Analysis of Silver Stained Cell Specimens: Nuclear Segmentation and Validation

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ANALYSIS OF SILVER STAINED CELL SPECIMENS: NUCLEAR SEGMENTATION AND EVALUATION

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1. Introduction
Cancer should be treated as early as possible to increase the chance for a healing. To this end, the diagnosis has to be based on specimens, which can be obtained without pain or even discomfort for the patient. This can, e.g., be achieved with cytopathological methods. These cell specimens can be acquired easily by brush biopsies or fine-needle aspiration biopsies (FNABs). Afterwards these cells are stained and investigated microscopically. Several stains are available and routinely applied, one of which is the silver stain.

2. Problem Description
Ribosomal RNA is replicated in the nucleus in so-called nucleolar organizer regions (NORs). In an active state these NORs are affine to silver and thus called AgNORs and indicate the active rDNA and, consequently, the regulatory processes of the cell growth mechanism, i.e., the proliferation activity of the cell. For cancer diagnosis, therefore, the count and size of the AgNORs is diagnostically relevant [4]. Staining by silver nitrate, however, exhibits strong contrast and intensity variations over the slide and, moreover, not only the AgNORs are stained. It is therefore a challenging task to detect the AgNORs within the nuclei under these varying intensities. Fortunately, this has been solved by improving the imaging of the microscopy images, i.e., by high dynamic range microscopy [1].

To automatically detect the AgNORs by this method, however, a robust delineation of the nuclei is required, which in some diagnostic cases has to be directly obtained from the images of the silver stained specimens.

3. Solution method
To achieve a segmentation of the nuclei, we follow a two-step approach [3]. First, we apply a mean shift segmentation, which is an over segmentation of the image. In a second step, those segments, which are part of a nucleus, are then grouped together into the desired nuclear segmentation. This is achieved by a model-guided region grouping.

4. Experimental results
We have applied this algorithm to 4006 images from 23 specimens of FNABs of the thyroid gland. The algorithm detected 8617 nuclei. To evaluate these segmentations we took advantage of our multimodal cell analysis [2] setup and acquired images of the identical cells in another stain. This Feulgen stain stains only the nuclei which allowed for a straightforward color-based automatic segmentation of the nuclei. These nuclear segmentations have been peer reviewed and accepted by experienced cytopathologists over the past years. Hence, we could compare the silver stain segmentations against an easy to generate, reliable, and commonly accepted gold standard. This comparison of both segmentations showed that our algorithm was able to automatically segment nuclei in silver stained specimens with a mean areal segmentation error of \( \Delta A = 12 \mu m^2 \).

5. Innovative contributions
We have shown that it is feasible to obtain reliable nuclear segmentations of silver nitrate stained specimens. Our segmentation algorithm is based on an intermediate over segmentation acquired with the mean shift algorithm. The regions of the over segmentation are then merged, guided by a shape model for the nuclei, which leads to a successful segmentation for almost every isolated nucleus. This algorithm provides the basis for a fully automatic analysis of silver stained specimens.

References