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HISTOPATHOLOGY IMAGE REPRESENTATION FOR AUTOMATIC ANALYSIS: A STATE-OF-THE-ART REVIEW

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Abstract

This paper presents a review of the state-of-the-art in histopathology image representation used in automatic image analysis tasks. Automatic analysis of histopathology images is important for building computer-assisted diagnosis tools, automatic image enhancing systems and virtual microscopy systems, among other applications. Histopathology images have a rich mix of visual patterns with particularities that make them difficult to analyze. The paper discusses these particularities, the acquisition process and the challenges found when doing automatic analysis. Second an overview of recent works and methods addressed to deal with visual content representation in different automatic image analysis tasks is presented. Third an overview of applications of image representation methods in several medical domains and tasks is presented. Finally, the paper concludes with current trends of automatic analysis of histopathology images like digital pathology.

Keywords: Histopathology; image analysis, computer-assisted; pattern recognition system; informatics computing, medical; state-of-the-art review

REPRESENTACIÓN DE IMÁGENES DE HISTOPATOLOGÍA UTILIZADA EN TAREAS DE ANÁLISIS AUTOMÁTICO: ESTADO DEL ARTE

Resumen

Este artículo presenta una revisión del estado del arte en la representación de imágenes de histopatología utilizada en tareas de análisis automático. El análisis de imágenes histopatológicas es importante en la construcción de herramientas para el diagnóstico asistido por computador, sistemas de mejoramiento automático de imágenes y sistemas de microscopía virtual, entre otras aplicaciones. Estas imágenes tienen una gran mezcla de patrones visuales con características particulares que hacen de su análisis una tarea difícil. El artículo discute estas particularidades, el proceso de adquisición y los retos particulares al realizar un análisis automático. En la segunda sección se presenta una revisión de trabajos y métodos recientes enfocados a la representación del contenido visual en diferentes tareas de análisis automático. En tercer lugar, se presenta una visión general de las aplicaciones para los métodos de representación en diferentes dominios médicos.
Finalmente el trabajo concluye con las actuales tendencias del análisis automático de imágenes de histopatología como la patología digital.

**Palabras clave:** Histopatología, análisis de imagen asistida por computador, sistema de reconocimiento de patrones, informática médica, estado del arte

### REPRESENTAÇÃO DE IMAGENS HISTOPATOLÓGICAS PELO ANÁLISE AUTOMÁTICO: REVISÃO DO ESTADO DA ARTE

**Resumo**

Este artigo é uma revisão do estado da arte na representação de imagens histopatológicas utilizadas nas tarefas de análise automáticas. O análise de imagens histopatológicas é importante na construção de ferramentas para o diagnóstico assistido por computador, sistemas de melhoramento automático de imagens e sistemas de microscopia virtual. Essas imagens tem uma grande mistura de padrões visuais com características particulares, que fazem do análise uma tarefa difícil. O artigo discute essas particularidades, o processo de aquisição, e os desafios particulares no momento de realizar uma análise automático. Na segunda seção se apresenta uma revisão dos trabalhos e métodos recentes, com foco à representação do conteúdo visual em diferentes tarefas de análise automático. Na terceira, se apresenta uma visão geral das aplicações para os métodos de representação em diferentes domínios médicos. Finalmente, o artigo conclui com as atuais tendências do análise automático de imagens histopatológicas como a patología digital.

**Palavras-chave:** Histopatología, análise de imagens assistido pelo computador, sistema de padrão de reconhecimento, informática medica, revisão do estado da arte.

### Introduction

Histology is an important area of biology which studies the cell anatomy and tissues of animals and plants in a microscopic level. Histology and histopathology images are very important for diagnosis purposes; these images are a fundamental resource to determine the state of a particular biological structure, to support diagnosis of diseases like cancer, or to analyze anatomy of cells and tissues. Medical doctors and biologists are trained in histology to interpret the appearance of tissues according with their structure, functionality and cellular organization at different organs, those features can be highlighted using several staining processes. This kind of images are used for both biological research and making clinical decisions, and commonly are used like ground truth for other studies such as x-ray and MRI [1], [2].

Automatic analysis of this kind of images is a relevant and prolific research area [3], [4], however, due to their visual richness and complex variety of structures, these images require specialized analysis depending on the organ and particular task. For example, Naghdy et al [5] considered a texture analysis using Gabor Filter to find relevant regions based on the fact that pathologists look at the magnified images of cervix biopsy, and grade cervical cancers based on the spread of abnormal cells into the epithelium layers. Colon cancer was analyzed in [6] by defining a homogeneity measure based on the texture of different parts of the tissue, which are characterized with the spatial organizations of its cellular and connective tissue components. It is noteworthy these organizations show differences, depending on the organ. To address prostate cancer diagnosis, Monaco et al [7] set gland’s area as a feature, knowing it has discriminant capability for benign and malignant glands. A hierarchical algorithm was presented to detect cancerous regions at lower resolutions, then refines Gleason grades in higher resolutions. Doyle et al [8] presented a model for automatic grading of breast cancer, using combination of texture and topological features, results not only showed a discriminative capability, but also gained an interpretable model based on graph theory.
Thereby, each problem (medical domain and application) has a different and specialized method that cannot necessarily be extended to other contexts. In addition to this, histology image representation poses important challenges because of their high visual variability due to different acquisition processes, anatomical variability, staining, image magnification and the type of cut [9].

Nowadays, automatic methods for image representation and analysis have been successfully applied in medical imaging. For example, there are several computational methods which take advantage of the increasing assortment of public and large biomedical image databases [10]. In fact, new research areas like digital pathology [1] and bioimage informatics [11] are emerging. Digital pathology is an image-based environment focused on the research of histology image analysis based on pattern recognition and experimental workflow [1], whereas bioimage informatics comprises image processing, data mining and database visualization, extraction, searching, comparison and management of biomedical knowledge inside massive image collections [11].

Image representation is the first key stage in histopathology image analysis workflows. The main goal of this paper is to give an overview of current techniques used to describe the visual content of histopathology images and their applications. Firstly, the nature of histopathology images, their characterization and acquisition process is detailed in Section 2, this Section also discusses the main challenges posed by the automatic analysis of this kind of images from a computational point of view. A review of the state of the art on visual content representation of histopathology images is described in Section 3. Different medical applications are presented in Section 4. Finally, current trends and conclusions are discussed in Section 5.

**Histopathology images**

Digital images are pixels matrices with intensities of each color channel. This is the lowest-level representation which does not provide semantic information by itself. Direct inspection of this low-level information alone does not provide an evidence of, for instance, a particular tissue being a tumor or how many nuclei cells there are present in the image. The fact that the high-level semantic information is not immediately apparent from the low-level pixel data is known as the **semantic gap** [12]. In histopathology images, such gap is particularly important mainly because of the high visual variability resulting from the diversity of tissues and structures and the particularities of the acquisition process.

**Characteristics of Histopathology Images**

Histopathology images have normal and abnormal biological structures, morphological and architectural characteristics which could be identified by pathologists depending on their experience, but some structures are small with respect to tissue region, and relevant patterns generally have high visual appearance variability. Most of visual variability is inherent of biological structures and anatomy. In addition, acquisition process adds noise and visual variability on each stage. In order to visualize this process, it is useful to review the histopathology image acquisition process depicted in Fig. 1. First, the biological sample is taken from an organ. Then, a fixation process is done over the biopsy to assure chemical stability on the tissue and avoid post-mortem changes [13]. After this, it must be cut into sections that can be placed onto glass slides. The sections are stained to reveal cellular components by chemical reactions. The most common dyes used are Hematoxylin - Eosin (H&E) which stain cell nuclei in a dark blue or purple and cytoplasm and connective tissue in a bright pink. Finally, the section is cover slipped to be viewed and digitized with a microscope.

The particular process used for fixation and staining produces different visual effects in the acquired images. Additionally, acquired images are affected by luminance and other factors associated to the acquisition technology used. Taking into account that these images are a 2D projection of a 3D object (organs), the biological sample has a different appearance depending on its orientation (e.g. longitudinal, oblique or cross-sectional [14]). Depending on the region of interest, the laboratory personnel could take different images at different magnification. Usually, the image resolution is related to the size or scale of biological structures that can be seen in the histology slide. These human factors add a new source of variability. Main issues that contribute with visual heterogeneity of images are depicted in Fig. 2, such as image magnification, type of cut, luminance and stain concentration.

**Magnification**: Magnification refers to increasing the proportion of biological structures which are visible under the microscope according to the set of lenses. Conventional microscopes have a standard set of objectives 2X, 10X, 20X, 40X and 100X. First row in Fig. 2 shows the appearance of tongue muscle tissue stained with Masson’s
trichrome staining at 10X, 20X and 40X. It is clear that, even being the same organ, appearance of those images is highly variant identifying different structures at different magnifications.

**Staining:** It is an auxiliary technique in microscopy to improve the contrast in a biological sample seen under a microscope. Dyes are used in both, biology and medicine, to highlight biological structures from different tissues according to biomedical or diagnosis interest. There are several types of dyes according to chemistry properties of biological structures which must be spotlighted [15].

Depending on the region or biological structure of interest, some types of stains are more appropriated than others. So, it is possible to get different images and visual appearances from one biopsy depending on the type of stain. The second row in Fig. 2 shows region between dermis and epidermis at 40X magnification stained with H&E and Masson’s trichrome respectively. It is noteworthy

**Fig. 1. Acquisition workflow diagram**

![Acquisition workflow diagram](image)

**Fig. 2. Visual variability in histology images.** First row shows variability due to magnification of same tongue muscle tissue. Second row shows variability due to staining and luminance. Third row shows variability of smooth muscle tissue due to section orientation (longitudinal and cross-section)

1 Adapted from http://library.med.utah.edu/WebPath/HISTHTML/HISTOTCH/HISTOTCH.html
how the performing of staining process affects in different way the luminance and the intensity of color channels. This behavior in histology images adds conceptual visual variability determined by the type of stain applied.

**Slice orientation:** The tissue appearance in histology images is related with the slice cut orientation. Last row in Fig. 2 shows how the tissue appearance changes when the cut is done in a longitudinal or cross-sectional orientation in smooth muscle tissue using the same staining (H&E). There are infinite possible cut orientations, which makes harder the characterization of a 3D organ by a thin 2D sample. Although there are standard protocols for slice cutting and histology image acquisition depending of organ, the final precision of the results depends on several and accumulative factors like the type of microtome used to take the slice, the composition of the sample, the experience of histotechnologist, the fixative used to harden the tissue, among others.

**Histopathology image representation**

**Automatic Histopathology Image Analysis Process**

A typical automatic histopathology image workflow is depicted in Fig. 3. The first step is image preprocessing in which raw image data is transformed in order to reduce visual variability and noise, as well as making it more suitable for the subsequent steps. Common tasks in this phase include pixels intensity normalization to deal with luminance artifacts, image scaling to reduce representation size and dimensionality reduction using techniques such as Principal Component Analysis (PCA).

The second step is feature extraction, whose purpose is to produce a more descriptive representation of the image making explicit important information which is not directly manifest from the raw pixels. There are two main types of features: region-based (local) descriptors and image-based (global) descriptors. Image-based descriptors try to describe the image as a single entity, while region-based methods assume image is composed of independent building blocks and, therefore the image can be modeled as a combination of such blocks. Sometimes, visual features in a region-based scheme are extracted from the most relevant parts of the image, commonly known as Regions of Interest (ROI), this can be achieved through segmentation techniques where background is removed to highlight relevant objects, or by applying techniques like Scale-invariant feature transform (SIFT) [16] to detect interesting points in the object. Either global or part-based, Feature extraction process calculates descriptors to describe in a concise way the content of the image.

In the third step interesting visual patterns are detected and identified, this is known as pattern recognition. This is usually accomplished using supervised machine learning methods. These methods learn a discriminative/classification model from annotated training data. The learned model is later used to classify new unseen images [17].

The performance of pattern recognition models is highly dependent on the features used; therefore picking the right features for a particular problem is the main motivation...
to provide a review of current representation techniques applied in histopathology domain.

Supervised machine learning algorithms applied to automatic image categorization require representative training sets of images. Because of the high histopathology image visual variability, a supervised learning method usually needs a large number of images from different patients to make successful generalizations [18]. In addition to visual variability, complex structures and patterns are presented in histology images. Then, different approaches have been applied to characterize and represent the visual information on histopathology images and solve particular problems (e.g. cancer detection and grading).

Visual features

A common characteristic present in many of the reviewed works is the fact that particular image analysis problems demand specific image representation schemes. The main reason is that different organs express different complex biological structures, increasing visual variability and making harder to close the semantic gap. Every approach needs to describe the image content within some data structure that captures its visual content and biological structures configuration. Different methods for visual features extraction have been proposed. An overview of the most common feature extraction schemes used for histopathology image representation in different works is listed in Table 1.

Visual features aim to describe the most relevant information to feed a specific Machine Learning (ML) algorithm, depending on the task and the type of the images, some features can be more efficiently than others. Visual content of images could be typically represented by using either all the pixels in the image for a unique representation (image-based descriptors) or splitting the image and extract a set of features per each segment (region-based descriptors). Independently of ROI to be analyzed (i.e. whole image or segments), in histopathology image domain, feature extraction methods are usually classified as follows [3], [19].

**Intensity features**: This kind of features provides information of the gray level or color of pixels located in the ROI. This feature extraction approach uses different color spaces. Samsi et al [20], [21] used the Hue channel from the HSV (Hue-Saturation-Value) color space conversion of the original image, while Oszdemir et al [18] worked on white/pink/purple color dimension. In [22], 11 color models were evaluated to compare the incidence over the performance in a classification task, they found that there is no single model which works better than others in every case. This can be supported in the results reported on [23], [24], where the first one reported RGB color space performed better than others, while second one ensures adding CIELab color information may improve classification capability.

**Morphological features**: These features provide information about the size and shape of the described region, object or image. In [7] gland area was used as discriminative criteria to classify between benign or malignant, while Dundar et. al.[25] used perimeter as feature descriptor to characterize cell size in segmentation process. Taking advantage of pathologist’s experience in diagnosis of Oral Submucous Fibrosis (OSF), Muthu et al [26] represented the image using morphological features like eccentricity,

<table>
<thead>
<tr>
<th>Feature type</th>
<th>Detail</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensities</td>
<td>Grayscale</td>
<td>[35]</td>
</tr>
<tr>
<td></td>
<td>RGB</td>
<td>[18], [22], [35], [43], [47], [54], [67]</td>
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<tr>
<td></td>
<td>HSV</td>
<td>[20–22], [35]</td>
</tr>
<tr>
<td></td>
<td>CIEL<em>a</em>b</td>
<td>[22], [24], [67]</td>
</tr>
<tr>
<td>Morphological</td>
<td>Area, perimeter, shape, etc.</td>
<td>[7], [25–29], [68–72]</td>
</tr>
<tr>
<td>Topological</td>
<td>Voronoi Diagram, Delaunay Triangulation</td>
<td>[8], [30], [31], [69]</td>
</tr>
<tr>
<td></td>
<td>Nearest Neighbor</td>
<td>[30], [31]</td>
</tr>
<tr>
<td></td>
<td>Minimum Spanning Tree</td>
<td>[8], [30], [31], [69]</td>
</tr>
<tr>
<td>Texture</td>
<td>Haralick</td>
<td>[8], [20], [21], [26], [33–35]</td>
</tr>
<tr>
<td></td>
<td>Gabor Filter</td>
<td>[5], [8], [45]</td>
</tr>
<tr>
<td></td>
<td>Co-occurrence texture</td>
<td>[24], [52], [73]</td>
</tr>
<tr>
<td></td>
<td>Haar wavelet coefficients</td>
<td>[41], [49]</td>
</tr>
<tr>
<td></td>
<td>LBP</td>
<td>[44], [45]</td>
</tr>
<tr>
<td></td>
<td>Bag of features</td>
<td>[36–43], [74]</td>
</tr>
</tbody>
</table>
perimeter, area equivalent diameter to describe cell nucleus. Not only classification tasks can be performed using this type of features, Dangott et al. [27] built an automated system for differential white blood cell (WBC) counting based on 19 features such as area, perimeter, convex area, solidity, orientation and eccentricity. Also, these features have been used to construct Content-Based Image Retrieval (CBIR) to find prostate histopathology images based on morphological similarity [28]. As well as [29] and some of mentioned works, most of the morphological measures estimation are done based on a previous segmentation, and therefore its performance depends on the precision of such segmentation.

**Topological features:** Topological features provide information about some structure within the image. This description is particularly useful on the segmentation task, where graph theory is commonly the most used in this group of features. A graph is created with a set of points of interest (e.g. nuclei detection), a Voronoi Diagram (VD) uses this set to build a diagram by divide the region with approximately the same area with graph’s vertices as center for each region. Delaunay Triangulation (DT) is built by fitting a set of triangles over this graph in such way that each circumcircle does not contain any vertex inside of them. Area, perimeter, angle and other geometrical features are calculated from this set of regions/triangles to describe visual content of such regions. Nearest Neighbor uses information like distance, density, closeness of N nearest neighbor as descriptor for each vertex in the graph. Lastly, Minimum Spanning Tree (MST) finds the shortest path in a graph, length of each edge can be used as descriptor. Basavanahalli [30] concatenated up to 50 features from DT VD MST and nearest neighbor to train a classifier to distinguish low and high grades in breast cancer histopathology images. Madabhushi [31] proposed a method that extract information from multimodal information, including magnetic resonance imaging (MRI), digital pathology and protein expression combining DT, VD, MST and NN descriptors by graph embedding method to characterize spatial arrangement of nuclear structures and, in conjunction with a SVM classifier, distinguish samples with different levels of Lymphocytic infiltration in breast cancer. In [8] a model was proposed to grade cancer in breast images by feature combination of VD and DT using graph embedding. In [27] DT also was used to find possible edges that might correspond to the boundaries between segmented nucleus.

**Texture features:** These features provide information about the variation of intensities presented in the region, helping to tissue identification. Haralick features [32] suggests a set of 28 textural features defined by several equations, some of those related with statistical properties such like correlations, means, variances among others. Depending on the domain application, only some of those features can be used. Kuse et al. [33] extracted 18 Haralick texture features to classify lymphocytes and non-lymphocytes, Chaddad [34] used 5 main Haralick’s coefficients from Gray Level Co-Ocurrence (GLCM) Matrix for texture analysis and colon cancer cell detection. Cinar et al. [35] extracted 7 Haralick features from normalized co-occurrence matrix for grayscale, RGB and HSV color spaces to indexing content in a CBIR system. In [8] calculated 6 Haralick features were calculated to combine them with topological and color features to grade breast cancer.

Bag of features is an adaptive approach to model image structures using a dictionary learned from images patches. Each patch can be represented through different descriptors, image representation is built with a frequency histogram where each bin shows how related is the image with each visual word of the dictionary. This model has obtained success results for basal-cell carcinoma detection [36–40], medulloblastoma [41] and renal cell carcinoma [42] classification. This kind of representation was used to build a CBIR system using Non Negative Matrix Factorization (NMF) by Vanegas et al. [43].

Local Binary Pattern (LBP) is a texture descriptor that labels the pixels by thresholding the neighborhood against current pixel, set 1 if neighbor is above it, 0 otherwise, then these values are concatenated following a circle around evaluated pixel to obtain 8 binary digits, to finally convert them in a 10-base number. This operator has been applied in histopathology images to identify oral cancer [44], [45], as well as a descriptor for image indexing for retrieval systems [43].

**Feature composition:** To improve the performance of the applied methodology, several authors have built more complex features by combination, or selection depending on statistical or another analysis [4]. In [35] color and texture features were extracted and normalized with null mean and unit variance, and then Non-negative Matrix Factorization (NMF) model was used to combine such features by dimensionality reduction. In [26] five biological characteristics were suggested by experienced oncopathologists: nuclear changes, polymorphism, nuclear irregularity, hyperchromasia and nuclear texture, then these features were extracted based on that type of characteristics. An unsupervised feature extraction was applied to remove any bias towards certain features which might afterwards
affect the classification procedure. Also, in [44], three texture features were extracted: (LBP), Higher order spectra (HOS) and Laws Texture Energy (LTE), then applied Analysis of variance (ANOVA) to extract features prior to classification to verify discriminating capability.

The above features, summarized in Fig. 4, are much more complex than others reported on this document, and all of them require a prior design and parameters have to be fitted according with the objective and domain. Previous classification demonstrates efforts have been oriented to build specific design for each domain, even for each task. However this representation could not be scalable for other problems.

Histopathology Image Classification for Diagnosis and Grading Support

One of the most common applications for automatic histopathology image analysis is detection and grading of cancer. Main problems where automatic histopathology image analysis has been applied are described as follows.

Prostate cancer

In Colombia, prostate cancer is the most common cancer in men and it is also one of the leading causes of death by cancer (more than 8000 new cases and 2400 deaths per year [46]). This type of cancer is graded from 1 to 5 using Gleason grading method, and it is based on structural features of the tissue, where Grade 1 has well defined patterns, while 5 grade patterns are difficult to differentiate. Automatic grading can be performed in two stages, a segmentation process to extract glands from the background and to get morphological measures from them, and then train a classifier to recognize their patterns and perform annotation of each grade.

[47] applied PCA in RGB color decomposition to remove correlations between channels, then k-means clustering algorithm is applied with resultant components for k = 4 to identify lumen, nuclei, cytoplasm and stroma with expert guidance, finally, a region growing method was applied to complete the segmentation. After that, morphological features of segmented regions are used as input for an LDA classifier [7] convolved the image with a Gaussian Kernel, using peaks as seeds for a region growing procedure. Glands area are estimated and used jointly with a MRF (Markov Random Field) to train a Bayesian estimator and classify glands as either malignant or benign. [29], [48] performed a semi-automatic gland segmentation using low-level, high-level and specific domain information. Then morphological and topological features were extracted from regions and used to train a binary Support Vector Machine (SVM) model, for classifying between 3 and 4 grades. Another approach using extracted features directly from image into a classification model has been applied.

![Fig. 4. Overview of common approaches for feature composition in histopathology image representation.](image-url)
in this domain. This approach commonly uses texture features like co-occurrence matrix [24], Haar wavelets [49] and text on histogram [50].

Cervix cancer

Cervix cancer is the most prevalent cancer in Colombia, 17.5% of new cases in women each year, and 97% of these new cases were diagnosed with a primary tumor histology [51]. Cervix cancer refers to cancer forming tissues of the uterine cervix, and is graded into three categories: cervical intraepithelial neoplasia (CIN) 1, CIN 2 and CIN 3 corresponding to mild, moderate and severe dysplasia.

In [52] segmentation was performed with a supervised model using texture features and an SVM classifier at different resolutions, after that, morphological measures of nuclei are used to train a multiclass SVM model with RBF Kernel and to grade cervix cancer [5] proposed a gabor-filter-based segmentation with a supervised learning approach, resulting a pixel-by-pixel classification into four classes: basal, stroma, normal and abnormal cell. Then, clustering and median filters are applied to count normal and abnormal nuclei. Finally, ratio between normal and abnormal is used as discriminant feature to grade the image. On the other hand, a standalone segmentation was proposed in [53] to identify cervical nuclei based on HSV color and morphological features, while [54] applied GMM (Gaussian Mixture Models) and grayscale features.

Colon cancer

It is the third most common cancer in the world for both women and men, in Colombia it is the fourth for both. Also, it is the fifth in Colombia leading causes of death for cancer. Assessment of cancer grading is based on visual abnormalities found by pathologists; this grade is subjective because it depends on interpretation given by the expert. Automatic methods have been proposed to detect and grade colon cancer.

[18] presented a strategy to classify samples as normal, low-grade and high-grade cancerous, representing images with features extracted from windows centered in random sampling points, and a k-means clustering is performed to get template sequences. Training images are represented with these templates sequences, then a markovian model is trained with such representations. Experiments showed the proposed model performs better than raw features, even when there was less data to train. A segmentation approach was shown in [34] using five measures of Haralick texture features, to detect three types of cells: carcinoma, benign and intraepithelial neoplasia, using a neural network as classifier obtaining at the end a computational simplicity of segmentation which is performed in a very short time [6] presented an unsupervised object-oriented segmentation algorithm based on texture features. K-means clustering is performed on the color intensities to detect and define objects referred to connective tissues, luminal structures and epithelial cell components. Two homogeneity measures were defined, object size uniformity and object spatial distribution uniformity, as textures features for each object, finally a region-growing algorithm is carried out to completed segmentation process. The proposed method was compared against JSEG algorithm, a pixel-oriented approach [55], obtaining better performance in terms of specificity and sensitivity.

Basal cell carcinoma

Basal-cell carcinoma (BCC) is the most common skin disease in white populations, its incidence is growing worldwide [56] and it represents more than 59% of skin cancer cases in Colombia. It has different risk factors and its development is mainly due to ultraviolet radiation exposure. Pathologists confirm whether or not this disease is present after a biopsied tissue is evaluated under microscope. In this evaluation, physicians aim to recognize some characteristic patterns or complex mixtures of patterns. This process is called differential diagnosis and it is mainly achieved by visual analysis. In [57], the structural patterns that characterize the basal-cell carcinoma are described and correspond to 11 different complex patterns.

[36] published one of the first models to diagnose BCC disease using BOF representation with two texture features: raw block and SIFT descriptor. This kind of representation can be extended to analyze semantic concepts by identifying visual patterns in BCC images [38], [40]. In order to support medical searching within BCC image collections, [58] proposed a method to ease its visualization and exploration using BOF with texture features. Looking for a more detailed diagnosis, [39] proposed an annotation model with probabilistic Latent Semantic Analysis (pLSA) and BOF representation as input features. [37] defined a kernel functions combination to build a semantic annotation framework, then such annotations were used to build a CBIR. Results showed an average improvement of 57% when compared to visual search based on low-level features and histogram intersection kernel as similarity measure. Other methods for automatic annotation for BCC collections has been proposed, [59], [60] applied NMF with BOF to build a latent
topic model with probabilistic support as main advantage for interpretability of results. A proper determination of Regions of interest (ROI) would allow to concentrate any processing effort on specific image areas to diagnose BCC disease, to find such Rols [61] proposed a supervised model inspired by visual cortex areas of the brain and the way they perceive the world. Diaz and Romero [62] have proposed a microstructural tissue analysis in basal cell carcinoma images using a stain correction of H&E images and an automatic method to identify morphological and architectural features by square regions in images based on latent semantic analysis and support vector machines.

Open trends problems and challenges

The most important challenge is that unlike natural images where high-level semantic concepts are related with connected areas and objects, in histopathology images high-level semantic interpretations are related to pathological lesions, morphological and architectural features, structural configuration, cells and biological patterns organization (context), and not only the presence of patterns is important but also their absence is. Such factors depend on the amount of magnification and the type of organ, which encompass a complex mixture of visual patterns that allow deciding about the illness presence. Dealing automatically with these factors is still an open problem [59].

On the other hand, thanks to recent advances in microscopical acquisition technology (scanners and robotic microscopes) it has been possible to collect huge numbers of histopathology images and make them publicly available through publicly accessible image databases [63]. Table 2 lists different open histopathology image databases accessible through the web. This trend is very positive for the progress of digital histopathology research, since it allows objective comparison of methods and strategies. However, standard evaluation protocols are required. An example effort in this direction is the publication of the MITOS dataset, by the International Conference on Pattern Recognition (ICPR), along with a set of evaluation metrics to encourage participation on their contest where the objective was to evaluate methods to automatically determine the mitotic count.

Nowadays one of the new challenges is to deal the growing size of these image collections (from hundred thousands to millions) and whole-slide-images sizes (20 GB or more) [64]. This phenomena is known as Big Data, and in pathology domain is opening new challenges, opportunities and approaches which are being addressed by a new area called Digital Pathology [65]. Finally, It should be noticed most of these Finally, It should be noticed most of these methods and frameworks reviewed in this work are addressed to support and to empower the diagnosis of pathologists rather than replace them [66].

### Table 2. List of public access histopathology image collections

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Size</th>
<th>Web page</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>HistologyDS[38]</td>
<td>2828 Images¹</td>
<td><a href="http://www.informed.unal.edu.co/histologyDS">http://www.informed.unal.edu.co/histologyDS</a></td>
<td>Universidad Nacional de Colombia</td>
</tr>
<tr>
<td>Stanford Tissue Microarray Database (TMA)</td>
<td>55874 images³</td>
<td><a href="http://tma.im/cgi-bin/home.pl">http://tma.im/cgi-bin/home.pl</a></td>
<td>Stanford University</td>
</tr>
<tr>
<td>MITOS</td>
<td>50 Images⁴</td>
<td><a href="http://ipal.cnrs.fr/ICPR2012/">http://ipal.cnrs.fr/ICPR2012/</a></td>
<td>The Ohio State University</td>
</tr>
<tr>
<td>caIMAGE</td>
<td>910 Images⁵</td>
<td><a href="http://emice.nci.nih.gov/caimage">http://emice.nci.nih.gov/caimage</a></td>
<td>National Cancer Institute (U.S.)</td>
</tr>
</tbody>
</table>

¹ http://www.informed.unal.edu.co/histologyDS is a subset of BiMed(http://www.informed.unal.edu.co/)
³ http://tma.im/cgi-bin/viewStain.pl?op=antibody
⁴ http://ipal.cnrs.fr/ICPR2012/?q=node/5
⁵ http://www.virtualpathology.leeds.ac.uk/slidelibrary/index.php
Conflict of interest: The authors declare that they have no conflict of interest

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