EMERGING TECHNOLOGIES, SIGNAL PROCEEING AND STATISTICAL METHODS FOR SCREENING OF CERVICAL CANCER *IN VIVO* - ARE THEY GOOD CANDIDATES FOR CERVICAL SCREENING?

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Abstract: The current cervical cancer screening test (the Pap smear) is a manual cytological procedure. This cytology test has various limitations and many errors. Excellent candidates for improving the performance of the cervical cancer screening procedure are electro-optical systems (EOSs), used for assessment of the cervical cancer precursors *in vivo*, such as digital spectroscopy, digital colposcopy and bioelectrical phenomena-based systems. These EOSs use the advantages of signal processing methods and can replace the qualitative assessments, with objective metrics. The EOSs can be used as an adjunct to the current screener or as a primary screener. We analyse and discuss the effectiveness of the signal processing and statistical methods for diagnosis of cervical cancer *in vivo*. This analysis is reinforced by the presentation of the scientific and clinical contributions of these methods in clinical practice. As a result of this analysis, we outline and discuss the *well-established estimates of the signal processing features* and the *ambiguous features*, that are used for classification of the cervical pre-cancer *in vivo*.

Keywords: computer-aided *in vivo* diagnosis, cervical cancer screening, image analysis, gynecological imaging, colposcopy,spectroscopy, signal processing methods,electro-optical systems,emerging technologies.

INTRODUCTION

Cervical cancer is the most frequent cancer for women under 35 years of age ([1] and [2]) and it has large impact on women's population worldwide. Approximate more than 500 000 new cases of cervical cancer are identified each year [2]. Cervical cancer results with high mortality in nearly 300 000 deaths annually, with 80% of them in developing countries [2]. The progress of the disease is relatively slow and it can be predicted. The development of the cancer precursors are modelled via stochastic modelling on a large scale of data [3]. It is well known, that in the early stages of the cancer precursors, the disease tends to regress naturally in 50% of the cases (on average), as presented in [4]. Therefore, as an effective measure to prevent mortality from the cervical cancer, the World Health Organization (WHO) proposed a cervical cancer screening procedure, based on the fact that the disease has a slow progression [3]. Currently, the only accepted cervical cancer screening procedure is the cytological screening test or the Papanicolau test (the "Pap smear test" - an established set of staining and fixation of cervical cells).

THE LIMITATIONS OF THE CURRENT CERVICAL CANCER SCREENING PROCEDURE

Cervical cancer screening is very important in the early stage of the disease, where only cancer precursors are detectable. Cytology screening is currently regarded as a mainstay of cervical cancer screening for many years, despite its errors and drawbacks. The cytology test involves taking cells from a transition zone between the ectocervix and the endocervix with a cytospatula/brush, followed by fixation. The Pap test's performance exhibits various limitations and they are well understood. One of the errors which has the largest impact is the "false negative," known to be between 20% to 40% as reported in [5] or between 6% to 55% as it was reported in [6]. Another error with a large impact on overall accuracy of the Pap-test is the initial or the "sampling" error, which is made, when the sample is taken from an inappropriate place on the ectocervix.

Alternative to the Pap smear test is the traditional colposcopy. Colposcopy is nearly a 70 year old technique for visualization of the cervix. Its sensitivity and specificity also ranges widely, and it has especially *low sensitivity* with ranging diagnostic accuracies. The ranges of colposcopy diagnosis for establishing the grade of the lesions are reported in [7], [8], [9] and the discrepancies are dependent either on the clinician's skills and experience and the stage of the lesion, which often can exhibit changes, not specific to the real grade of the lesion (taken as qualitatively visual assessment) as reported in [10] and [9]. Colposcopy's sensitivity ranges from 64 to 99% and its specificity ranges from 30 to 93%, when compared to the biopsy histology [11]. The positive predictive value of any colposcopic abnormality for any histological abnormality is reported to be very good, reaching 80% [11]. It is a recognized fact that the colposcopy, followed by biopsy is *the critical diagnostics procedure* for establishing the grade of abnormality, when the patient is referred by the cytological test as in [12] and elsewhere.

In addition, the possibilities of rapid computer automation, digital image analysis and digital storage capability are becoming unlimited. Therefore, we consider that a *quantitatively-supported diagnosis* using measurable features of cervical cancer precursors can be used as a support to the traditional cytology decision, where the

cervix is analyzed from a gross anatomical point of view, using signal processing methods, that can increase the specificity and sensitivity of the cervical cancer screening [13].

FEATURES FOR CANCER DETECTION RELATED TO THE ANATOMICAL FEATURES ON THE ECTOCERVIX

The features most commonly analyzed using signal processing methods are:

- the magnitude of the signal

- the local spatial or temporal relationship of the signal in a specific neighborhood

- the frequency content of the signal or the time-frequency decomposition of the signal

- the first, second and higher order statistics of the signal and the associated probability distribution models, when the signals are modelled as a random processes

The aim of these emerging technologies examining the ectocervix *in vivo* is to "translate" these methods into signal-based features, which can distinguish between a normality state and the disease state. Therefore, we need to relate the most prominent anatomical features of the cervical cancer precursors to the signal processing-based features or models. The problem with distinguishing cervical cancer precursors is that, they are too complex for stochastic modelling only, and no single colposcopic feature can be taken as complete evidence for presence of pre-malignancy or early invasive neoplasia. Any condition that causes an increased cellular division, an abnormal increased cellular metabolism or increased vascularization can produce atypical colposcopic finding in the cervical epithelium. Normal variants such as pregnancy, oral contraceptive pill usage, estrogen withdrawal and supplementation may produce atypical colposcopic features. Certain benign conditions such as squamous metaplasia, regeneration, repair; inflammation and infection may also produce dramatic colposcopic atypia. In general, as abnormal colposcopic patterns are, which are considered to be "translated" in technical terms are the following anatomical features:

- *acetowhite epithelium*, caused by increased cellular density or abnormal intracellular keratins. This feature can relate to color luminance and chromaticity values.

- a *punctation* or *mosaic pattern* - the "courser" the mosaic, the higher the lesion. These features can refer to texture patterns and frequency-space relations.

- *atypical and enlarged blood vessels*, often associated with growth of tumor(s).This feature can be related to a combination of edges, texture, color and frequency-space position.
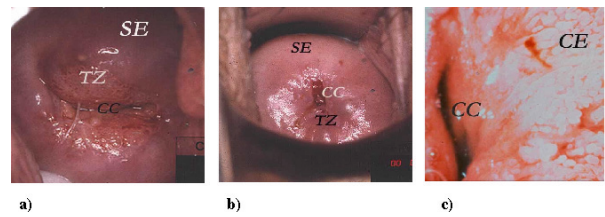

Fig. 1: a) Digitized cervicographs with visible transformation zone (TZ) and squamous epithelium (SE) of normal cervix. b) The cervical canal or os (CC) appears centrally and is surrounded by the TZ. c) The columnar epithelium (CE) has a prominent villous structure.

One of the most frequently used index by trained colposcopists as a subjective feature discrimination is the well known Reid's index [17]. The Reid's index has a system of weights (points) for features such as margins of lesions, color and texture in order to reinforce more objectiveness in the classification or diagnosis of stages of cervical abnormalities. One of the most significant landmarks on the ectocervix (Figure 1.a) is the transformation zone (TZ), where the cervical intraepithelial neoplasia (CIN) is found in more then 90% percent of cases [16].

For the last twenty years only a few research groups worked to establish an objective relationship between the anatomical features of the cervical precursors and their signal processing counterparts. These related signal processing features considered to be key factors for alternative cervical cancer diagnosis are:

- *Texture* is a valuable feature as it was discussed in [22] and it is used as diagnosis for CIN2 and CIN3 in the context of clinical testing. *Texture* was reported in [24], [29] and [30] as an important feature from image analysis point of view.

- The *relative magnitude of the green and blue* regions of the perceptual *color* in RGB-color images are reported to be the principal colors for normality, as it was discussed in [14]. The range of the visible color is concluded to be as a "per-spectral" response as it was reported in [22].

- The signal analysis, in *functional analysis* using the *magnitude-time reaction to acetic acid* (as topical application on the ectocervix) is an important physiological feature that can be measured via signal or image processing methods and it was reported in [20].

The above mentioned features for detection of cervical cancer *in vivo* are focal points for future research into alternative methods. These methods can work together with the current automated processing methods in cytology (while detecting cervical cancer precursors *in vitro*) or they can fully replace the current procedures.

Colposcopy and especially spectroscopy are examples of the EOSs, where they already have demonstrated
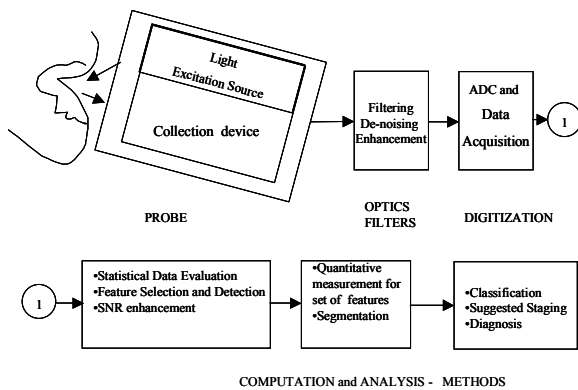
Light Excitation Source

Collection device

Filtering De-noising Enhancement

ADC and Data Acquisition

1

PROBE   OPTICS FILTERS   DIGITIZATION

1

•Statistical Data Evaluation
•Feature Selection and Detection
•SNR enhancement

•Quantitative measurement for set of features
•Segmentation

•Classification
•Suggested Staging
•Diagnosis

COMPUTATION and ANALYSIS - METHODS

Fig. 2: The main components of a digital electro-optical system for cervical cancer screening *in vivo*, illustrating the processes of data collection, pre-processing, data acquisition, post-processing, feature collection and quantitative evaluation, classification and computer-based support for diagnosis and staging of pre-cancer.

their clinical values for detection of cervical neoplasia as in [14], [15], [19], [20] and [21]. The "ideal" EOSs should "*combine screening, diagnosis and treatment in one visit* " from a patient [21]. The aim of achieving the multitasking of EOSs is still in the future, because their effectiveness should exceed the accuracy range of the previous screening tests, which should be confirmed by clinical tests in order to be accepted as a primary screener.

1 DATA ACQUISITION AND SIGNAL PROCESSING METHODS FOR DETECTION OF CERVICAL CANCER PRECURSORS *IN VIVO*

The process of tissue classification is based on acquiring data using EOSs, which on the other hand uses electro-magnetic radiation-specific processes for an interrogation of the ectocervix, followed by measurement of the cervical tissue response to it, as displayed in Figure 2. The differentiation among the types of EOSs depends only on the type of the device-specific processes, such as: broadband light, which is used in digital colposcopy system; narrowband light, used in spectroscopy systems; or electrical current(s), used in bioelectrical phenomena-based systems.

The data collection starts with obtaining the data as a result of the interaction of the cervix with electromagnetic radiation. This is followed by pre-processing (optical or analogue pre-filtering) of the signal, followed by digital acquisition using an Analog-to-Digital Convertor (ADC), which always requires smoothing and involves quantization of the data. The next step is the signal and image analysis.

The data analysis contains three steps (Figure 2). The initial step includes evaluation of the data, by examining the relevancy of the data for determining the stage of the cervical neoplasia. In this stage, the selection of the *essential features*it are emphasized and used for discrim-

ination of tissue types, such as excitation-emission pairs for tissue interrogation, types of anatomical patterns or relevant colors.

The second stage of the analysis is focused on estimation of values with relation to normal or abnormal tissues. These are the color and texture-related characteristics, and statistical evaluation of the regions of interest (ROI- see Figure 2).

The final goal is often assumed to be an accurate segmentation of the cervical image, where a particular area of clinical interest (neoplasia or TZ) is highlighted, followed by a suggestion for classification of the degree of SIL. Final segmentation of ROI in color colposcopy images, related to anatomical features of pre-cancer or TZ *have not been attempted before* (to the best of our knowledge), while a gray-scale differentiation of the TZ was achived using specific two-dimensional (2D) band-pass frequency-space methods in [31].

1.1 Multivariate Statistical Algorithms and Neural Nets in Digital Spectroscopy

Digital spectroscopy, used for cervical cancer detection utilizes only two of the spectroscopy techniques, based on non-coherent light sources. They are the *absorbtion* and the *scattering spectroscopy*, often used collectively, as in [26], [27], [15], [19] and [21]. The fluorescence spectroscopy is a technique in which the molecules from the tissue absorb certain wavelengths of light and re-emit longer wavelengths of light, yielding a characteristics of "fluorescence spectra." The scattering spectroscopy is a technique, in which the photons of different wavelengths are scattered differently by cells yielding "scattering spectra". It is well known that the *diseased* and the *normal tissues* have different absorptions and scattering properties when interrogated with a narrowband (visible or ultraviolet) light, as in [26] and [27].

A major advantage of digital spectroscopy is that a limited number of specific *excitation-emitting pairs* can be correlated to certain stages of the cervical disease, therefore, the specificity and the sensitivity results in improved discrimination performances, as reported in [14], [19] and [21].

One of the first significant results for the application of digital spectroscopy is the work reported in [14]. In these experiments, the optical spectroscopy *detects only the biochemical changes of the tissues*, without taking into account the two-dimensional spatial relationships of the data. The experiments in [14] utilizes a composite multivariate statistical algorithm (MSA), which proves for the first time the statistically significant separability of the optical characteristics of the SE and CE and squamous intraepithelial lesions (SIL). Also, it proves that an automatic separation of low grade (LG) and high grade (HG) stages of neoplasia is possible to be achieved via interrogation of the cervix with narrowband light of three wavelengths. The results obtained for this discrimination task yielded similar effectiveness, measured in paired specificity and sensitivity, when is was compared to the

same measures for the *visual impressions from experienced colposcopists*. The discrimination between the abnormal tissue and the normal one, using MSA, yielded 20% improvement in specificity, but had 10% less sensitivity, when compared to *the visual impressions from experienced colposcopists*.

Further, K. Tumer et al. [19] performed experiments with neural networks (NN), using multilayered perceptrons (MLPs) and a NN with radial basis functions (RBF). As a result, the RBF-based neural network yielded reduced variability for its classification accuracy and demonstrated an improved sensitivity, when compared to the automatic methods of the MSA and the MLPs. In comparison with the *expert-based Pap smear test* and the *expert-based colposcopy tests*, the RBFs outperformed both of them in accuracy in terms of sensitivity. The RBFs outperformed the colposcopy in its specificity.

Both methods - the MLPs and the RBFs types of neural networks exhibits some drawbacks in their design and in their method of implementation. The MLP design has a drawback, which is associated with an "ill-posed" problem, because of the interdependency among the spectral cervical data, when the *complete data* set has been used. An additional drawback of the RBF neural network algorithm is in the initial step of the network training, when an "a-priori" knowledge, established by "ad hoc" techniques was used to initialize the weights, using a portion of the weights with pre-defined values from an unsupervised clustering scheme - the "K-means" algorithm.

The digital spectroscopy and digital colposcopy begin to merge and the smoothing between the borders between the two methods was demonstrated by D. Ferris et al. in [15]. This experimental work uses a multispectral fluorescence map of the ectocervix and a collection of data both from the entire cervix and also from annotated diseased quadrants of the cervix. It reports the establishment of the mean values and the variations of the LG SIL and HG SIL and represents measures for normal cervical tissue. Statistical analysis (MSA) was also applied for the discrimination of CIN 1 and CIN 2. The spectroscopic and the cytologic results were compared with those of biopsy and colposcopy using receiver operating curves (ROC) analysis of the device Pap smear. Analysis on the results of the data taken from the entire ectocervix and analysis on the data taken form diseased quadrants from the ectocervix were performed independently. The results of these analysis were objectively measured via ROC performance and subsequently compared the same way to the performance of the expert Pap smear tests results both for the CIN 1 and CIN 2 threshold levels. The Multimodal Hyperspectral Imaging (MHI) system outperformed the ROC of the Pap smear in both analyzes. The performance of the MHI for the quadrant based discrimination of CIN 2 reached 100% Optimized sensitivity and 95 % optimized specificity (the optimization method is described in more details in the paper).

1.2 Statistical Methods, Multiscale Image Analysis and Image Models in Digital Colposcopy

The excitation source in digital colposcopy is a white broadband, non-coherent light, sourced by a halogen lamp followed by an optical guide (fibre optics) to the probe. The total cervical tissue reflectance is detected by a light-sensitive device, such as charge-coupled devices (CCD), and it is then acquired as an image(Figure 3).

The tissue-light interaction with different types of tissues (e.g. SE and CE) is expressed in different reflectances and it is dependent on the tissue and the cells' proliferative status [20] and [28]. For example, the light-tissue interaction of the CE as a monolayer yields a brighter red appearance, because of the close proximity of the underlying vascular plexus, compared to the SE which is a multilayer and its appearance is pinkish and more smoother.

The cervical image formation is based on the reflectance characteristics of the tissue excitation-emission light and digital colposcopy's electronic sensor, as illustrated on Figure 3. The incident light with spectral power density $L_c(x, y)$ of the illuminant appears as a function of the spatial position with spatial coordinates (x, y). The illumination reflectance of the ectocervix $\Xi_c(x, y)$ is formed by the incident light c and the ectocervix tissue reflectance on the same spatial position.

The resultant radiance of the ectocervix or power spectral density at the surface of the optics is a function of the scene reflectance $\Xi_c(x, y)$ and the spectral density of the illuminant $L_c(x, y)$. The relationship between the scene reflectance and the illuminance yields the scene radiance $r_c(x, y)$:

$$r_c(x, y) = \Xi_c(x, y).L_c(x, y). \qquad (1)$$

The image irradiance $u_c(x, y)$, which reaches the CCD, or the photodetector is:

$$u_c(x,y) = \int\int h_{\mathbf{t},c}(x - t_1)h_{\mathbf{t},c}(y - t_2)r_c(x,y)dt_1dt_2 \qquad (2)$$

where c represents broadband continuum spectrum of visible light and the $h_{\mathbf{t},c}$ is the impulse response of the optics and the equation depicts the spatial and spectral relationship and interdependency of the formed image. In general, this formula can be applied to form a digital spectroscopy image as well, when the broadband light c is replaced with a narrowband light with certain bandwidth and wavelength λ.

The equation (2) describes the transfromation of the scene radiance from the cervix to the image irradiance, which reaches the data acquisition device.One of the requirements for a good image formation is that, the scene radiance $r_c(x, y)$ must be kept relatively constant, which is ensured by the calibration of the illumination source.

The illumination model of the cervix is a non-planar illumination model, because the cervix is placed in a cavity which is one of the most elastic and non-rigid organs in human body. In order to model the illumination con-
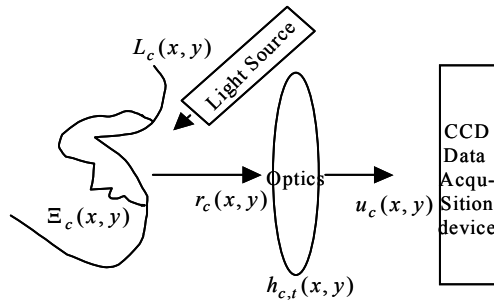
Fig. 3: An illumination model of cervical image formation in digital colposcopy. The incident source is a broadband light.

tent of the cervical image one has to apply an appropriate three dimensional (3D) model of the anatomy, that surrounds the ectocervix. A possible idealized model of the 3D environment of the ectocervix is a *convex-conical elongated cavity.*

There are several illumination problems or artifacts, which makes the digital image analysis of these images a challenge. The cavity-based image is one of them, where the central portion of the image appears to be less illuminated, when compared with the stronger illumination of the SE, that belongs to the vaginal walls. Another illumination "artefact" of the colposcopy image is the "speckles" or the "bursts" of light, named "specular reflection" (SR), caused by the strong reflection of the light from the moist cervix, as the cervix uteri is an internal organ.

A particular advantage of digital colposcopy image is *its familiarity* among the medical community, which is perceptively similar to the conventional colposcopy image. This colposcopy image has been known in gynecology for more than 70 years, but with the advances in digital technology, the diagnostic accuracy can be improved, so "*the experienced colposcopist can benefit from computerized support*" and "*. . . . eventually access to distant consultations.*" as in [12]. These manipulation on the colposcopy images can be grouped (as placed in the ascending order of complexity and expert knowledge for the processes) in the following categories:

- *Archiving and storage for follow up and medical records*

- *Pre-processing and Image enhancement:* This type of process includes noise removal and perceptual image enhancement.

- *Feature Evaluation and Quantitative Measurement:* These include establishment and selection of set of features for discrimination of tissues with different stages of neoplasia across the colposcopy image. Related features are: local color chromaticity and texture.

- *Region Selection and Segmentation:* The most complex method is the creation of an automated algorithm for region selection and segmentation of

the region of interest (ROI). The ROI can be assumed to be either the TZ, condyloma (part of SIL medical feature), a region of increased vascularity, a region of tumor or cysts, region of LG or HG SIL. Often the selection of the ROI depends on the use of digital colposcopy system if it is used as a primary screener, biopsy site adjunct or adjunct to Pap smear test.

One of the first works in digital analysis on these features was presented in 1990 in [17]. In this work E. Craine et al. reported that *the color is not a perceptually significant diagnostic* feature in digital colposcopy. Also, they stated that the 8 bit–depth of the image and close to half megapixel spatial resolution is the *minimum requirement for quality diagnosis* using digitized colposcopy images (regarding perceptual evaluation), which nowadays is considered as quite low resolution.

Ten years later, B. Pogue et al. [22] studied the color again as a discrimination feature for differentiation between HG SIL and sqaumous metaplasia, using pixelwise measurements of chromaticity. This study concluded that *the color has no statistical significance* in the above mentioned discrimination task. Several features related to texture were studied, but only the Euler number measure was found to be a statistically significant measure for HG SIL in the sqaumous metaplasia tissue discrimination task.

Ji et al. explored and studied the features of 6 textural patterns, related to HG SIL and accumulated a 24-dimensional feature, each one forming an objective measure for the CIN1 and CIN 2 related texture patterns. Each texture pattern represented a specific characteristic of a particular neoplasia. It was reported that the most significant features for discrimination were the densities of the line intersections in thresholded images, the entropies and the local statistical moments (the zeroth to the third moment). Based on these multidimensional features, a classifier was built, which performed with close to 95 percent accuracy of the classification [24].

The features of the TZ was studied in [30] and it was reported that there is a significant difference in the the power spectral density on the textured TZ mid frequency bands in the gray scale images, established via the Short Time Fourier Transform method (STFT). Also, in this work a possibility was discussed for creation a visual reference map to the ROI, based on the Power Spectral Density content of the ROI[29] . Similar discrimination was achieved using specific bandpass filters, known as Gabor filters, described in [31].

1.3 Methods used for Bioelectrical Phenomena based systems

Studies on a technique that aims differentiation between malignant and normal cervical tissues, using application of low level electric current was initiated by Langman and Burr in 1947 [32]. Two years later, in [33] they reported that there is a possibility for successful differentiation of the cervical malignant tissue form the normal one, using the method of bioelectric phenomena for examina-

tion of the ectocervix *in vivo*.

A digital method, performed by a specific probe, based on the combination of the so described phenomena is reported in [34] and [35]. The Polarprobe methods uses both electrical (low voltage) simulators combined with separate optical stimulator and optical receiver. The electrical stimulation of the cervical tissue is achieved simultaneously via light sensitive electrodes, placed on the surface of the ectocervix, from the area, where the sample is taken. A series of low level voltage (1.25 V pulses of 260 microseconds duration) are applied. The response of the tissue is measured and recorded via computer.

It was reported that the response curves have different decays in malignant and normal tissues, according to [33], because of the differences in malignant and the normal tissues' resistances. A discrimination is achieved as the responses from a portion of cervix of a patient is compared to the well established reference of previously "recorded" responses, taken from tissues of *healthy cervices only*. Thus, the examined area of the cervix can be classified via statistical analysis to determine a decision on the degree of abnormality of the cervix (if any).

The additional spectroscopic stimulation is added to the current probe to reduce the ambiguities and the variability of the data [35]. The optical stimulation uses a bandlimited light source, counterparted with a photodiode detector on the tip of the probe. The combination of the tissue responses from the electrical and the optical stimuli taken from the individual probe and applied on a patient, are led into computer via intelligent interface. The data is analyzed via discriminant multivariate analysis, using first and second order statistics. The analysis uses a "look-up table" for normal and abnormal cases, gathered in a large studies as "*a-priori*" reference.

2 DISCUSSION

Digital spectroscopy and colposcopy and the signal processing methods associated with them are a valuable approach for prevention of cervical cancer, because they have shown improved performances in paired sensitivity and specificity, when compared with the cytology test and traditional colposcopy. Statistical and signal processing methods as MSA, band-pass filtering and texture analysis have also proven to be successful in establishing important features of cervical cancer precursors. Although these methods are still in a research state, they exhibit various advantages for improved performance in prevention of cervical cancer. They have the benefits of non-invasiveness, recordability and repeatability within a short time frame. In addition, we studied the previous work in this direction and we know that there are certain features in digital colposcopy and spectroscopy, which are well established. For example, one of them is the excitation-emission pairs for interrogation of the ectocervix (measured features) that achieve a good differentiation between the CE from the SE and separation from HG lesions and LG lesions and they are discussed in [14].

The success of the experiments in [21], using RBF, that outperformed the traditional colposcopy and cytology results, suggest that one possible probability distribution model for the narrowband data from the excitation-emission pairs is the Normal distribution or Gaussian distribution model. For future, the underlying model can be explored further, where a spatial interaction using image analysis can also be involved. This again means a merge of spectroscopy with colposcopy.

Digital spectroscopy has benefits of using its specificity. The specificity of spectroscopy added to the merits of digital colposcopy can measure the objective features of cervical cancer precursors.

Contrary to the visual impressions from the traditional colposcopy, we can state, that the *contribution of the color* as a feature in the image analysis *is unclear*.

Other features, such as the margins of the TZ, the vascular pattern of the diseased tissue and the normal cervix are still not fully defined by a specific set of measurable values possibly derived via statistical methods or signal processing methods. In addition to this, only one research group performed a complex segmentation algorithm, based on the combination of the already discussed features as described in [15]. They used an universal software package, which is based on Human Visual System (HVS) performance for detection of precursor, but they did not evaluate the measurable content of the cancer features via analysis.

The usage of these emerging technologies, with the associate signal processing methods for cervical cancer screening procedures *in vivo* can be placed in the following categories. They can be used as:

Adjunct to the Pap Smear test in parallel: It is already known that the cytology tests, combined with the colposcopy has proven to have an increased value in diagnostic sensitivity and specificity, which was discussed in [13]. The usage of the digital EOSs can be adjunct (in parallel) to Pap smear-based screening to increase its overall sensitivity. Introduction of a digital colposcopy during cytology screening, for example, should be in the early stages of the screening process. Thus, the EOS as a parallel test can lead to a decrease of "false negatives," which subsequently will result in increased cost-effectiveness, due to the slow disease progression. Metrics of salient features, taken from abnormal and normal ectocervices can be used as a reference bank such as the textures' measures, related to the CIN2 and CIN3 grades as measured in [24], the measures of the time-intensity relations of cervical tissue responses after acetic acid application as in [22] and the healthy ranges of the scattered reflection in narrowband light for the SE and CE, as measured using spectroscopy systems in [14].

Triage Scenarios: Thus, the digital EOSs can be used also in "triage" cases, where the images or the data from a patient can be used after a positive Pap smear test for determination of further management, treatment or continued colposcopy/ cytology surveillance. The EOSs can offer digital storage of the image or telemedical facilities in case of remote location of the patient, for example in

the Aboriginal communities in Australia.

Assist in Biopsy: The next possible usage is to assist in localizations of biopsy in a hospital environment, where an automatic computer-aid can lead the medical officer, which can record the biopsy site for further examination.

Primary Screening: The EOSs can be a primary cervical cancer screener. This can eliminate some of the problems within developing countries, such as:

- the physical storage of the samples and immediate transportation of the samples

- the proper fixation and proceedings of the cells from cervix in a well- equipped laboratory conditions (due to lack of resources in developing countries, where infrastructure and facilities for these procedures are expensive or limited).

Currently, the knowledge in the direction of the emerging technologies, which are based on EOSs is incomplete and insufficient to fully replace the cervical cancer screener and any achievement in this field requires subsequently large scale clinical testing.

3 CONCLUSIONS

A limited number of research groups are involved in the search for alternatives to the cytology test for cervical cancer screening *in vitro,* due to various reasons discussed in the beginning of this paper. The major contributors for *in vivo* assessment of cervical cancer are digital colposcopy and digital spectroscopy and partially the bioelectrical phenomena-based systems, combined with appropriate signal and statistical processing methods.

Digital spectroscopy and colposcopy have already exhibited proven benefits for the medical practitioners/clinicians, but there is no published data and no large scale comparative studies on the accuracy and effectiveness of their paired sensitivity and specificity. This is because, the current EOSs for *in vivo* cervical cancer testing are still considered as emerging technologies and they are overshadowed by the well-established cytology testing technology, which is cheaper and has been around for about 50 years.

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