The CerviSCAN project - Project description and current progress

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***Abstract*—Cervical cancer is the second most common type of cancer among women in spite of the fact that it through screening easily can be detected and cured before it becomes invasive. Current screening procedures are too complex and costly for use in developing countries. The CerviSCAN project is an attempt to create a automated cervical cancer screening system that will lower the cost and increase the throughput of samples. This paper accounts for the current progress of the project as well as some of the planned future work.**

I. Introduction

Cervical cancer is the second most common type of cancer among women. During 2005 it caused a quarter of a million deaths worldwide, of which 80% occurred in developing countries. Without sufficient improvements to screening and treatment methods the mortality rate is predicted to increase with as much as 20% during the coming decade [1]. Current screening programmes mainly use the staining and visual inspection method developed by Papanicolaou during the 1940s which, since it was instated, has helped reduce the mortality rate by 50-70%. However, even though the Papanicolaou (Pap) test, commonly know as the ”Pap smear”, has been very successful it is dependent on a specialist performing the visual inspection. In developing countries specialists may be few and far between which means that large populations of women never go through a screening. Even in regions with well functioning screening programmes there are weaknesses to the procedure. Manually screening large numbers of samples is a monotone and tiresome work which often leads to fatigue related mistakes being made [2].

Since the mid 1950s, several attempts to create an automated system for cervical screening have been made [3]. However, the first commercially available automated scanning devices did not appear until at the end of the millenia [4]. The main problem with these devices is that they are complicated, expensive and require sophisticated technical maintenance. This has hampered their spread in industrialized countries and made them almost non-existent in poorer ones.

The CerviSCAN project is an attempt to create a cheaper, more accessible cervical screening system which can be distributed at a relatively low cost in poorer regions of the globe.

II. Project goals

The main purpose of the CerviSCAN project is to both speed up and lower the cost of the cervical cancer screening process. This is, as has already been mentioned, an old problem which so far remains, at least to some extent, unresolved. So far two main suppliers of automated screening system exist: FocalPoint(formerly AutoPap), developed by TriPath Technologies and currently part of the large lab technology company BD. This system can automatically determine that about a quarter of the screened specimens are normal. The rest has to be screened in the conventional way. The other company is CYTYC Corporation which has developed an improved but expensive way of making specimens, the so called ThinPrep processor for Liquid Based Preparations. Those preparations are used for improved visual screening but they also offer a machine to assist in that screening.

The systems described above both use a screening approach known as a rare event (RE) search. This demands that all cells visible in a sample are analysed in order to determine whether any of them show any sign of malignancy. The problem with this approach is that the number of cells in a sample range in the 100,000 whereas the number of malignant cells can be as few as 10, leaving a very small margin of error.

A different approach to sample screening is to search for a phenomenon known as malignancy associated changes (MAC). When human screeners or cytologists look at the cell specimens they search for so called diagnostic cells, i.e. cells that are clearly malignant based on their morphology and chromatin structure. It was, however, discovered during the early research on cell image analysis that also seemingly normal cells on specimens with malignancy were influenced by the malignant process in such a way that they showed subtle differences in their chromatin pattern that could be detected by image analysis [5]. With this discovery came an alternative strategy for developing a screener: Rather than looking at all the more than one hundred thousand cells on a specimen, searching for the few clearly diagnostic cells one could carefully analyse a few hundred cells and statistically determine if their chromatin distribution was normal or modified towards a malignant pattern.

The problem with the MAC approach is that the analysis of the chromatin pattern requires perfect focus and it has been very hard to develop systems that at

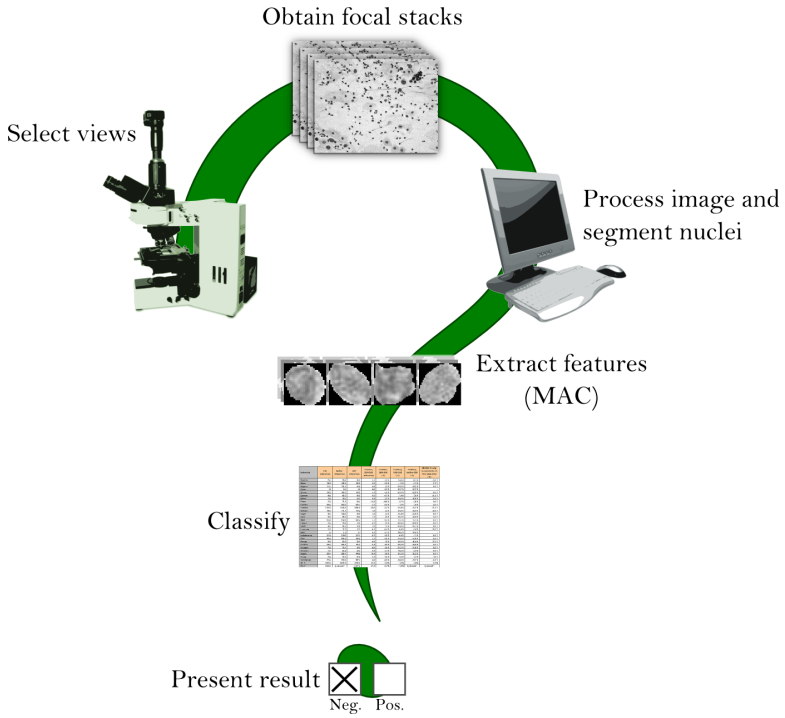

Fig. 1. Flowchart for the suggested analysis method. A microscope with a high aperture lens which is mounted with a piezo driven distance is used to acquire focus stacks of the sample. The stacks are processed and the nuclei segmented. Robust features are calculated and used for classification. The sample can then be listed as healthy or a candidate for manual analysis.

sufficient speed and accuracy can give exact focus for all cells throughout an entire sample. This has negatively effected the robustness of any systems created. Even so, a few groups around the world have been able to show the potential of using the MAC approach [6], [7].

However, these previous approaches were limited to a single 2D image of the sample. By moving the lens vertically while acquiring multiple images into a stack we get detailed information about the chromatin pattern for each cell even if different cells are located at different focus levels. This mimics what is done for visual analysis of difficult cases, the cytologist moves the fine focus up and down while looking at the cell.

Our hypothesis is that through this more robust description of the chromatin distribution we will get better discrimination between normal cells and cells influenced by malignant processes in their neighbourhood causing the determination of MAC to be more sensitive and robust than what has been achieved previously.

We hope that we based on such quantitative determination of MAC can create a computer assisted PAP-smear screening system based on a simple standard microscope equipped with a piezo actuated high numerical aperture lens and a high resolution monochrome camera connected to a standard computer, i.e. a much simpler and less expensive set-up than current automated systems. A suggested flow chart for such a system can be seen in Fig. 1.

III. Project Status

The main points of the flowchart shown in Fig. 1 serves to illustrate some of the principal hurdles that need to be surpassed to reach a working product. The following sections will give a short description of these steps and also give an account of the work that has been done so far within the framework of the project.

A. View selection

The initial step, view selection, refers to the process of choosing image fields for capturing. Here the level of complexity varies depending on the available hardware as well as the specifications for the image capturing process. An early decision that has to be made is whether to capture enough images to cover the entire sample or if a more intelligent approach for choosing a number of fields that represents the sample to a suitable degree should be used.

The main problem with trying to digitize one entire sample is the amount of data generated. For the CerviSCAN project, images are acquired with a resolution of 0.2 μm per pixel. A standard PAP-smear has a sample surface of at least 2×5 cm. This means that if an entire sample is digitized 25 billion pixels are captured. Add to this the intended acquisition of focus stacks at each position, a process that currently generates 41 images per field, and the amount of data for a single specimen becomes unreasonable.

The problem with excessively large datasets could be avoided if a smaller number of fields could be chosen from each specimen in a statistically sound fashion. However, because of the often very small ratio of non-healthy cells compared to normal ones, as was discussed in Section II, this approach would demand a classification

method based on the MAC mentality since this would not depend on finding the often very few clearly malignant cells.

Currently, the view selection for the CerviSCAN project is completely manual process. Initial versions of a finished product will use a semi-skilled individual that will capture the necessary image fields.

B. Stack acquisition

Cells found on PAP-smears are not distributed as a flat 2D surface. Instead the thickness on the specimen can measure up to around 100 μm for areas with high amounts of debris and around 10-20 μm in more general fields. This fact creates problems when developing automated systems for diagnosing slides since there in almost all image fields will exist nuclei that are not in the current focus layer.

As was already mentioned in Section II, the goal of the CerviSCAN project is to develop methods focused around acquiring image stacks using piezo controllers attached to a high numerical aperture objective. This makes it possible to obtain in focus information throughout an entire image field.

Currently the system operates using a E-662 Piezo server controller (Physik Instrumente GmbH & Co. KG, Karlsruhe, Germany) connected to a 40×, 0.95 NA objective. The stacks consists of 41 images with a 0.4 μm step length, thus covering 16 μm of material. This has been heuristically shown to work well for suitable image fields, i.e., fields that do not contain a too large amount of debris.

C. Generation of synthetic data

When developing image segmentation and feature extraction algorithms one common problem is obtaining ground truth data for training and testing algorithms. It is very tedious to manually mark and classify thousands of cells but this can be done. It is, however, not at all feasible to accurately outline the nuclear borders for thousands of cells as ground truth for the segmentation. Therefore we have in parallel with the development of the image acquisition system developed software for synthetic image generation. The software, called PAPSYNTH, uses, to the best of our knowledge, the first method for generating synthetic bright-field images of cells as they appear in PAP-smears. Although the current version only creates 2D images, i.e., images without depth, the software has still acted as a valuable asset in the development of several methods within the CerviSCAN project because of its ability to create realistic images that have a known ground truth. The software has since its creation been presented at ISBI 2010 [8].

D. Stack processing and nuclei segmentation

As has been described above in Section III-B the cellular material in a PAP-smear is distributed at different depths. The first step of an analysis in the process described in Fig. 1 is thus to locate the cells in the focus stacks that have been acquired. One way to do this is to merge the images from different focal levels into a single image with perfect focus throughout, a process known as extended depth of focus [9]. An example of the result of such an operation can be seen in Fig 2. Here a wavelet based method, similar to the method described in [9], has been implemented and used.

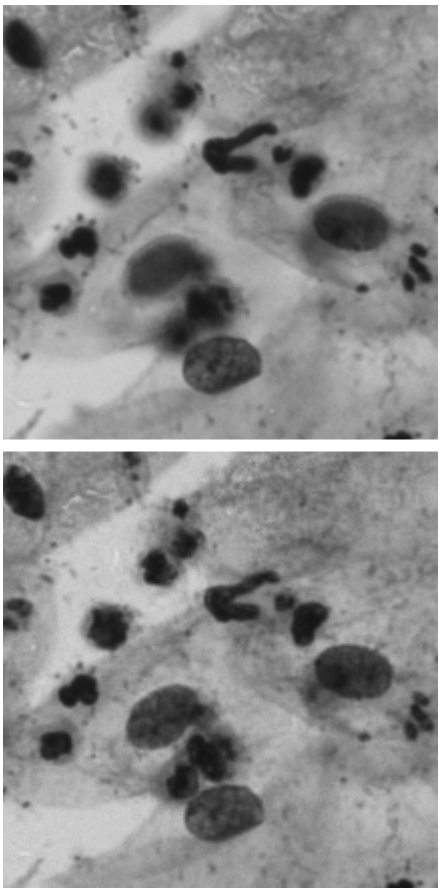

Fig. 2. **Top:** A single focus plane taken from an image stack. Some cells are in focus while others are to blurred for details to be visible. **Bottom:** The same area after having applied an extended depth of focus method to the focus stack.

As was stated in Section II a single PAP-smear usually contains a few hundred thousand cells. Segmenting those cells is a task made harder by a number of factors such as folding cells, surrounding blood cells and foreign objects. An example of a difficult image field can be found in Fig. 3. Variations in stain intensity between batches of specimens further complicates the analysis process by making it hard to use segmentation methods that focuses solely on any kind of grey-level thresholding mentality.

For the CerviSCAN project a segmentation method based on the Canny edge detector [10] followed by a closing algorithm has been created. When using edge detection algorithms, e.g., the Canny edge detector, it is common that the resulting edge map has gaps in the object borders. To achieve a segmentation based on the edge detection result, such flaws need to be corrected. The method created through this project generates a non-Euclidean distance transform of the edge map, derived from local gradients in the image. The distance map

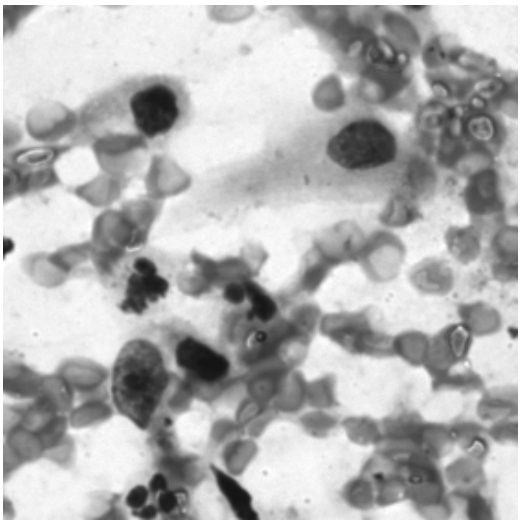

Fig. 3. Image field taken from a standard PAP-smear. Difficulties for nuclei segmentation include folded diagnostic cells, uneven staining and obscuring blood cells.

is then used to perform anisotropic dilation, which we call Riemannian dilation since the distances are derived from geodesic distances in a Riemannian manifold [11]. The method was shown to produce good results and was published at ISVC 2009 [12].

E. Extract MAC features

Extracting MAC features is the key step of the CerviSCAN process. As was stated in Section II the existence of MAC has been proved. However, they have also proved to be notoriously hard to detect in a robust fashion, especially in a practically applicable environment.

This step constitutes the frontline of the current research within the project. With the addition of segmented nuclei that have been expert classified into a number of known classes the next logical step is the texture analysis. Focus will lie on finding features that works well for distinguishing the MAC behavior. Initial efforts will be aimed at extending work done by Rodenacker and Bengtsson [13] to make as much use as possible of the new way of handling the focusing problem. However, at the moment there are no finished results to report.

F. Classify

Because the CerviSCAN project has a medical application any false negative result could prove to have fatal implications. This means that the classification step is going to be put under close scrutiny.

To train any classifier it is important to have an abundance of material that has been pre-classified by an expert. To that end a special protocol which allows experts to put markers inside nuclei has been created. Each marker contains information such as position, cell type and if any proof of malignant changes are present. The software has been used to gather a large database of nuclei classified into a number of known classes that will be used for future classifier development.

IV. Future work

Future work within this project will be heavily focused towards developing novel texture measures that are able to give a robust classification of cell nuclei based on the MAC approach.

An extension of the synthetic data generation model is also planned to take place following the development of the texture analysis work. The intention is to use the statistical descriptions of features obtained from the training data and incorporate that into the synthetic model, thus making the generated images behave in accordance to larger cell populations. The improvements will be applied to shape as well as texture behavior. Also the extension of adding depth to the data, including a correct approximation of the point spread function in the z-direction.

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