The Relevance of Computer-Aided-Diagnosis Systems in Microscopy Applications to Medicine and Biology

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INTRODUCTION

Microscopy is a branch of medical sciences strictly related to image analysis and interpretation. Various sectors of medicine make use of micrographs[1] for different purposes. Moreover, since different biological substrates can be used, micrographs are usually divided into cytological and tissue images.

Humans are limited in their ability to distinguish similar objects, and to diagnose diseases during image interpretation because of noise and of their nonsystematic search patterns. In addition, the vast amount of image data generated by imaging devices makes the detection of potential diseases a burdensome task and may cause oversight errors. Developments in computer vision and artificial intelligence in medical imaging have shown that computer-based systems can be employed in different fields of medicine and biology, especially in those based on digital images (e.g., radiography, mammography, and echography, to name a few).

In microscopy, many qualitative or semiquantitative features have to be analyzed, demanding for qualified personnel that are not always available. Moreover, in several microscope applications the lack of quantitative information limits their reproducibility. For these reasons, in the last years the main research efforts on micrographs have been directed toward automated image processing and analysis, particularly in the field of both image segmentation and classification. The former aims at subdividing an image into its constituent regions or objects, whereas the latter works toward the recognition of image parts or objects detected by the segmentation process.

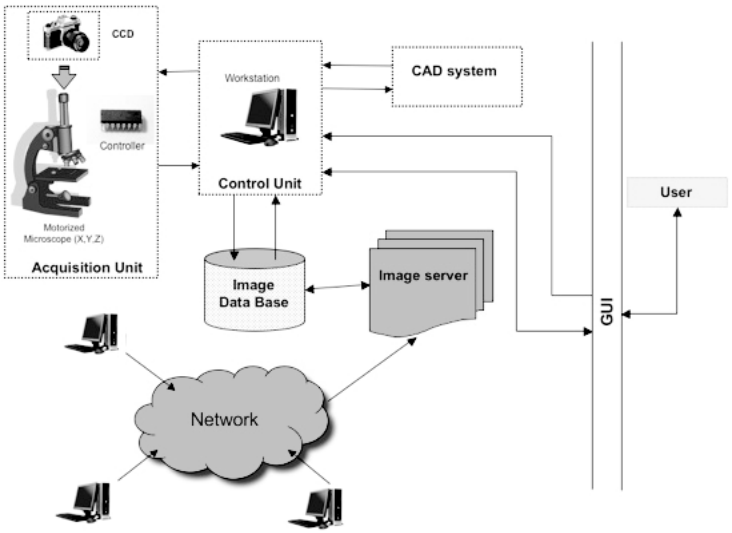
In this respect, many results have been achieved in a wide range of microscopy applications, such as the analysis of blood smears, chromosomes, tumour cells, brain, bone marrow, skin lesions, or autoantibodies analysis. These results can be attained, since the strategies in microscopy analysis have been expanded by ongoing automation of sample preparation, field selection, focusing, and imaging. Consequently, scientists and physicians are nowadays able to collect large sets of high-quality microscope images.

Figure 1 shows a typical architecture of a computer-based system devised to analyze the micrographs. The user controls and interacts with the system through a Graphical User Interface (GUI), which is located at a workstation. The workstation controls a full-motorized microscope, whose parameters, such as focusing, movement stage, objective, illumination, and magnification can be flexibly set. Moreover, the microscope is equipped with a digital camera to acquire one or more images of the sample under examination. The digital images are transferred to the workstation, and then they are automatically post-processed, stored, and shared on the Web.

Such architecture should act as a computer-aided diagnosis (CAD) system. It is well-known that such systems play an important role since they not only support the specialist in the image analysis task, but they also provide a set of useful functionalities that help in speeding up the routine part of the work.

In this article, we discuss the use of computer-based systems in microscopy, focusing on cytological images. We initially present recent results on image segmentation, and then we argue that it makes sense moving from a structural approach to a semantic interpretation of micrographs. In this respect, we focus on the relevance of using CAD tools to overcome the current limitations of microscopy, investigating several peculiar objectives of such systems. A short review of the literature demonstrates that the development of a

Figure 1. Typical architecture of a computer-aided diagnosis (CAD) system



flexible CAD applicable to various working scenarios is a future trend in microscopy healthcare systems. To support our position, we briefly describe a tool that analyzes and classifies fluorescence images.

BACKGROUND

The main contributions that healthcare information systems have given to microscope applications are basically related to the following two areas:

- **Image segmentation** (i.e., partitioning the image into regions as well as locating objects, e.g., cells)
- **Image classification** (i.e., recognizing the patterns or the objects of an image)

The classification systems may use data computed by image segmentation, thus integrating information that could be provided to the specialist to help him/her in the decision-making process.

Classically, image segmentation is defined as the partitioning of an image into not overlapping, constituent regions that are homogeneous with respect to some characteristic, such as intensity or texture. In the case of cytological micrographs, image segmentation is related to cells detection, which has to satisfy the following four main requirements:

- One micrograph has to be evaluated in a very short time to enable high throughput in screening many slides.
- Results must be reproducible to guarantee a reasonable statistical interpretation of the data.
- Robustness is needed, since cells vary in shape, density, and fluorescence properties.
- Microscope images may be taken at different magnifications so that the detection system has to be easily adaptable to cells' size changes.

Many cells segmentation methods have employed image-processing techniques dealing with domain-specific problems. Nattkemper, Ritter, and Schubert (2001) and Theis, Kohl, Kuhn, Stockmeier, and Lang (2004) use an adaptive neural classifier mapping each image point m to a fluorescent micrograph to a confidence value $C(m)$ in [0;1], indicating how probable a cell lies in this image patch or not. This function is then used as a local filter on the whole image, providing a probability distribution with local maxima at cell positions. Analysis of maxima by thresholding reveals the number and position of the cells. Perner, Perner, and Muller (2002) and Chen, Zhou, and Wong (2006) localize fluorescent cells applying global thresholding by the Otsu's algorithm (Otsu, 1979). The algorithm well locates the cells with their cytoplasmic structure, but not the nuclear envelope itself. To overcome such limitations, Perner et al. (2002) use morphological filters, whereas Chen et