

Automatic Classification of Cervical Cell Patches based on Non-geometric Characteristics

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Abstract: This work presents a proposal for an efficient classification of cervical cells based on non-geometric characteristics extracted from nuclear regions of interested. This approach is based on the hypothesis that the nuclei store much of the information about the lesions in addition to their areas being more visible even with a high level of celular overlap, a common fact in the Pap smears images. Classification systems were used in two and three classes for a set of real images of the cervix from a supervised learning method. The results demonstrate high classification performance and high efficiency for applicability in realistic environments, both computational and biological.

1 INTRODUCTION

With approximately 530,000 new cases per year worldwide, cervical cancer is the third most frequent tumor among the female population, behind breast and colorectal cancer. It is responsible for 265,000 deaths per year, being the fourth most frequent cause of cancer death in women (World Health Organization, 2018). However, this neoplasm has a slow development, which increases the chance of cure when the precursor lesions are identified early by cytopathological examination.

The most eminent screening test for the detection of cervical cancer in its early stages is Pap smears, introduced by George Papanicolaou. Its polarization was due to its low cost and easy access in developing countries, as well as its great capacity for differentiating the types of lesions found, which is extremely important for the correct diagnosis. Although this technique is widely used, it presents significant false negative, false positive and unsatisfactory results, with causes attributed to different stages of the process. Therefore, in Brazil, it is recommended that cytopathology laboratories implement a quality monitoring with the objective of improving the performance of the results obtained in this exam.

Based on this objective, new technologies such as

cytology in liquid basis, molecular biology and the semi-automation of the reading of the cytopathological examination have been implemented in the health market. The benefits of liquid cytology do not justify its high cost, which makes it inaccessible to large laboratories, including those that serve the Unified Health System in Brazil (SUS). Efficient diagnosis from molecular biology is only really effective when jointly used in with the cytopathological examination. Thus, conventional cytology is the technique chosen to perform the Pap test, not excluding the need for association with other strategies to improve the quality of cervical cancer screening.

The cytopathological interpretation is performed by qualified specialists and is based on the visual recognition, in optical microscope, of the alterations of the nucleus, cytoplasm, and other celular information present in the smears. These changes are still associated with clinical opinions. After the application of this screening technique, enlarged images containing the cellular characteristics are obtained by means of a photocopy of the Pap smears. However, due to the high complexity of the fields analyzed microscopically and consequently of the images obtained, this process is configured as slow, exhaustive and error-prone.

In images containing cells overlap and clusters,

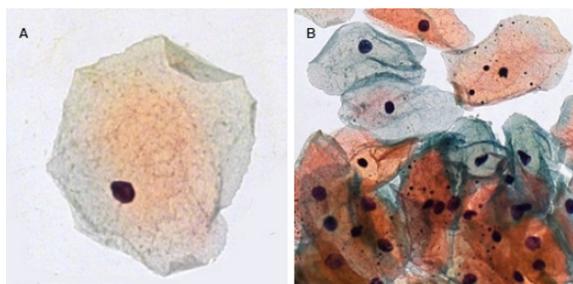


Figure 1: Isolated (A) and overlapping cells (B) present on Pap smears. Note that the area of the cytoplasm is clearly visible in A while in B the exact edges of the cytoplasm areas are ambiguous.

detection of the cytoplasmic boundary is a difficult problem as exemplified in Figure 1 and to date there are no efficient methods capable of performing this automatically. However, the detection and segmentation of nuclei in images containing certain degree of cells overlap and clusters have been successfully addressed by several studies (Plissiti et al., 2011; Plissiti et al., 2011; Sobrevilla et al., 2010). The results, which mostly use images from the cytopathological examination of the liquid-based cytology, indicate that the nuclear characteristics may be sufficient to differentiate lesions present in cervical images. Regarding classification of lesions, some authors also good results with nuclei but using isolated cells (Lorenzo-Ginori et al., 2013).

Based on the above, it is noted that the measures adopted to guarantee the quality of the cytological examination are still insufficient. Therefore, based on the viability provided by the use of computational methods to improve this process, it is evident the need to investigate technological strategies that seek to improve health services in the scenario of screening for this neoplasm. In this sense, the aim of this work is to perform the classification of real Pap smears images by extracting non-geometric features present in cell nuclei, excluding the use of segmentation techniques or neural networks. The idea is to generate something similar to the screening done by the pathologist on the slides, i.e., to evaluate parts of an image and to identify regions with lesions without the cellular individualization. From this, we intend to investigate the stiffness necessary for the proposed system to provide efficient aid for diagnosis in a biological and medicinal environment.

This paper is organized as follows, Section 2 presents literature based on cervical cell classification. Section 3 details the used methodology describing all its steps. The results are discussed in Section 4. The conclusions are exposed in Section 5. And then, the further works are introduced in Section 6.

2 RELATED WORKS

The literature presents some techniques for the classification of cervical cellular microscopy images. The most widely used public image base among them is Herlev, which contains 917 Pap Smears images and is provided by the University Hospital of Herlev, Denmark (Jantzen et al., 2005). Its data set consists of 7 classes of cervical cytology images with single cell, being: superficial squamous, squamous intermediate, columnar, moderate dysplasia, moderate dysplasia, severe dysplasia and carcinoma in situ. Some works that are based on this collection of images are mentioned below:

Mariarputham and Stephen (2015) presents a cell classification system, based on texture information extracted from the nucleus and cytoplasm, using neural networks and supervised learning methods. It is emphasized that there is no unique set of characteristics capable of providing efficient diagnostics for any and all classes of a proposed classification system. In addition, SVM algorithm is presented as an efficient solution for classification.

Lakshmi and Krishnaveni (2014) describes a method for automated extraction of multiple characteristics of nuclei and cytoplasm, using a parametric probability density function associated with Maximization Expectation algorithm and clustering. Their results confirm the efficiency of the proposed system to differentiate lesions between low grade (LSIL) and high grade (HSIL).

Singh et al. (2015) proposes a classification technique using Random Forest. For this, it considers the texture characteristics of the nucleus and cytoplasm, investigates the efficiency of these characteristics for the recognition of normal and altered cells and presents metrics to measure the efficiency of the system.

Walker et al. (1994) despite using his own database, presents preliminary results for the classification of cell nuclei using textural features of the Gray Level Co-Occurrence Matrix (GLCM) and linear discriminant analysis to reduce the dimensionality of the characteristics extracted. His studies demonstrate that the texture characteristics extracted from GLCM provide efficient means for discriminating normal and altered cervical cells.

All the previously mentioned works use the extraction of texture characteristics associated with the extraction of geometric characteristics and a preprocessing that contains cellular segmentation. In a different way, Plissiti and Nikou (2012) presents a framework for efficient classification of cervical cells into normal and altered categories based exclusively

on the extraction of texture characteristics from the core area. Non-supervised classifiers and non-linear clustering techniques are used, as well as genetic algorithms for resource selection. Also examined is the efficiency of nonlinear dimensionality reduction schemes to produce an accurate representation of the multiple cell characteristics. This provides results that allow to analyze the efficiency of systems based on the exclusive extraction of characteristics coming from the nuclei when compared to the systems that use extraction of characteristics of the complete cell.

In the state of the art, there are methods that employ Deep Learning, as in Arajo et al. (2019). This paper presents a computational tool for cytological analysis using Deep Learning (CNN) techniques for cell segmentation in conventional Pap smears images containing a high degree of cell overlap. Its results demonstrate high efficiency for the proposed approach, as well as robustness for the presence and interference of neutrophils, noises and other artifacts very common in Pap smears that compromise automated classification. Despite the effectiveness, techniques that use Deep Learning and neural networks, present some dysfunctions: they need a large number of images for training; present high computational cost; and, mainly, do not allow the identification of the attributes used and their respective amounts. Something that makes it impossible to correlate the computational technique with the biological context and thus leads us to seek alternative solutions, as well as the system presented here.

Differently from the techniques mentioned above, our proposal uses a database of real cervical cytology images with multiple cells obtained from pap smears images. In addition, the segmentation and extraction of geometric characteristics are not used, in order to allow the classification of images where it is not possible to identify cytoplasmic and nuclear boundaries.

3 METHODOLOGY

This section describes the stages of development of this article. Section 3.1 specifies the image database used. Section 3.2 describes the pre-processing step to which the images are submitted. Section 3.3 presents the textural features extracted from the previously selected set of images. Section 3.4 introduces the supervised learning method used for classification, as well as describing the system of class division chosen for this system. Finally, Section 3.5 describes the process of analyzing the results obtained on the basis of statistical metrics. The proposed system architecture is represented in Figure 2.

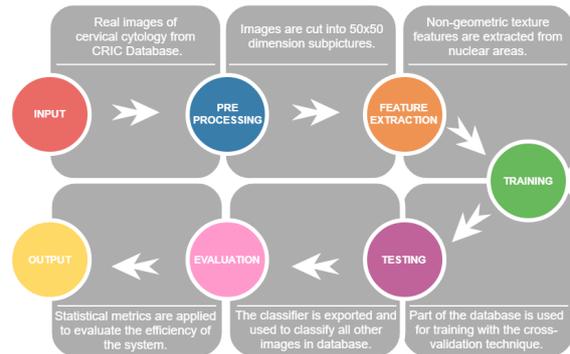


Figure 2: Architecture of the proposed system.

3.1 Database

All images used were obtained from the the Brazilian Health System (Arajo et al., 2019). This database consists of 11473 cellular nuclei obtained from 400 1392x1040 images. All of them are scanned from the use of an optical microscope associated with a 40x magnification camera and individually represent segments of the slides that may have different numbers and cell types. This private database is a product of a multidisciplinary team of researchers in computer science and biology who provides a collection of real images of human cervical cytology smears representing a range of different cervical cell lesions interpreted by independent cytopathologists, which are listed below:

1. Normal cells;
2. Atypical squamous cells of undetermined significance (ASC-US);
3. Atypical squamous cells, cannot exclude a high-grade lesion (ASC-H);
4. Low-grade squamous intraepithelial lesion (LSIL);
5. High-grade squamous intraepithelial lesion (HSIL);
6. Scamous cell carcinoma (SCC);

3.2 Pre-processing and Training Database

As mentioned, since we do not use nuclei or cytoplasm segmentation, all parts of the image are used for the training and construction of the classification model. In this preprocessing step the database images are cut out in 50x50 pixels throughout their size, as exemplified in Figure 3.

These cuts are made in an orderly manner from left to right and top to bottom. However, it is arbitrary in relation to the exact position of the cells and

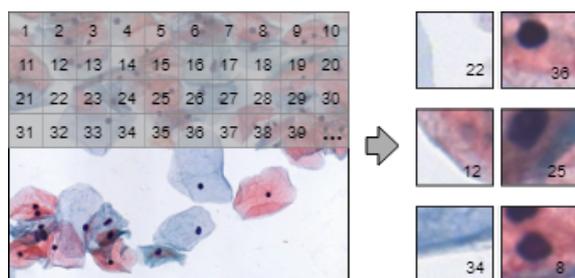


Figure 3: Example of preprocessing step. The numbering represented in this image is unrealistic only for demonstration purposes, as well as the size of the cutouts.

nuclei, as illustrated in Figure 3. The definition of the information for the training is very important because they accurately compose the set of information regarding each lesion and lead to a good accuracy in the result. Accordingly, the pre-processing step results in reduced-size images which:

- They comprise sufficient nuclear information to be encompassed by any of the classes of lesions described below;
- They comprise insufficient nuclear fragments to be considered within some class of lesions and are thus categorized as noises;
- They comprise cell overlaps and are only enclosed within injury classes if they include at least 60% of the nuclear information of any of the cells involved;
- They do not comprise any nuclear information and therefore are also included in the noise category;

To verify if there is enough information in a clipping to match one of the nuclear classes of the classification system, the data provided by the database is used in the training step regarding the location of the nuclei within the images. Based on the positions of the nuclei, a comparison is made between cut-outs made from the central positions of all nuclei present in the image and the arbitrary cut-off performed by the pre-processing at that time, as illustrated by Figure 4. In addition, this cut-out around the central position (x, y) of an image core is used as input to the training and testing step, along with the arbitrary cut-offs obtained, in order to allow the classifier to also learn how to categorize cores as a whole.

As a consequence, the overlap value of these images is obtained, which, if having a value equal to zero, is indicated as position cutouts that do not correspond to image cores. If a value greater than zero is detected, the juxtaposition of the cutouts is detected and in the specific case of having a value greater than or equal to 60% of the area of the cut, it is determined



Figure 4: Example of a comparison between cuts, where: (A) represents the cut form a core central position; (B) represents the cut being performed by a preprocessing at that instant (C) represents the intersection between two cuts, which, in this case, have higher or equal value to 60% of their individual areas.

that it has enough information to be framed as a cell nucleus region and is identified as one of the classes of lesions, different from the noises.

The proposed trimming creates a new unit delimited in the region near the cellular nucleus, with less information, alternatively for the segmentation that is not used. The size of this cut was empirically defined from a series of tests and parameter adjustments where the best results were presented by the images in the dimension chosen here. All cutouts obtained from pre-processing are used as input to the sorting step. It should be noted that the classification step does not use this information regarding the position of the nucleus, but rather a comparison between the attributes of a region of the image with those used in the training.

3.3 Feature Extraction

From the study presented in Section 2, a subset of characteristics with a high discriminative capacity to be extracted from the set of cutouts defined as training was defined. All selected features refer to information related to the texture of the images and do not undergo segmentation preprocessing to be obtained due to the research objective. Are they:

- Average Intensity;
- Maximum Intensity Value;
- Minimum Intensity Value;
- Local Binary Pattern (LBP);
- Histogram of Oriented Gradients (HOG);
- Gray-Level Co-Occurrence Matrix (GLCM);
- 7 Hu Moments;
- Haralick's Texture Features (Haralick, 1979):
 - Angular Second Moment (Energy);
 - Contrast;
 - Correlation;
 - Variance;
 - Entropy;

- Maximal Correlation Coefficient;
- Inverse Difference Moment (Homogeneity);
- Sum Average, Sum Variance and Sum Entropy;
- Difference Variance and Difference Entropy;
- Information Measure of Correlation I and II.

3.4 Classification and Testing

The manual classification of the entire dataset of the base used was done by specialists of the area and was used as terrestrial truth. For the classification proposed here, two and three classes systems were used, shown in Figure 5 and described as follows:

- **2Class:** In this system, the lesions are grouped into two classes. In the first class only normal cells and in the second lesions ASC-US, ASC-H, LSIL, HSIL and SCC, forming the class of altered cells. The classification using this system aims to classify images only from the presence or absence of lesion.
- **3Class:** In this system, the lesions are grouped into three classes. In the first class, there are only normal cells. In the second, there are the lesions of light severity ASC-US and LSIL. And finally, in the third class, there are the lesions of high ASC-H, HSIL and SCC. Throughout the remainder of this document, the second class is referred to as mild injuries and the third class is referred to as serious injuries. This proposal aims to classify images based on the diagnosis and treatment given to the patients detected with these groups of lesions. Where: patients without lesion (normal class) after receiving two negative results of the examination, only need to repeat it after 3 years; Patients with light-class lesions need follow-up and should repeat the exam within 6 months or 1 year; patients with severe class injuries require special care and must perform colposcopy and/or biopsy.

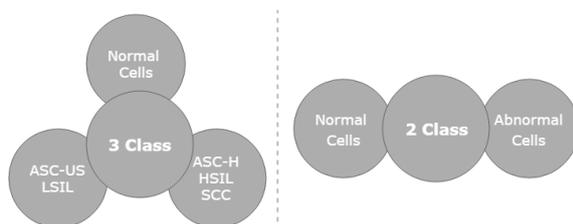


Figure 5: Classification system used.

In both systems a further class is included that includes cutouts that do not have relevant classification information, such as blade bottoms or other non-nuclear elements. The purpose of this class is to allow

the classifier to learn to ignore information that is not important for cell sorting. This class will be referred to as noises in the remainder of this document.

For the classification was used the algorithm Support Vector Machine (Bishop, 2006). This method of supervised learning is a formally discriminative classifier that identifies and constructs a model with a class separation hyper plane. It receives as input a set of data and predicts, for each given input, which of the possible classes the input is part of, making it a non-probabilistic linear classifier. In the training stage, all the image cutouts defined in Section 3.2 were used. In addition, K-Fold cross validation is applied to ensure the generality and impartiality of the results obtained, using $K=10\%$.

3.5 Evaluation

For the evaluation of the results and classification performance, some metrics were extracted. First, for the calculation of statistical measures, the number of true positives (TP), which refer to altered nuclei correctly classified as altered, true negatives (TN), which refer to normal nuclei correctly classified as normal, false positives (FP), which refer to normal nuclei erroneously classified as altered and false negatives (FN), which refer to altered nuclei erroneously classified as normal. The statistical measures are described below:

3.5.1 Precision

Is the percentage of data that is correctly classified for the class to which it truly belongs, i.e. normal as a normal class or altered as altered class in the 2-class problem. In the 3-class problem, it is applied directly to the correctly classified data in the normal classes, mild lesions and severe lesions. Precision is defined as:

$$Precision = \frac{TP + TN}{TP + FN + TN + FP} \quad (1)$$

3.5.2 Sensitivity

Is the percentage of changed data that is correctly classified as changed (true positive). The sensitivity is defined as:

$$Sensitivity = \frac{TP}{TP + FN} \quad (2)$$

The sensitivity calculation in the 2-class problem is simple. However, in the 3-class problem, we need to regroup ASC-US, LSIL, ASC-H, HSIL and SCC to form a single class of altered cells. After that, the sensitivity calculation is the same as in the 2-class problem.

3.5.3 Specificity

Is the percentage of normal data that is correctly classified as normal (true negative). Specificity is defined as:

$$\text{Specificity} = \frac{TN}{TN + FP} \quad (3)$$

Similar to the Sensitivity calculation, the computation of Specificity in the 2-class problem is simple, whereas ASC-US, LSIL, ASC-H, HSIL and SCC need to be regrouped as a class of altered cells in the 3-class problem.

3.5.4 F1 Score

Is a relationship between precision and sensitivity to provide a single, balanced measurement for the system. The F1 Score is defined as:

$$F1 = 2 * \frac{\text{Precision} * \text{Sensitivity}}{\text{Precision} + \text{Sensitivity}} \quad (4)$$

4 RESULTS AND DISCUSSION

The classification was made from texture characteristics extracted from images obtained from the Pap smears examination. Different combinations of characteristics were experienced from the use of Principal Component Analysis (PCA) as a dimensionality reduction technique. The best results were presented using all the characteristics described in Section 3.3.

The step-by-step procedure of the system proposed here is shown in Figure 2. As discussed in Section 3.4, two distinct classification experiments are proposed, one with two classes (2Class), investigating the presence or not of image damage, and another with three classes (3Class), allowing differentiation not only between the presence or absence of lesions, but also between mild or severe lesions.

The performance of several classification algorithms was analyzed and compared. The most efficient method for separating the data set was the SVM with accuracy of 89.7% for the classification in two classes and 85.1% for the classification in three classes. Other results obtained are presented in Table 1 and Table 2. It is important to note that, in order to calculate these metrics, the information about the noise class was disregarded, that is, any values obtained from the confusion matrix involving the noise class were not accounted for.

In order to provide effective aid in the detection of lesions in images obtained from Pap smears, the effectiveness of the results obtained was investigated

Table 1: Results for 2 Class patches classification.

Metrics	Values
Precision	0.897
Recall	0.917
Specificity	0.883
F1 Score	0.907

Table 2: Results for 3 Class patches classification.

Metrics	Values
Precision	0.851
Recall	0.954
Specificity	0.778
F1 Score	0.899

in both computational and biological bias. According to the experts who performed the manual classification of the database, as the objective of the system is to provide a classification tool or preliminary ranking of the images obtained in the slides, not excluding the function of the cytopathologist at the end of the structure to make the diagnosis official in the scenario of a possible presence of injury, but rather providing support for decision-making, emphasizing that the main problem that must be tackled within the proposed structure are the false negative classifications, i.e. do not find lesions that actually exist.

In these situations, the diagnosis of an injury is not detected, causing the patient to create a false tranquility and remain at risk of developing the cancer. The experts also explain that false positive diagnoses are not essential problems in the context of the real application of this system, because these images will be analyzed by the cytopathologist for final diagnosis, and if the blade indicated with lesions does not actually have them, the diagnosis will be given as normal and the patient will receive the correct diagnosis. However, in false negative diagnoses, the blade that contains lesions and is classified as normal is not designated for evaluation in the second instance by the cytopathologist and in this way the system could lead to incorrect diagnoses.

From this, several experiments were performed and the performance of the classification technique was measured by varying the defined parameters in order to obtain the greatest possible decrease of the amount of false negatives reached by the system. The obtained results are satisfactory for the context of the application in real environment, being: 1.87% of false negatives in the system of 3 classes and 3.41% in the system of 2 classes. It is also worth mentioning that, throughout the development of this article, the used techniques were chosen in order to reduce as much as possible the computational cost of the proposed structure. This is due to the fact that, from a single Papan-

icolaou slide, are obtained between 10 to 15 thousand images with a 40x magnification and, as in a realistic environment there is too many of these slides for analysis, in order that the structure here proposed has functional applicability in this environment, the classification of an image must happen quickly. Making elementary techniques stand out in relation to robust techniques.

5 CONCLUSION

Precisely classifying cell nuclei in real images of Pap smear is a necessary condition to provide more accurate and reliable diagnostics. Since in this type of image the information about nuclear and cytoplasmic boundaries is complex and computationally infeasible, this paper presents a structure for the classification of real cervical cytology images from the extraction of non-geometric textural features without the use of learning from neural networks or from segmentation algorithms.

The proposed structure has realistic application to help in the diagnosis and screening of cervical cancer. A supervised learning classifier, SVM, was used for classification and system performance was measured with actual cervical cytology images, created from the Pap smear, provided by a private searchable imaging database.

The results obtained by our experiments indicate the optimum performance of the proposed system in the process of categorization of lesions present in Pap smears images, presenting high precision and low false negative index. This implies that the efficient characterization of an actual cervical cytology image is feasible only with the use of non-geometric extraction features.

In the medical and biological context, the proposed structure serves as a preliminary Pap smears classifier that determines the likelihood of lesions in an image and signals them to be analyzed by a cytopathologist when necessary and provide a definitive diagnosis of more practical, efficient and with quality assurance. In addition, correlating biology and computation, pertinent conclusions can be inferred regarding the rigidity or flexibility required for a system to have effective applicability in real environments.

6 FUTURE WORKS

As future works we intend to investigate the efficiency of the proposed system when applied in a larger number of real images not cataloged and to construct a

system that allows the return of these regions to the analysis of the cytopathologist. Another important factor to be examined are the sets of descriptors, performing a more systematic investigation for the inclusion of information that allows the increase of the precision of the method.

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