal video of cervical epithelium and their corresponding Gaussian Markov random field segmented frames and hand segmented frames. (a) Original frame. (b) Frame (a) segmented using Gaussian Markov random fields. (c) Frame (a) segmented by hand. (d) Original frame. (e) Frame (d) segmented using Gaussian Markov random fields. (f) Frame (d) segmented by hand.

epithelium and found 1194 nuclei. The algorithm found 1071 of those nuclei and an additional 166 nuclei that did not correspond to a user identified nuclei. Thus, the Gaussian Markov random field segmented frames found 90% of the nuclei and had a 14% error rate. Figures 3(a) and 3(d) are frames from this confocal video, figures 3(b) and 3(e) are their corresponding Gaussian Markov random field segmented images, and figures 3(c) and 3(f) are their corresponding hand segmented images. As figure 3(c) demonstrates, most falsely detected nuclei occur at very bright pixels. Furthermore, figure 3(e) shows that most missed nuclei occur when the nuclei are very light.

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