# Computer-Aided-Diagnosis (CAD) for colposcopy

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## ABSTRACT

Uterine cervical cancer is the second most common cancer among women worldwide. Colposcopy is a diagnostic method, whereby a physician (colposcopist) visually inspects the lower genital tract (cervix, vulva and vagina), with special emphasis on the subjective appearance of metaplastic epithelium comprising the transformation zone on the cervix. Cervical cancer precursor lesions and invasive cancer exhibit certain distinctly abnormal morphologic features. Lesion characteristics such as margin; color or opacity; blood vessel caliber, intercapillary spacing and distribution; and contour are considered by colposcopists to derive a clinical diagnosis. Clinicians and academia have suggested and shown proof of concept that automated image analysis of cervical imagery can be used for cervical cancer screening and diagnosis, having the potential to have a direct impact on improving women's health care and reducing associated costs. STI Medical Systems is developing a Computer-Aided-Diagnosis (CAD) system for colposcopy – ColpoCAD™. At the heart of ColpoCAD™ is a complex multi-sensor, multi-data and multi-feature image analysis system. A functional description is presented of the envisioned ColpoCAD™ system, broken down into: Modality Data Management System, Image Enhancement, Feature Extraction, Reference Database, and Diagnosis and directed Biopsies. The system design and development process of the image analysis system is outlined. The system design provides a modular and open architecture built on feature based processing. The core feature set includes the visual features used by colposcopists. This feature set can be extended to include new features introduced by new instrument technologies, like fluorescence and impedance, and any other plausible feature that can be extracted from the cervical data. Preliminary results of our research on detecting the three most important features: blood vessel structures, acetowhite regions and lesion margins are shown. As this is a new and very complex field in medical image processing, the hope is that this paper can provide a framework and basis to encourage and facilitate collaboration and discussion between industry, academia, and medical practitioners.

**Keywords:** Computer-Aided-Diagnosis (CAD), automated image analysis, uterine cervical cancer, colposcopy

## 1. INTRODUCTION

Uterine cervical cancer is the second most common cancer in women worldwide, with nearly 500,000 new cases and over 270,000 deaths annually[1,2,3]. Because invasive disease is preceded by pre-malignant Cervical Intraepithelial Neoplasia (CIN), if detected early and treated adequately, cervical cancer can be universally prevented[4]. While almost 80% of the cases occur in developing countries where regular screening is unavailable or underutilized[5], there are nearly 15,000 new cases diagnosed and 6,000 deaths annually in the United States (US) and Canada. In the US each year approximately 50 million women undergo cytological screening[6], with some 7% (3.5 million) requiring additional follow-up[7,8]. It is estimated that the cost for colposcopic follow up and interventional treatment of abnormal cytological screening approaches 6 billion dollars annually in the US[9].

Prophylactic Human Papillomavirus (HPV) vaccines, currently under development, have the potential to prevent cervical cancer. HPV is necessary, but not sufficient alone, for the development of cervical cancer. A monovalent HPV type 16 vaccine has been shown to be both safe and effective in preventing HPV type 16 cervical infections and HPV 16-related cervical cancer precursors[10]. Bivalent (HPV types 16 and 18) HPV vaccines could prevent 75% of all cervical cancers[11]. However, these vaccines will not be commercially available for at least 3 to 5 years. Further, they will not prevent all cases of cervical cancer. Because vaccination should occur prior to initiating sexual intercourse, it may be 60 years before the risk to various populations will be effectively reduced. The cost of the vaccine will also be substantial, perhaps equivalent to that for Hepatitis B vaccine. The poor and geographically isolated, who are at greatest risk for cervical cancer, may not benefit at all.

Colposcopy is the primary diagnostic method used in the US to detect CIN and cancer, following an abnormal cytological screen (Papanicolaou smear). The purpose of a colposcopic examination is to identify and rank the severity of lesions, so that biopsies representing the highest-grade abnormality can be taken, if necessary. A colposcopic examination involves a systematic visual evaluation of the lower genital tract (cervix, vulva and vagina), with special emphasis on the subjective appearance of metaplastic epithelium comprising the transformation zone on the cervix. For this purpose an optical colposcope is used, which has been in use for almost 80 years. A colposcope is a low powered binocular microscope with a built in white light source and objective lens attached to a support mechanism[12]. A green filter may be used to accentuate vasculature. During the exam, a 3-5% acetic acid solution is applied to the cervix, causing abnormal and metaplastic epithelia to turn white. Cervical cancer precursor lesions and invasive cancer exhibit certain distinctly abnormal morphologic features that can be identified by colposcopic examination[13,14,15,16]. Lesion characteristics such as margin shape; color or opacity; blood vessel caliber, intercapillary spacing and distribution; and contour are considered by physicians (colposcopists) to derive a clinical diagnosis[17]. These colposcopic signs, when considered aggregately, determine the severity of the neoplasia and discriminate abnormal findings from similarly appearing, anatomically normal variants. Various colposcopic indices, based on grading lesion characteristics, provide clinicians structured approaches to predicting histologic findings [13,14,15]. However, due to the subjective nature of the examination, the accuracy of colposcopy is highly dependent upon colposcopist experience and expertise. Even in expert hands, colposcopy suffers from low specificity leading to many unnecessary biopsies[18]. These avoidable biopsies cause an increased risk of infection, patient discomfort, delayed treatment and substantially increased costs.

Digital imaging is revolutionizing medical imaging and enabling sophisticated computer programs to assist the physicians with Computer-Aided-Diagnosis (CAD). Clinicians and academia have suggested and shown proof of concept to use automated image analysis of cervical imagery for cervical cancer screening and diagnosis. In one study, a computer system demonstrated greater agreement rates with histologic diagnoses (85%, k=0.77) than did colposcopists' impressions (66%, k=0.40)[19]. In another, the computer system was readily able to discriminate CIN 3 from normal epithelium and immature metaplasia[20]. One computer system for colposcopy has also demonstrated an ability to serially monitor untreated low grade lesions for evidence of progression or regression[21]. Since intercapillary distances increase proportionally with disease severity, another computer system was able to measure these tiny distances to successfully predict the specific level of cervical neoplasia[22].

Various image processing algorithms have been developed to detect different colposcopic features. At the University of New South Wales (UNSW), Australia, Van Raad developed algorithms to detect the transformation zone using an active contours model (snakes) at multiple scales[23,24] and a novel wavelet-based algorithm looking at local frequency content[25]. Yang et al., at Texas Tech University, developed a segmentation algorithm to detect acetowhite epithelium using a statistical optimization scheme (deterministic annealing) for accurate clustering to track the boundaries of the acetowhite regions[26]. Gordon and coworkers, at Tel-Aviv University, developed a segmentation algorithm for three tissue types in cervical imagery (original squamous, columnar, and acetowhite epithelium) based on color and texture information[27]. The set of regions in the images was represented by a Gaussian mixture model, while an Expectation-Maximization algorithm was used to determine the maximum likelihood parameters of the statistical model in the feature space. As a result, the labeling of a pixel could be affiliated with the most probable Gaussian cluster according to Bayes rule. Ji et al [28, 29] presented a generalized texture analysis algorithm for classifying the vascular patterns from colposcopic images. They investigated six characteristic pathological vascular patterns, including network capillaries, hairpin capillaries, two types of punctation vessels and two types of mosaic vessels. Others have applied a combination of conventional statistical and structural texture analysis approaches. For example, Balas [30] and Orfanoudaki et al.[31] analyzed the temporal decay of the acetic acid whitening effect by measuring the intensity profile over time. Furthermore, several approaches for tissue classification have been developed: a simple colposcopic image classification method by artificial neural network using the lesion contour features[32], a rule based medical decision support system for detecting different stages of cervical cancer based on the signs and symptoms from physical examination[33], the classification of cervical tissue based on spectral data using multi-layered perceptrons and Radial Basis Function (RBF) networks[34] and multivariate stochastic training algorithms[35]. At the 2004 SPIE Medical Imaging conference, Prof. Daron G. Ferris, M.D. gave a key-note presentation "Analysis of digitized Cervigram™ images for the early detection of cervical cancer", where he as a clinical practitioner encouraged researchers and engineers to start developing automated image analysis algorithms and systems for the detection of uterine cervical cancer[36]. This varied evidence supporting the feasibility of automated image analysis to detect cervical neoplasia is encouraging.

CAD for colposcopy could have a direct impact on improving women's health care and reducing associated costs. A product realization where a CAD system is incorporated into a low-cost hand-held device, creating in effect a

machine expert colposcopist, could improve screening cost-effectiveness in developing countries. Similarly, a product realization, where a CAD system operates as an adjunct to colposcopy could minimize the high variability among colposcopists and establish a consistent, higher standard for accuracy. Consequently, fewer false-positive biopsies or ultimately no biopsies would be required.

STI Medical Systems has been developing Hyperspectral Diagnostic Imaging (HSDI$^{TM}$) fluorescence and reflectance spectroscopy imaging technology and products for cervical cancer for several years. Recognizing that fluorescence spectroscopic imaging contributes only one (additional) feature to the complex task of diagnosing cervical cancer, we have transformed our strategy for cervical cancer detection to include a versatile CAD system, capable of incorporating many features (including spectroscopy). STI Medical Systems' CAD system for colposcopy is called ColpoCAD$^{TM}$. At the heart of ColpoCAD$^{TM}$ is a complex multi-sensor, multi-data and multi-feature image analysis system. Here, we present a functional description of the envisioned ColpoCAD$^{TM}$ system, the system design and development process of the image analysis system, and preliminary results of our research on detecting the three most important cervical neoplasia pathological features: blood vessel structure, acetowhite and lesion margin. As this is a new and very complex field in medical image processing, the hope is that this paper can provide the framework and basis to encourage and facilitate collaboration and discussion between industry, academia, and medical practitioners.

## 2. COMPUTER-AIDED-DIAGNOSIS (CAD) SYSTEM

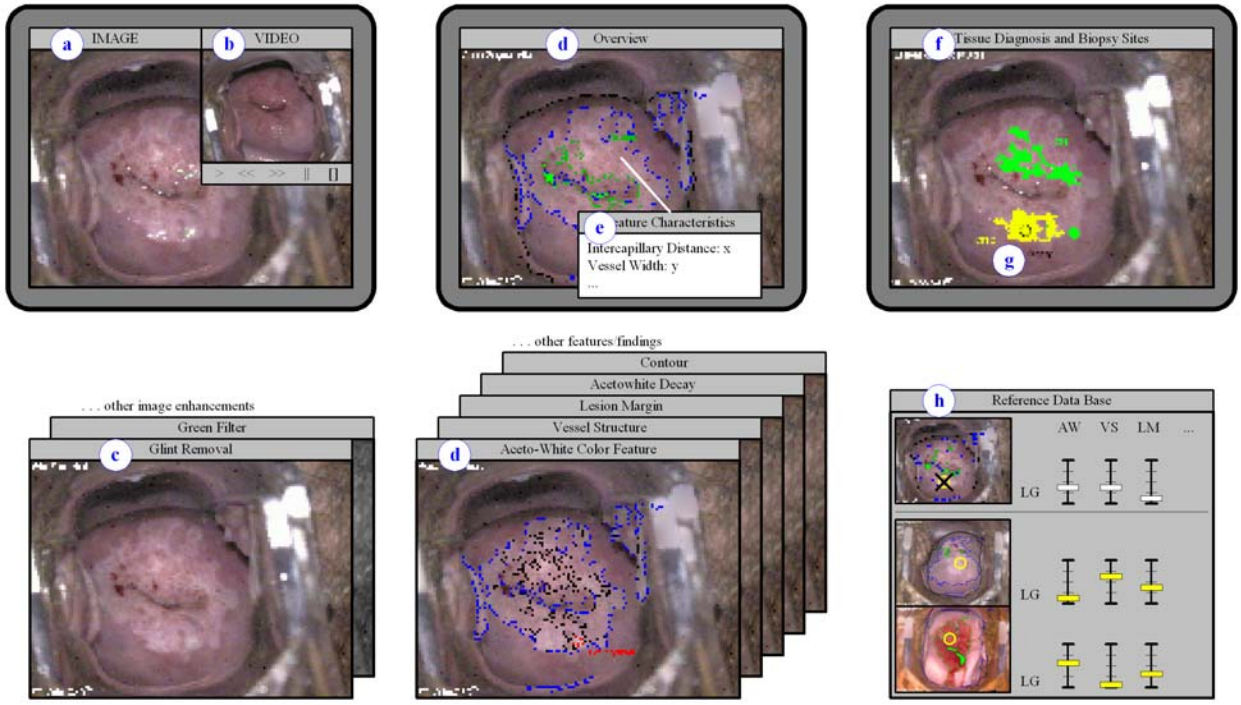


Figure 1: Rendered views of a "technology based" CAD system for colposcopy.

a. High-resolution still images from the examination are displayed to the physician on a high-resolution monitor,
b. Live video of the examination can be viewed and replayed,
c. Images and video can be enhanced using image enhancements like glint removal, green filter, etc.
d. Automated extraction and display of diagnostic features, such as: acetowhite regions, vessel structure, lesion margins, acetowhite decay, and contour etc. These can be displayed to the physician either in an overview or individually,
e. Feature measurements can be provided to the physician on demand,
f. Automated lesion detection and tissue diagnosis can be shown to the physician,
g. Suggested biopsy sites can be indicated to the physician, and
h. Reference images of similar lesions and their characteristics can be brought up from a reference database and shown to the physician for comparison.

A CAD system for colposcopy includes all functions that are related to colposcopy and that can be provided by a computer, from automation of the clinical workflow to automated patient diagnosis and treatment recommendation. The CAD system is a software program that may run on various processing platforms such as computers, DSP/FPGA processing boards, embedded systems, etc., and that interfaces to a cervical data acquisition system such as a digital colposcope, video colposcope, optical colposcope with camera, film based camera with scanner, digital camera, etc.. In this paper, we first provide a functional description of the envisioned CAD system for colposcopy. Second, we present a modular and open system design for the image analysis system that is at the heart of the CAD system. Third, we present a development process that effectively manages the complexity of developing such an image analysis system.

## 2.1 Functional Description

The envisioned functionality of the CAD system for colposcopy originates from a technology driven vision which captures all feasible CAD system functionality. An artist's rendering of a "technology based" CAD system for colposcopy is shown in figure 1. The CAD system architecture is flexible, so that a range of products (screening device, colposcopy adjunct, etc.) can be based on this framework. It is important to realize that each product realization is unique and has its own business and human factors requirements that will determine which of the CAD system functions need to be developed and implemented for any specific product.

The envisioned functions of a CAD system for colposcopy are comprised of the following components:

1. Modality Data Management System
2. Image Enhancement
3. Feature Extraction
4. Reference Database
5. Diagnosis and directed Biopsies

Note that the order in which the functions are listed reflects the degree of assistance or automation in the patient diagnosis. Therefore, those functions can also be used to describe the diagnosis assistance or automation level performed by a CAD system. It is important to note that the current outline of the CAD system for colposcopy provides automated image analysis for the examination of the ectocervix, but does not include the examination of the vulva, vagina and endocervical canal, which are also part of the colposcopic examination. Those examinations still need to be provided by the colposcopist.

**Modality Data Management System**

The Modality Data Management Systems (MDMS) provides a data management infrastructure for digital colposcopy. The MDMS can provide:

- Management (storage, playback, etc.), display and annotation of the acquired data,
- Automation of the workflow related to colposcopy, including:
  - Administration of the patient data and history,
  - Electronic forms (consent form, colposcopy form, etc.),
  - Patient education and information material (videos, etc.) and entertainment (TV, soap operas, etc.),
  - Colposcopy support material (cervical atlas, reference database, treatment guidelines, patient management recommendations, etc.),
  - Letter generation (follow up, etc.),
  - Documentation (results, follow up, etc.),
  - Interfaces and integration to
    - Picture Archiving and Communication System (PACS),
      Digital Imaging and Communication in Medicine (DICOM) is the standard defining the communication between a modality and a PACS system. Note that currently no specific DICOM standard for digital colposcopy exists. Once a couple of companies express interest in such standardization, a new DICOM standard for digital colposcopy can be defined.
    - Pathology laboratory,
    - Accounting system (billing) and
    - Telemedicine.

It is necessary to account for differences in data collection inherent to transitioning the colposcopic exam from an optical to a digital device. For example, changes in image resolution can be addressed by using a high-resolution still camera instead of video camera to provide high-resolution imagery. Cervical topological features can be visualized in

the digital mode using 3D monitors with stereoscopic image/video feed or 3D digitization. A further practical issue in creating a MDMS is the need to make the computer in a physician's examination room available for universal use. The computer cannot be limited to one modality, but rather needs to be able to support the automation of the entire workflow and all modalities in a practice. This also means that the CAD system for colposcopy needs to integrate well with other workflow automation and modality support applications. Today, colposcope manufacturers provide only stand-alone image or video management systems as add-ons to their digital and video colposcopes.

**Image Enhancement**

A "digital colposcope" can provide numerous image enhancements, including:

- Green filter to accentuate vasculature, as used in almost all colposcopes.
- The characteristics of the imagery can be changed so it appears to come from a different colposcope (and/or light source). Mapping the color-space of one colposcope to that of another can provide the same image appearance.
- General image enhancements, like contrast, brightness, zoom, sharpening, etc. as can be found in standard commercial image processing packages like Photoshop®.
- Glare removal to provide information in the image regions that are normally destroyed by glare. Note that the colposcopist uses glare patterns to assess the contour of the lesions (3D topology), therefore glare-free images should only be provided in addition to images with glare. Glare can be removed by designing the acquisition system with cross-polarization (preferred) or by software. Using software to remove the glare only allows interpolating the destroyed image regions, but does not recover the underlying information and may also introduce artifacts in the imagery by removing regions that are mistaken for glare.
- 3D topology-based illumination normalization to lighten up dark regions on the periphery of the cervix. 3D reconstruction of the cervix allows compensating for the differences in illumination due to the 3D topology of the cervix.

**Feature Extraction**

A colposcopist uses different features to assess the cervix; those features can automatically be extracted from the cervical data and shown to the colposcopist to help him in his assessment. A core feature set includes the visual features used by colposcopists. This feature set can be extended to include new features introduced by new instrument technologies, like fluorescence and impedance, and any other plausible feature that can be extracted from the cervical data.

- Colposcopic features include:
    - Anatomic
    - Acetowhite
    - Blood vessel structure
    - Lesion margin
    - Contour
    - Lugol's iodine staining

Images enhancements can be provided that enhance specific features in the imagery, in particular colposcopic features. The individual features can also be classified in terms of their significance to the tissue diagnosis: normal, low-grade, high-grade and cancer. The extracted and classified features can be presented to the colposcopist individually or combined as overlay on an image of the cervix (preferable a universal reference image - typically a color image after acetic acid application); similar to the colposcopic impression annotation. An overlay allows the colposcopist to relate the different extracted features back to their location on the cervix. Companies developing new instrument technologies for detecting cervical neoplasia, such as we and others have done using fluorescence and reflectance spectroscopy [37,38,39], typically introduce their technology as a separate stand-alone solution that provides only the specific feature they detect with their device.

**Reference Database**

A colposcopic diagnosis can be assisted, by providing, based on selected feature parameters, matching examples of reference lesions/cervixes including their diagnosis (and feature parameters). The key is to be able to characterize all lesions by their feature parameters. A reference database can be built up from cervical data sets (preferable LEEP specimens that have greater tissue coverage) for which the diagnosis and the feature parameters of all lesions are available. The ground truth for the diagnosis can be determined by expert colposcopists and pathologists. The feature

parameters can as well be determined by expert colposcopists and pathologists or automatically be calculated by feature extraction algorithms. The search keys of the reference database are the feature parameters; a reference database search then provides matching examples. The search feature parameters can be input (or modified) manually or the feature parameters for a designated location or the highest grade lesion of the cervix under examination can be provided by the feature extraction algorithms. Bringing up examples of varied or different feature parameters than present in the current cervix under examination might also be helpful for the assessment.

**Diagnosis and directed Biopsies**

Tissue diagnosis provides the colposcopist with the automated detection, localization and classification (in terms of severity: normal, low-grade, high-grade or cancer) of all lesions on the cervix. The classification results can be presented as overlay on an image of the cervix, preferable a universal reference image. Note that not one feature alone can provide reliable tissue diagnosis. All available features, starting with the obvious visual ones used by colposcopists, and adding those from new instrument technologies should be integrated into one system to optimize performance. Automated assessment of the adequacy of the examination (visualization of the entire transformation zone) should also be provided, as this affects patient management options. The goal of colposcopy is to direct where biopsies should be taken. Based on the feature extraction and tissue diagnosis, the CAD system can determine the minimum number of biopsies needed, identify where these sites are located and display their locations as overlay on an image. Ultimately, it is envisioned that the patient diagnosis can be derived directly from the computer's analysis, once clinical studies demonstrate sufficient performance compared to standard colposcopy and pathology.

## 2.2 Image Analysis System - System Design

At the heart of the CAD system for colposcopy is a complex image analysis system that provides the core processing for feature extraction and tissue diagnosis.

The image analysis system design is driven by the following objectives:

- To build the core system on visual features used by colposcopists
- To fuse of all available data in order to optimize performance
- To provide the flexibility to work on data sets from different instruments
- To provide a means to develop the system systematically

The system takes calibrated (gray balance, color calibration, etc.) data of the cervical examination as input and provides as output the detected features and their classification, the tissue diagnosis for all locations on the cervix and an assessment of the examination adequacy. Calibration parameters (pixel size, etc.), demographic parameters (age, pregnancy, etc.), patient history (screening result, etc.) and a system sensitivity parameter are used as the parameters of the system. The system architecture is open, modular, and feature-based. It is designed for multi-data (different moments in time, different contrast agents like acetic acid, Lugol's iodine, 5-aminolevulinic acid, etc.), multi-sensor (RGB still / video camera with white light, 3D data acquisition system, hyper-/multi-spectral camera with white and/or UV light, impedance acquisition system, etc.), and multi-feature (colposcopic features, feature from new instrument technologies, other plausible features that can be extracted from the data, etc.) fusion. The architecture identifies three basic processing layers: (1) data registration, (2) feature extraction and (3) feature classification. In the data registration layer, all calibrated exam data gets spatially registered to a selected reference image. This is necessary so that all extracted features can be fused in the feature classification layer and feature extraction modules can exchange data between them. The feature extraction layer is divided into distinct modules by evaluating distinct anatomical and physiological phenomenology for each module. Each feature extraction module can use any of the registered data sources for processing, and also, data can be exchanged among modules. Furthermore, each feature extraction module can fuse different algorithms that redundantly extract the same feature parameters to improve performance. The feature classification layer consists of the tissue diagnosis module that provides the classification of each individual feature and combines the outputs of all feature extraction modules in order to determine the tissue diagnosis for all locations on the cervix, and the determination of the adequacy of the exam. The exam adequacy determination can be based on its own specific feature extraction modules and/or the feature parameters from other feature extraction modules. Different instruments provide different data sets, implying that different feature sets will be calculated depending on the instrument used. For simplicity, feature extraction modules should be designed to depend only on one data source and only to use data from other feature extraction modules that use the same data source as input. Nevertheless, the fusion of different data sources to extract specific features should be done at the feature extraction layer and not carried over into the feature classification layer. So, feature extraction modules that use different data sources and data from other feature

extraction modules that use different data sources should be designed with this in mind so that they work under all possible data source combinations! Because the tissue diagnosis system performance is dependent on the fusion of all available features, the system should be designed so that it can be trained automatically for any combination of features.

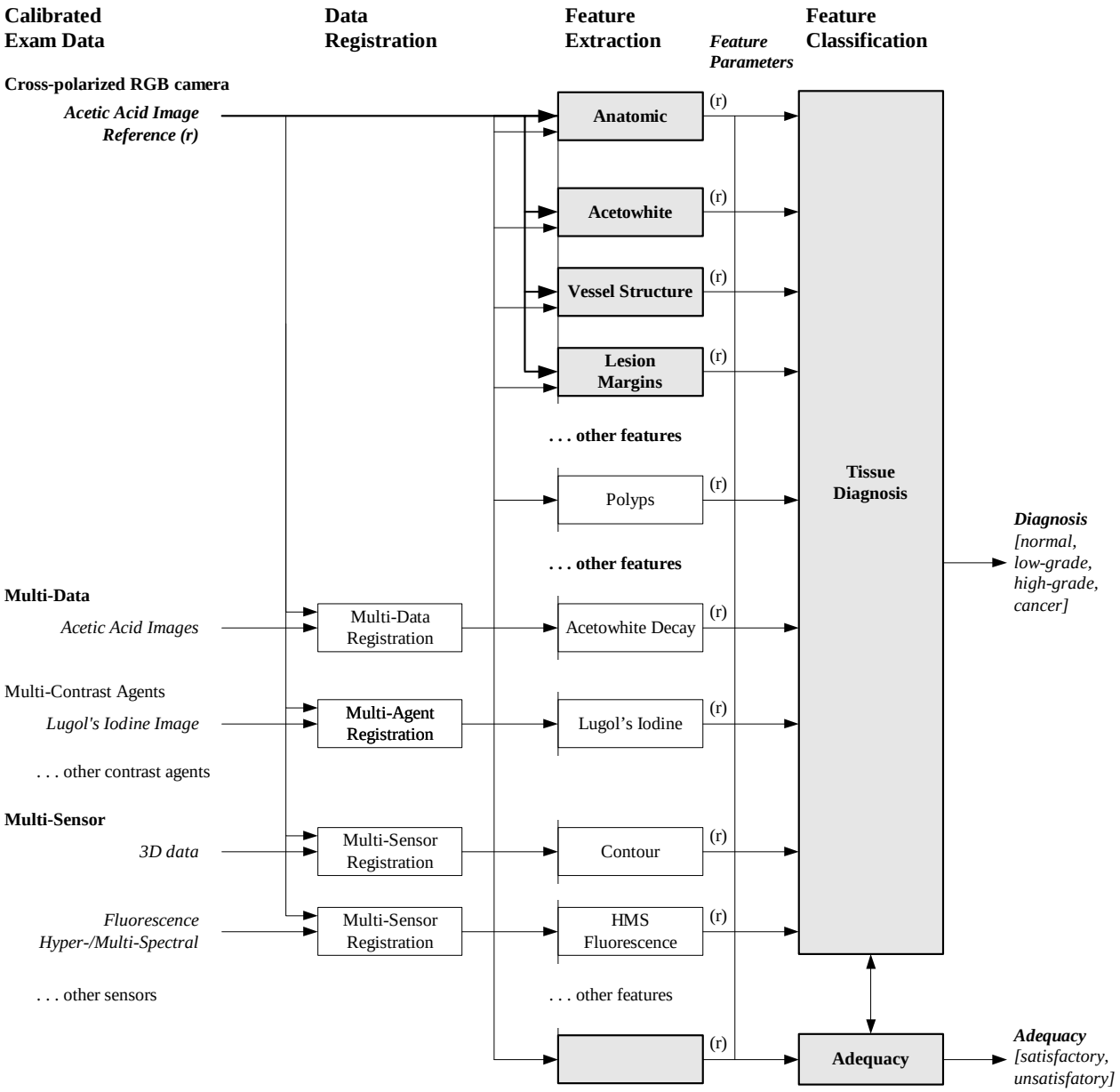


Figure 2: Illustration of the system design for the image analysis system.

Figure 2 illustrates one possible conceptual system configuration. The core system (in gray) consists of the extraction of the anatomic features and the three most important colposcopic features: acetowhite, vessel structure, and lesion margins; the determination of the adequacy of the exam, and the tissue diagnosis. It uses only one RGB color image as input, therefore, by definition, this should be the reference image and no data registration is required. The RGB color image should have been taken with cross-polarization to eliminate the glare and at sufficient resolution to resolve the blood vessel structures. The RGB color images should at least be gray balanced and color calibrated and the size of the pixels be known from a camera calibration. The reference image should be taken at the moment in time after application of 5% acetic acid when the acetowhite effect is still visible and the blood vessels can be seen again (blood

vessels are difficult to be seen right after the application of acetic acid). This is a compromise for the acetowhite and vessel structure feature extraction modules. When more images become available after application of acetic acid, the acetowhite and vessel structure feature extraction modules should each use the most appropriate image as their input to optimize performance. The temporal decay of acetowhite feature parameter cannot be assessed with one image alone and is therefore identified as a separate feature extraction module that requires a series of images after application of acetic acid. The contour (3D topology) feature as well cannot be assessed with one cross-polarized image alone and is therefore identified as a feature extraction module that needs additional data. The contour feature presents a special problem, as a colposcopist uses the glare pattern associated with surface relief, stereoscopic view and the movement of the colposcope for its assessment. For the digital colposcopy system, we propose to use 3D reconstruction to assess the contour feature. A 3D reconstruction system can be implemented in different ways, including: add a non-polarized image to use shape from shading, add an image from a different view point (stereoscopic view) to use stereovision (combined with shape from shading), acquire images taken with special light patterns (Moire, structured light, etc. ) projected onto the cervix to reconstruct the 3D surface, or use laser range finders. The 3D topology of the cervix can also be used for precise measurements of lesions to follow their progression over multiple exams. The Lugol's iodine feature is also considered an extension of the core system as an image with Lugol's iodine as contrast agent needs to be acquired. Any extension of the feature set will lead to improved system performance. The core system can be extended with the extraction of other colposcopic findings that will have an impact on the tissue diagnosis. Some of the other colposcopic findings (e.g. endocervical polyps) can be assessed using the same reference image, while others (e.g. keratosis) might require additional data. In general, any other plausible feature, like texture analysis, that can be extracted from the data sources can be added to the system.

Additional features can be added to the system as data from new instrument technologies becomes available, such as fluorescence hyper- or multi-spectral imaging spectroscopy, 3D data acquisition systems, or impedance acquisition systems. However, when more than one image is used as input, all data needs to be registered to the reference image. Note that the cervix undergoes soft-tissue movements and that when data has been acquired at different moments in time, the registration algorithms need to account for this kind of movement.. Image registration algorithms must also accommodate common "contaminants" such as blood, mucus and debris. There are several different types of data that need to be registered against the reference image. Multi-data registration of an acetowhite decay sequence against the reference image seems to be the easiest registration problem, as the reference image is one of the images in the sequence, and the acetowhite effect only changes slightly from image to image. However, it is a significantly more challenging task to register not only multi-data, but also multi-exam data, to the pixel level when images taken several months apart, as envisioned by some to detect lesion changes over time. In this case, the appearance of the cervix can change considerably over such a long timeframe. One approach to this problem is to register multi-exam data at a higher processing level, such as at the level of the diagnosed lesions. Currently, we consider this function to be performed outside the image analysis system using its output from the tissue diagnosis. The multi-data registration of images taken with no contrast agent, like an image taken prior to the acetic acid application, or different contrast agents, like Lugol's iodine, against the reference image might also be very challenging. The images look very different due to the different effects of the contrast agents, the fact that the cervix has been manipulated during the application of the contrast agent, and the fact that the instrument might have moved. An image taken prior to the acetic acid application, without the acetowhitening effect present, would be the best data source for the detection of blood vessel structures and keratosis. To work around the registration problem, we can use an image taken long time after the application of acetic acid instead where the acetowhite effect has faded considerably. For the multi-sensor registration of data acquired by different sensors, like 3D acquisition systems and fluorescence hyper-/multi-spectral imaging systems, a reflectance image that is spatially correlated to the sensor data needs to be provided so that this image can be registered against the reference image. This task is simplified by acquiring the data from different sensors close to the moment in time when the reference image is taken. We have previously described a means to embed (and thereby register) a reflectance image in fluorescence hyperspectral data, when the acquisition of the reflectance and fluorescence data cannot be interleaved[40].

### 2.3 Image Analysis System – Research Development Process

The quality of an image processing algorithm development depends highly on the quality of the available data sets. Unfortunately, existing cervical image databases share many shortcomings, including: glare, no camera calibration, no color calibration, only one image in a patient data set, no pathology ground truth for entire cervix with all different tissue classes – at most biopsies typically for high-grade lesions, and no ground truth feature annotations. Glare in the

images is an obstacle for image processing algorithms; because the affected pixels are saturated and therefore no longer contain any color information. Consequently, saturation introduces artifacts in feature extraction algorithms, such as acetowhite region or vessel detection. Camera calibration is crucial for the detection of blood vessel structures, as the scale in the imagery needs to be known. Color calibration is crucial for the color classification and detection of acetowhite regions. For the development of a multi-data, multi-contrast agents, multi-sensors fusion system, complete data sets per patient are required, data sets limited to one image per patient only allow for the development of feature extraction modules for that specific data source. Data sets from Loop Electrosurgical Excision Procedure (LEEP) patients are excellent for the development of the image analysis system as the specimens not only include high-grade dysplastic or cancerous tissue, like biopsies would, but also frequently include normal tissue and low-grade lesions. Therefore, LEEP patients provide a rich distribution and variety of all tissue classes and different colposcopic findings. Cervical imagery is very complex and cannot easily be interpreted by an algorithm developer; expert colposcopists and pathologists annotations are required to provide the ground truth for the development. Many cervical images have been acquired using a customized 35mm camera, the Cerviscope®, from National Testing Laboratories (NTL). Sufficient resolution should not be an issue in Cerviscope data sets, as the resolution can be defined in the picture scanning process. However, images taken from video colposcopes seem to have insufficient resolution to resolve fine blood vessel structures. Such shortcomings severely limit the utility of existing cervical image databases. Another reason for the paucity of high quality standardized imaging data and an impediment to develop CAD systems for colposcopy is that standard colposcopic examination involves visual inspection of the cervix by a colposcopist using an optical colposcope, but images of the cervix are not routinely taken. Furthermore, a potential source of digital imagery, digital colposcopy, is still in its infancy.

Another critical component of the CAD system development is the definition of the feature parameters (i.e. a quantitative expression of qualitative characteristics, such as the "straightness" of a border, or "whiteness" of an acetowhite lesion), the outputs of the feature extraction modules. The variation in feature parameters must be related to disease severity. In the case of colposcopic features, the parameters need to be defined and refined in collaboration with expert colposcopists, while trying to understand and simulate the experts' conscious and subconscious assessment. A systematic, iterative approach for defining and refining the feature parameters is made possible by defining the feature parameters at a level where it is meaningful to the colposcopist and by providing ground truth annotations for those defined feature parameters. It is possible that the feature parameters get refined or changed as algorithm development evolves. Should this occur, new annotations reflecting these changes need to be rendered. The definition of the feature parameters is a difficult exercise because colposcopists typically define colposcopic findings in qualitative terms, rather than quantitative terms that a computer can understand. One way to look at the feature parameters for the different colposcopic features is to look at the different colposcopic indices or assessments systems, like Coppleson [41,42], Stafl and Mattingly [43], Reid[44, 45], Kierkegaard[46], and Rubin and Barbo[47], that have been defined by colposcopists in an attempt to formalize colposcopy. Those assessment systems use qualitative terms to describe the observable phenomena of the colposcopic features and classify them by their implied severity (severity score, tissue classes). For our purposes, equivalent quantitative feature parameters need to be defined, so that a computer knows what to extract from the images to distinguish between different tissue classes. This is an iterative process whereby expert colposcopists will redefine the feature parameters and their influence on the tissue classification based on the output of the evolving image processing algorithms. The question that needs to be answered is: Does the computer, using the defined feature parameters, furnish the same tissue classifications as the expert colposcopist using his qualitative assessment? If not, the feature parameters may need to be refined.

STI Medical Systems has defined a set of parameters for the colposcopic features that are assessed by colposcopists. We are currently acquiring extensive multi-data, multi-contrast agent, and multi-sensor high-quality and calibrated data sets from LEEP patients with comprehensive annotations by expert colposcopists and pathologists. This detailed and extensive data resource will facilitate the development of a CAD system for colposcopy.

STI Medical Systems has developed an Algorithm Integration System (AIS) and an automated Performance Evaluation Engine (PEE). An illustration of the research development process using the AIS and the PEE is shown in figure 3. The AIS allows outputting all intermediate data calculated by every algorithm in the system. When executed over a large data set, the input and output data for entire data sets can be accessed for each individual algorithm. The PEE controls the AIS and evaluates each algorithm against its "ground truth" annotations and determines the overall performance of the system by providing a Receiver Operator Characteristic (ROC) curve. The AIS also provides data selection, algorithm selection and parameters variation to evaluate different system configurations. This platform enables the CAD system development effort to focus on developing and refining the image processing algorithms.

Typically, a hand-selected data set of a manageable size will be used in an algorithm development testbench. For algorithms that depend on results from other algorithms in the system, the AIS can provide the required intermediate data for the development data set. The development data set can be extended with specific data sets that cause problems when the algorithm is integrated into the AIS and gets evaluated against the complete training data set.

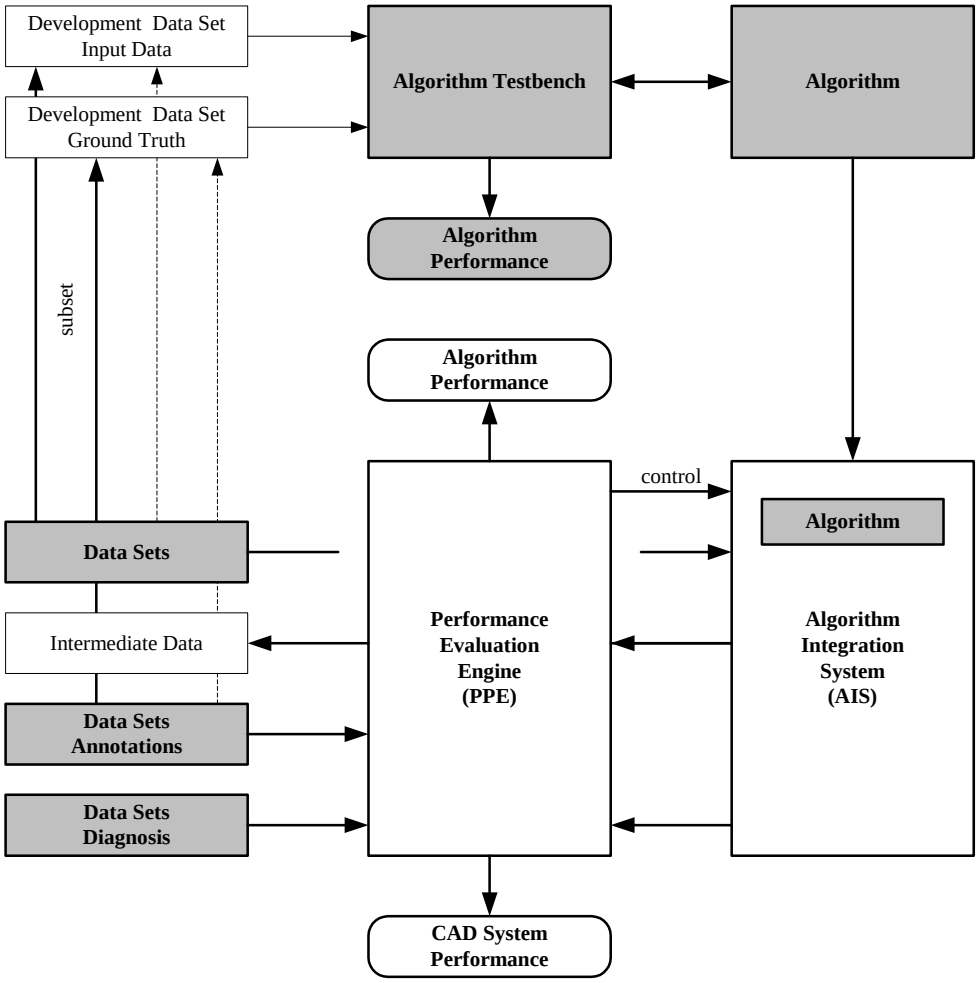


Figure 3: Illustration of the research development process for the image analysis system.

## 3. PRELIMINARY RESULTS

We conducted a technology exploration project for the development of a CAD system for colposcopy prototyping image processing algorithms for glare removal, anatomical feature detection, acetowhite region detection, and blood vessel mosaic and punctation structure detection using a RGB image data set from 111 human subjects participating in a clinical study of our HSDI™ instrument[48,49]. Given that the instrument design was intended primarily for hyperspectral fluorescence spectroscopic imaging, the RGB image was subject to some of the limitations previously outlined.

Although glare is undesirable in imagery used for image processing, it is a reality that must be managed in existing cervical image databases or when using an instrument that does not provide cross-polarized imagery. Two examples of our glare removal algorithm[50] are shown as part of figure 4. Colposcopists assess the color of the acetowhite regions. Unfortunately, most cervical imagery is not color calibrated, as is true for our HSDI data set, making the analysis of color very challenging. Therefore, we prototyped the detection of multi-level acetowhite regions on the basis of different intensity levels rather than color information[51]. The resulting defined acetowhite regions also serve as an input for lesion margin analysis (e.g. shape). The detection of acetowhite regions requires the knowledge of cervical anatomic features, like the cervix, columnar region and the os, to guide and adapt the processing. Examples of the anatomic feature detection and acetowhite region detection algorithms are shown as part of figure 4.

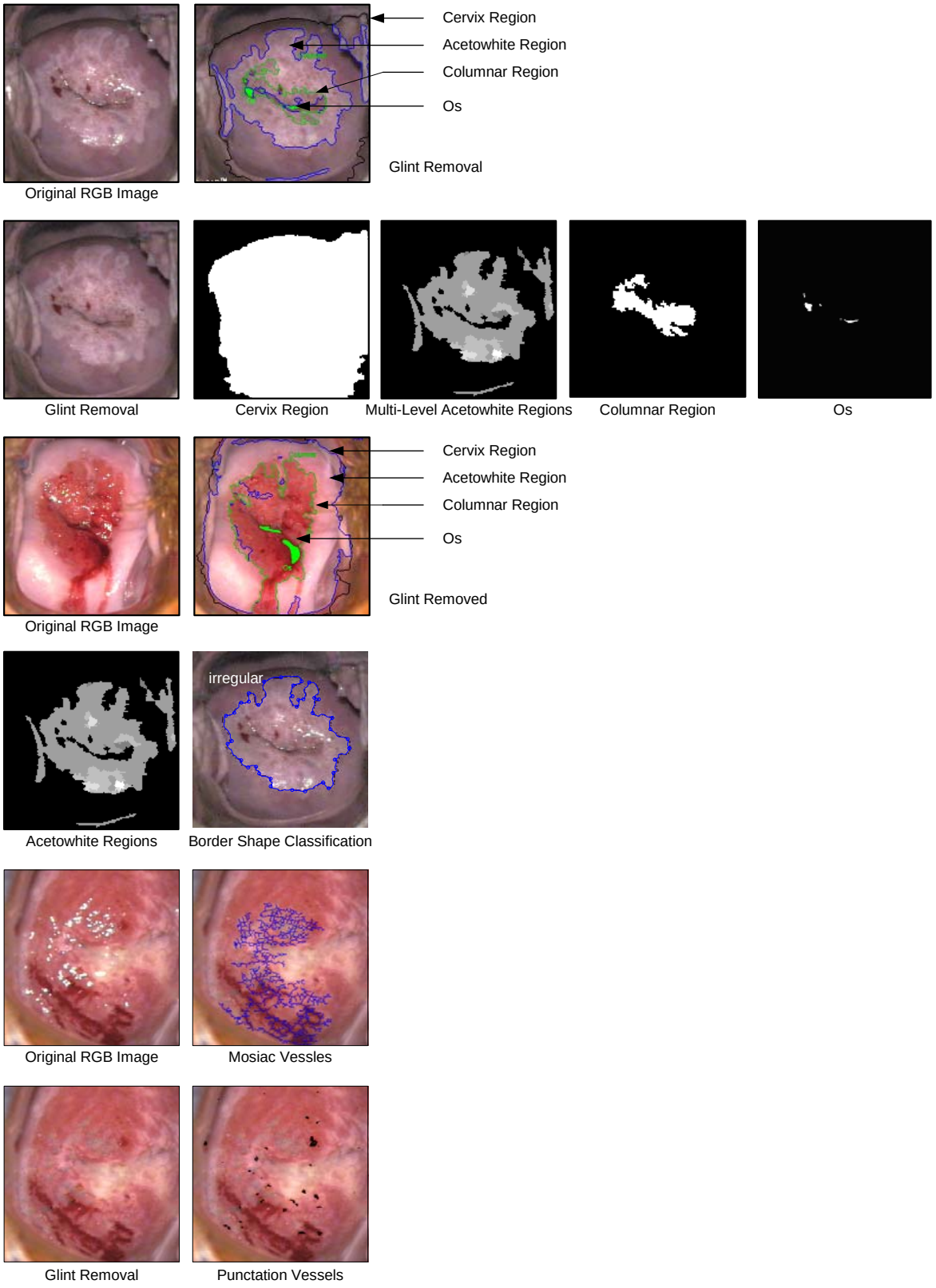


Figure 4: Preliminary results.

A lesion margin characteristic assessed by colposcopists is the smoothness of the lesion margin. We developed an algorithm prototype to classify every location of a lesion margin to be either smooth or irregular. As part of figure 4 we show an example of the shape classification algorithm output. We have also developed algorithm prototypes to detect mosaic and punctation vessel patterns. Examples are shown as part of figure 4. The examples also illustrate the challenges posed by variation in anatomy and pathology among patients, and by variation in lighting and instrument settings encountered in the imagery.

## 4. FUTURE WORK

Our goal is to improve women's health care by providing cost-effective CAD-based systems for cervical cancer screening and diagnosis. A CAD system for colposcopy, a "machine colposcopist expert", has the potential to revolutionize cervical cancer screening and diagnosis in developing as well as developed countries. CAD for colposcopy is based on the development of a very complex image analysis system that in order to achieve the highest possible performance requires the collaboration of experts in a wide variety of disciplines, like image registration, mathematic morphology, machine learning, 3D reconstruction, human factors, and databases to name just a few. Recognizing the complexity and the importance that the performance of such a system plays, we would like to introduce a new concept for the research and development of this complex image processing system, by extending our in-house research and development to an "industry guided open academic research collaboration". This is a similar progression, except applied to research, to what happened in the defense industry a couple of years ago when its role migrated more to that of a system integrator. We are looking for collaboration partners who want to give their research a special meaning by contributing their expertise to the research and development of a real product that fights one of the major problems in women's health care, cervical cancer. Note that CAD for colposcopy is a new field in medical imaging that presents great opportunities to apply existing state-of-the-art technologies to a new application. We provide an environment that allows experts in their respective fields to contribute directly to the development of this image analysis system. STI Medical Systems offers a vision for the overall system development, including an extensive, high-quality data set (unique in its kind) with the associated ground truth (feature parameters) annotations for algorithm development, an automated performance evaluation, the overall system integration, and the final product realization.

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