A virtual microscopy system to scan, evaluate and archive biomarker enhanced cervical cytology slides

Cytological screening for cervical pre cancers has led to a reduction of cervical cancer incidence. Worldwide it is a subjective and variable method with low single-test sensitivity. New biomarkers like p16 that specifically highlight abnormal cervical cells can improve cytology performance. Virtual microscopy offers an ideal platform for assisted evaluation and archiving of biomarker-stained slides. Current automated Pap evaluation systems are based on conventional microscopes and assist the cytology evaluation process by reducing the number of normal slides to be analyzed. Yet these systems are not suited for generating and archiving virtual slides at a large scale. Expert cytologists and slides need to be at the same physical location and multi-observer evaluations require physical sending of slides. A Slide scanner on the other hand, e.g. Hamamatsu NanoZoomer 2.0 HT, is capable of generating digital microscopic images of cytological slides at different focus levels to visualize three-dimensional structures within the cytological sample. After completion of image acquisition, digital images can be studied in seamless levels of magnification. Storage of these digital slides on an image server allows for viewing independent of the physical location of pathologist and sample.

"Based on a NanoZoomer 2.0 HT we developed the prototype of a system capable of scanning cytological slides, automatically separating cell clusters and individual cells, detecting nuclei and cytoplasm, and identifying biomarker-stained cells", tells us PD Dr.-Ing. Niels Grabe, Scientific Head of the TIGA center. "We implemented a virtual microscopy system allowing highly efficient automated prescreening and archiving of biomarker-stained slides."

According to Bernd Lahrmann (PhD student) all slides were scanned with 20× resolution (0.46 µm/pixel) resulted in image sizes of 65K x 60k pixels. For the image database the NDP Serve image server of Hamamatsu Photonics was used. "We developed image processing algorithms capable to detect positive stained cells on the slides, like the one shown in Fig 1" he explains his work. "After removal of artifacts, based on the specific HSV channel values determined earlier, the algorithm was tested with reference samples and yielded very good agreement with the known manual scoring results. To make it more user friendly we developed a novel web server application (CyTIGA server) which provides a user interface for cytological evaluation as shown in Fig. 2, Bernd Lahrmann explains. "

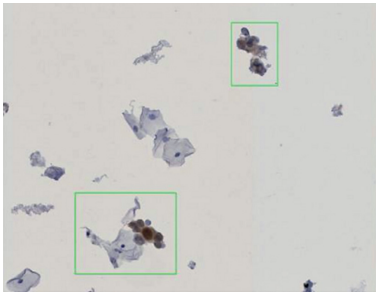

Figure 1: Stained cells, detected by CyTIGA

"The CyTIGA server provides one-click diagnostic decision-buttons but also offers virtual slide browsing features. This allows interactive navigation

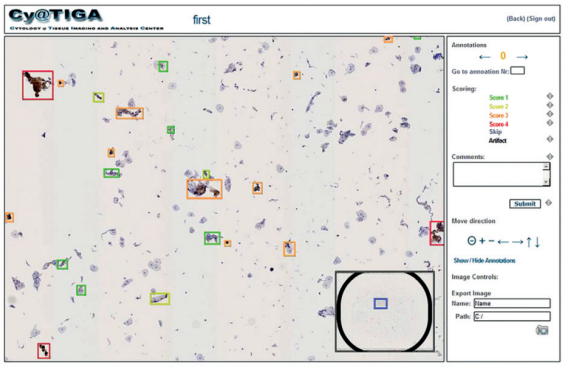

Figure 2: Scoring results of the CyTIGA server

through the slide guided by a pre-computed navigation route visiting all or only biomarker-stained objects. The one-click decision-buttons allow fast and simple scoring of each object by an expert."

But of course such an automatic evaluation algorithm is only useful for daily diagnosis, if it excels manual scoring, which is always subjective and prone to errors by cells not detected or the fact, that not the whole slide is used for evaluation. First tests were done with positive results in favor of the CyTIGA system. The sensitivity of the algorithm to detect biomarker-stained cells was very high (89.1–100 %) on the full slides and even higher than the manual evaluation (84.4–98.2 %) with specificity above 98.9 % for both, manual and automatic analysis.). Furthermore CyTIGA stores statistical information like number of cells, number of positive events etc., information not available for further analysis after manual scoring.

PD Dr.-Ing. Niels Grabe

Bernd Lahrmann

The TIGA Center is a cooperative project which started in 2007 at the University Heidelberg with the goal of establishing a bioinformatics platform dedicated to the quantitative analysis and modeling of tissues. A strong emphasis is placed on clinically relevant research projects. At the heart of the TIGA's technology platform are automated microscopic scanners for whole slide imaging of glass slides. By integrating such imaging systems in a technical pipeline ranging from organotypic in vitro cell cultures to computational tissue modeling the TIGA generates a wealth of yet unexploited clinically highly relevant tissue data.

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For further information see "A virtual microscopy system to scan, evaluate and archive biomarker enhanced cervical cytology slides", Cellular Oncology 32 (2010) 109-119 and http://tigacenter.bioquant.uni-heidelberg.de/

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