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Mitosis detection in histological images.
Algorithms based on machine learning
and their performance compared to
humans.

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Abstract

Acknowledgements

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Glossary

AI Artificial Intelligence. 13

BR Bloom and Richardson Grading System. 3, 6

CAD Computer Aided Diagnosis. 8

CNN Convolutional Neural Network. 19

FN false negative. 15

FP false positive. 15

GLCM Gray-level Co-occurrence Matrix. 10

GLEM Gray-level Entropy Matrix. 10

GLRM Gray-level Run-length Matrix. 10

HE Hematoxylin and Eosin. 5

HPF High Power Fields. 6

LBP Local Binary Patterns. 10–12

ML Machine Learning. 13, 14

MRI Magnetic Resonance Imaging. 12

NGS Nottingham Grading System. 3

NN Neural Network. 16

RF Random Forest. 15

ROI Region of Interest. 8

SVM Support Vector Machine. 16

TN true negative. 15

TP true positive. 15

VAR Rotation Invariant Variance Measure. 11, 12

WT Wavelet Transform. 12

Chapter 1

Introduction

“Quote 1”

Author 1

First part topics

- Detection problems in Computer Vision and in particular in biomedical imaging
- Relation between detection and classification
- Mitosis Detection as a component in breast cancer assessment
- Machine Learning used to automate the mitotic count task
- The validation problem:
 - from clinical point of view
 - from ML point of view

Second part topics

- General overview of the work: automatic Mitosis Detection in breast cancer histological images and comparison of the performances between humans and algorithms.
 - some literature
 - specificity of this work
 - achievements

- research directions

Third part topics

- Structure of the work
 - Section 1: state of the art...
 - Section 2: approach to the problem and model
 - Section 3: design of a mitosis detection algorithm
 - Section 4: design of a user study
 - Section 5: experimental results
 - Section 6: Conclusions
 - Appendixes: implementation details

Chapter 2

State of the art

“Rem tene, verba sequentur”

(Know the subject, the words will follow)

Marcus Porcius Cato Censorius

2.1 Background

Breast cancer classification divides breast cancer into categories according to different schemes¹, each serving a different purpose. The purpose of classification is to select the best treatment[16].

Within the last decade, histological grading has become widely accepted as a powerful indicator of prognosis in breast cancer. The grading depends on the microscopic similarity of breast cancer cells to normal breast tissue, and classifies the cancer as well differentiated (low grade), moderately differentiated (intermediate grade), and poorly differentiated (high grade), reflecting progressively less normal appearing cells that have a worsening prognosis. Although grading is fundamentally based on how biopsied, cultured cells behave, in practice the grading of a given cancer is derived by assessing the cellular appearance of the tumor.

The Nottingham Grading System (NGS) (also called Elston-Ellis) is a modification [13] of the Bloom and Richardson Grading System (BR)[6, 17]. NGS is judged more reproducible and is the recommended grading method [1].

NGS grades breast carcinomas by adding up scores for:

¹<http://www.breastpathology.info/>

- tubule formation,
- nuclear pleomorphism,
- mitotic count

each of which is given 1 to 3 points. The scores for each of these three criteria and then added together to give an overall final score and corresponding grade as follows [10]:

3-5 **Grade 1 tumor** (well-differentiated). Best prognosis.

6-7 **Grade 2 tumor** (moderately-differentiated). Medium prognosis.

8-9 **Grade 3 tumor** (poorly-differentiated). Worst prognosis.

Lower grade tumors, with a more favorable prognosis, can be treated less aggressively, and have a better survival rate.

Mitotic activity (see 7 for some details) is one of the strongest prognosticators for invasive breast carcinoma. It is expressed as the number of mitotic figures per tissue area. Early detection plays an important role in reducing cancer mortality. The current procedure for breast cancer grading is manually performed by pathologists, for both nuclear pleomorphism [11] and mitotic count. Breast tissue samples of patients are taken and examined under microscopes. Pathologists grade the tissue samples based on the deviation of the cell structures from normal tissues. A pathologist may have to examine a great amount of slides [44]. This process can be time consuming and subjective (see 3.5.1).

In the following subsection we give a short overview of the mitosis count procedure[2].

2.1.1 Tissue preparation

After tumor excision is performed, the excised material is sent for analysis in a pathology lab. The tissue preparation process starts with making smaller cuts of the material that are then fixed in formalin and (after processing) embedded in paraffin.

Using a high precision cutting instrument (microtome), thin sections are cut from the paraffin block, which are then put on glass slides. The final stage of the tissue preparation process is the staining of the sections with stains that

highlight specific structures of the tissue so they are better visible under a microscope. The standard staining protocol uses the Hematoxylin and Eosin (HE) stains. The hematoxylin dyes the nuclei a dark purple color and the eosin dyes other structures (cytoplasm, stroma, etc.) a pink color.

2.1.2 Digital Pathology

Recent years have brought the trend of digitization of histological slides. Digital slide scanners 2.1, in combination with digital slide viewers, aim to provide the experience of viewing a digital slide on a computer monitor in a manner analogous to viewing it under a microscope, but with all the added benefits of the digital format (ease of annotation, image analysis, collaborative viewing etc.). The output of the digital slide scanners are multi-layered images, stored in a format that enables fast zooming and panning. Depending on the area of the tissue that is present on the slide and the magnification and resolution at which the slide is scanned, the lowest layer of the digital slide can be up to several tens of thousands of pixels in width or height. Currently, digital slides are mainly used for research, education and remote consultation purposes. Their use for routine diagnosis and prognosis is not yet common [27]. Availability of automatic image analysis algorithms that can aid pathologists in their work can be a major incentive for acceptance of digital slides in the routine pathology lab workflow.



Figure 2.1: Aperio ScanScope XT scanner

2.1.3 Mitosis Counting

Mitotic activity is one of the strongest prognosticators for invasive breast carcinoma and it is expressed as the number of mitotic figures per tissue

area. As part of the BR grading system, mitotic activity is routinely assessed in pathology labs across the world. In addition, the mitotic activity can be used as a prognosticator independently of the BR grading system. Typically, the pathologist receives a panel of slides for each case that is to be graded. He or she then proceeds to select one slide where the histological grading will be performed. The mitosis counting is performed in 8-10 consecutive microscope High Power Fields (HPF) [26]. A HPF has a size of $512 \times 512 \mu m^2$ (i.e. an area of 0.262 mm^2), which is the equivalent of a microscope field diameter of 0.58 mm . The standard guidelines are to select an area that encompasses the most invasive part of the tumor, at the periphery and with highest cellularity. Depending on the number of figures counted, a mitotic activity score is assigned. Cases with 7 or fewer mitotic figures present are assigned score 1 (best prognosis). Cases with more than 12 mitotic figures are assigned score 3 (worst prognosis). The intermediate cases are assigned score 2.

2.1.4 Challenges in Mitosis Detection

Because of the aberrant chromosomal makeup of many tumors (aneusomy, polysomy, translocations, amplifications, deletions), the appearance of mitotic figures in the images can significantly differ from the textbook examples of a splitting nucleus [29]. In addition, imperfections of the tissue preparation process result in tissue appearance variability, which can present a challenge also for an automated mitosis detection system.

Most commonly, mitotic figures are exhibited as hyperchromatic objects. In addition, they have absence of a clear nuclear membrane, “hairy” protrusions around the edges and basophilia instead of eosinophilia of the surrounding cytoplasm. However, these are more guidelines than hard rules, and the bulk of the training of pathologists is done by looking at specific examples of mitotic figures. One of the main challenges in spotting mitotic figures is that other objects such as apoptotic nuclei can have similar appearance, making it difficult even for trained experts to make a distinction [52]. Lymphocytes, compressed nuclei, “junk” particles and other artifact from the tissue preparation process, can also have hyperchromatic appearance. The images in Figure 2.2 and in Figure 2.4 try to give an idea of the difficulty of the task.

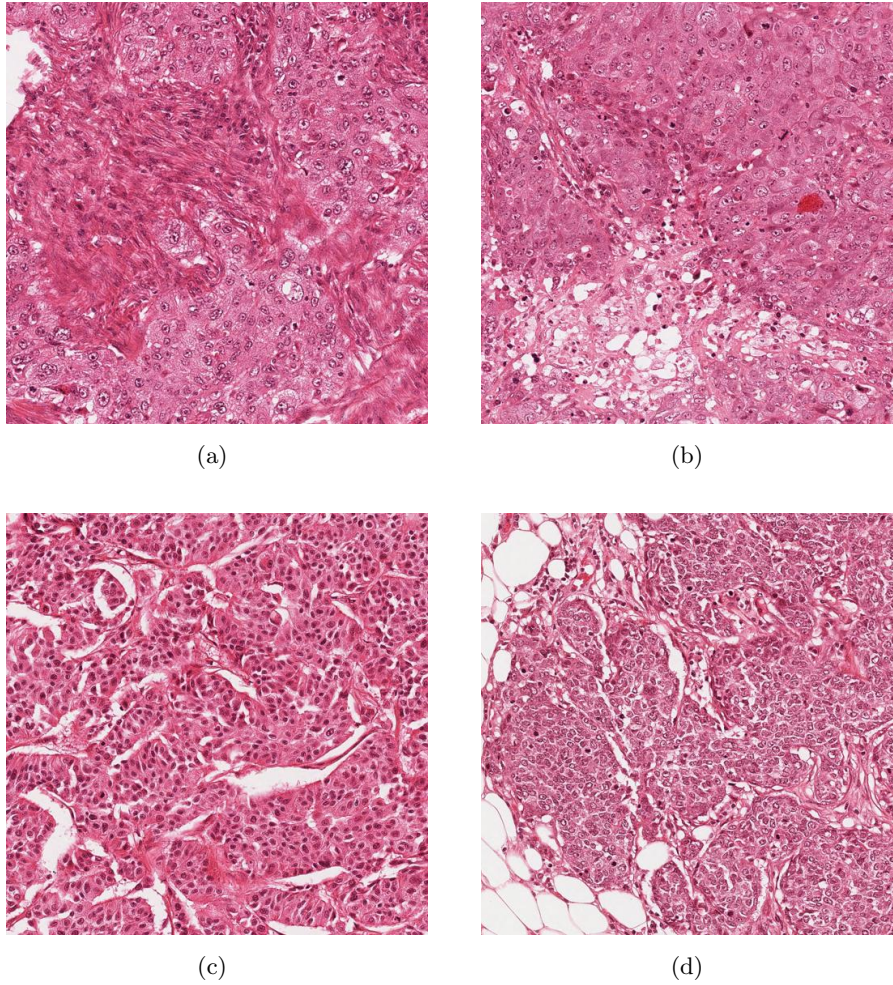


Figure 2.2: Examples of digital histological images

2.2 Mitosis Detection and Computer Vision

The task of automatic mitosis detection involves topics in various fields of research, in particular

- Image Analysis
- Machine Learning

We consider a framework in which, in the whole image, some candidates are detected and then classified as mitosis or non-mitosis.

In this chapter we give an overview of the main aspects concerning *image analysis* and in the following one (2.3) we analyze the *machine learning* elements.

2.2.1 Overview of Medical Imaging

Over the past decade, dramatic increases in computational power and improvement in image analysis algorithms have allowed the development of powerful computer-assisted analytical approaches to radiological and histopathological data[18]. Digitized tissue histopathology has now become amenable to the application of computerized image analysis and machine learning techniques. Analogous to the role of Computer Aided Diagnosis (CAD) algorithms in medical imaging to complement the opinion of a radiologist, CAD algorithms have begun to be developed for disease detection, diagnosis, and prognosis prediction to complement the opinion of the pathologist[50].

2.2.2 Software Tools

The imaging modalities rely heavily on computational approaches. In fact, in many cases the computational technology is just as important as the optics, not just for the digital capture that all systems now use but in many cases also for visualizing and properly interpreting the data. The article in [12] reviews each computational step that biologists encounter when dealing with digital images and the overall status of available software for bioimage informatics. It is worth highlighting the existence of open-source software tools like *Fiji* [47] and *ImageJ* [48], which supply some basic features for *object detection* and *feature extraction*[46].

2.2.3 Features

The concept of feature is used to denote a piece of information which is relevant for solving a computational task[37]. A feature is defined as an “interesting” part of an image, and features are used as a starting point for many computer vision algorithms. They can be the result of a general *neighborhood operation*[28] applied to the image, or specific structures in the image itself. Types of image features include:

- Edges
- Corners
- Blobs or Regions of Interest (ROIs)
- Ridges or elongated objects (i.e. blood vessels in medical images)

Other examples of features are related to motion in image sequences, to shapes defined in terms of curves or boundaries between different image regions, or to properties of such a region[21].

The feature concept is very general and the choice of features in a particular computer vision system may be highly dependent on the specific problem to be considered.

2.2.4 Feature Detectors

Many algorithms have been developed to detect specific features, and a complete overview of them is beyond the scope of this work. Some of the most famous ones, like *Canny edge detector*[9], *Harris edge and corner detector*, or SUSAN [51] are available in most widely used commercial and open-source Computer Vision software packages (i.e. MATLAB Image Processing Toolbox² or OpenCV³).

Features are sometimes extracted over several scalings. One of these methods is *Scale-invariant feature transform*; in this algorithm, various scales of the image are analyzed to extract features[33] (the underlying theory can be found in [31]).

2.2.5 Image Segmentation

Segmentation is the process of partitioning a digital image into multiple segments (sets of pixels) in order to simplify or change the representation of an image into something that is more meaningful and easier to analyze[30]. Image segmentation is typically used to locate objects and boundaries (i.e. features) in images. Such a process assigns a label to every pixel in an image so that pixels with the same label share certain visual characteristics[52].

2.2.6 Texture Algorithms

An image texture is a set of metrics designed to quantify the perceived texture of an image. Image texture gives information about the spatial arrangement of color or intensities in an image or in selected region of it[14]. Image textures are used in *segmentation*(see 2.2.5), or *classification* of images (see

²<http://www.mathworks.com/products/image/index.html>

³<http://opencv.org/>

2.3). To address the issue of texture analysis, the so called “statistical approach” is more widely used as it is easier to compute. This approach sees an image texture as a quantitative measure of the arrangement of intensities in a region.

Co-occurrence Matrix

Co-occurrence matrix captures numerical features of a texture using spatial relations of similar gray tones. Numerical features computed from the co-occurrence matrix can be used to represent, compare, and classify textures [23, 58]. The following are a subset of standard features derivable from a normalized co-occurrence matrix, as described in [20]:

$$\text{Contrast} = \sum_{n=0}^{N_g-1} n^2 \left\{ \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} p[i, j] \right\}, \text{ where } |i - j| = n \quad (2.1)$$

$$\text{Correlation} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} (i, j) \cdot p[i, j] - \mu_x \mu_y}{\sigma_x \sigma_y} \quad (2.2)$$

$$\text{Entropy} = - \sum_i \sum_j p[i, j] \cdot \log(p[i, j]) \quad (2.3)$$

Where:

- N_g is the number of gray levels in the quantized image,
- $p[i, j]$ is the (i, j) th entry in a normalized gray-tone spatial dependence matrix,
- $\mu_x, \sigma_x, \mu_y, \sigma_y$ are the mean and the standard deviation of respectively $p_x = \sum_{j=1}^{N_g} p(i, j)$ and $p_y = \sum_{i=1}^{N_g} p(i, j)$.

Various algorithms use texture feature like Gray-level Co-occurrence Matrix (GLCM) [40], Gray-level Run-length Matrix (GLRM) [35] or Gray-level Entropy Matrix (GLEM) for image classification, also in medical [8] and biological imaging [61].

Local Binary Patterns

Local Binary Patterns (LBP) is another type of feature used for classification in computer vision. LBP is a simple yet very efficient texture operator which labels the pixels of an image by thresholding the neighborhood of each pixel with the value of the center pixel and considers the result as a binary number.

The distance and the number of neighbors can be selected, as shown in Figure 2.3[39]. The notation (P, R) is used for pixel neighborhoods which means P sampling points on a circle of radius of R .

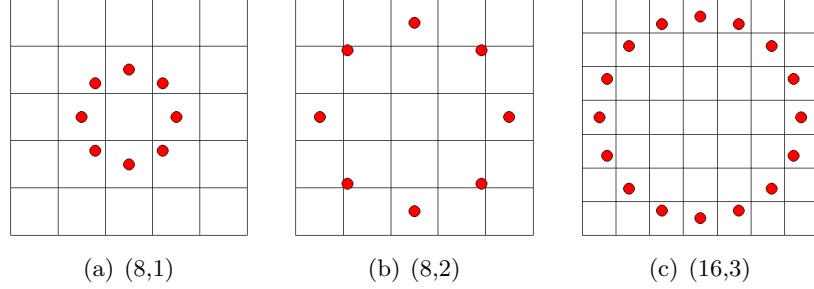


Figure 2.3: Examples LBP neighbors and distances

The computation of the LBP code of a pixel of coordinates (x_c, y_c) is given by:

$$LBP_{P,R} = \sum_{p=0}^{P-1} s(g_p - g_c) \cdot 2^p \quad \text{where } s(x) = \begin{cases} 1, & \text{if } x \geq 0 \\ 0, & \text{otherwise} \end{cases} \quad (2.4)$$

This operator used jointly with a simple local contrast measure provided very good performance in unsupervised texture segmentation. Another extension to the original operator is the definition of so called uniform patterns, which can be used to reduce the length of the feature vector and implement a simple rotation-invariant descriptor. This extension was inspired by the fact that some binary patterns occur more commonly in texture images than others. A LBP is called uniform if the binary pattern contains at most two bitwise transitions from 0 to 1 or vice versa when the bit pattern is traversed circularly.

. In the computation of the LBP labels, uniform patterns are used so that there is a separate label for each uniform pattern and all the non-uniform patterns are labeled with a single label. For example, when using $(8, R)$ neighborhood, there are a total of 256 patterns, 58 of which are uniform, which yields in 59 different labels.

The uniform and rotation invariant LBP can be further enhanced by combining it with a Rotation Invariant Variance Measure (VAR) operator, with the same parameters (P, R) , that characterizes the contrast of local image texture[38]. Both operators are also computationally attractive, as they can be realized with a few operations in a small neighborhood and a lookup table. The VAR operator is described by the following relations:

$$VAR_{(P,R)} = \frac{1}{P} \sum_{p=0}^{P-1} (g_p - \mu)^2 \quad \text{where } \mu = \sum_{p=0}^{P-1} g_p^2 \quad (2.5)$$

LBP(P, R) and VAR(P, R) are complementary and a feature set made by the combination of the two is expected to be a very powerful rotation invariant measure of local image texture. It is also possible to use joint feature sets composed by operators with different neighborhood.

Wavelets

The Wavelet Transform (WT) is having greater importance medicine and biology. The main uses of the WT concern the analysis of one-dimensional physiological signals obtained by electrocardiography (ECG) and electroencephalography (EEG), including evoked response potentials[55]. A survey of recent wavelet developments in medical imaging can be found in [54]. These include biomedical image processing algorithms (e.g., noise reduction, image enhancement, and detection) and image reconstruction and acquisition schemes (tomography, and Magnetic Resonance Imaging (MRI)).

2.2.7 Object detection and recognition

Object detection is a computer vision technology that deals with detecting instances of semantic objects of a certain class (such as humans, traffic signs, mitotic cells) in digital images. Humans recognize a multitude of objects in images with little effort, despite the fact that the image of the objects may be in different orientation, or in different size/scale. Objects can even be recognized when they are partially obstructed from view. This task is still a challenge for computer vision systems and represents the connection between Image Analysis topics and Machine Learning. Viola and Jones proposed a well known object detection framework [57, 56], which involves the sums of image pixels within rectangular areas, using the so-called Haar-like features, a name that resembles the Haar wavelet adopted in [41]. The technique generates a large amount of features and uses the boosting algorithm *AdaBoost* to reduce the over-complete set, by selecting the best features and training classifiers that use them. The evaluation of the classifiers generated in the learning phase can be quick, but generally not enough to be run in real-time. For this reason, the classifiers are arranged in a cascade in order of complexity, where each subsequent classifier is trained only on those selected samples which pass through the preceding classifiers. If at any stage in the

cascade a classifier rejects a sample, no further processing is performed. The cascade therefore has the form of a degenerate tree.

2.3 Machine Learning

Machine Learning (ML), a branch of Artificial Intelligence (AI), deals with the ability to define and to build systems that can learn from data. The core of ML deals with the representation of data and their generalization. Representation deals with the way the system describes the data. Generalization deals with the ability of the system to perform on unseen data samples. In Machine Learning, the observations are often known as *instances*, the explanatory variables are termed *features* (grouped into a *feature vector*), and the possible categories to be predicted are *classes*.

ML algorithms can be divided into different types:

- **Supervised Learning** generates a function that maps inputs to desired outputs usually called *labels*, because they are often provided by human experts classifying the training examples.
- **Unsupervised learning** models a set of inputs. It can also be referred to as *data mining* and knowledge discovery. Here, labels are not known during training.
- **Semi-supervised learning** combines both labeled and unlabeled examples to generate an appropriate function or classifier.
- **Reinforcement learning** learns how to act given an observation of the world. Every action has some impact in the environment, and the environment provides feedback in the form of rewards that guides the learning algorithm.

There exists a great variety of ML algorithms, and a detailed review is beyond the scope of this work⁴.

We focus, in our analysis, on *Pattern Recognition* and in particular on *Supervised Learning* methods.

2.3.1 Pattern Recognition

Pattern recognition is the assignment of a label to a given input value [5, 53]. In its most general form, pattern recognition involves:

⁴A list of ML algorithms can be found in http://en.wikipedia.org/wiki/List_of_machine_learning_algorithms

- **Classification** is the problem of identifying to which of a set of categories a new observation belongs, on the basis of a training set of data containing instances whose category membership is known,
- **Regression** is a technique for estimating the relationships among variables, assigning a real-valued output to each input,
- **Sequence labeling** refers to the assignment of a categorical label to each member of a sequence of observed values, in particular by making choices which depend on the one made for nearby elements (e.g. speech tagging)
- **Parsing** is the process of analyzing a string of symbols according to the rules of a formal grammar.

2.3.2 Classification

Among the different types of learning methods and pattern recognition techniques we focus our attention on *classification* which, in general ML terminology, is an instance of *supervised learning*.

The formal definition of a supervised classification problem can be stated as follows: an unknown function g maps the input instances $x \in X$ to the output labels $y \in Y$:

$$g : X \rightarrow Y \quad (2.6)$$

Equation 2.6 represents the *ground truth*.

The *training set*

$$T = (x_1, y_1), \dots, (x_n, y_n) \quad (2.7)$$

is assumed to represent the mapping of g in an accurate way. The classifier then tries to build a function $h : X \rightarrow Y$ that approximates as closely as possible the correct mapping. The measure of the performance (see 3.5 for details) is generally done on a separate set of data (the *test set*) whose labels are known but whose data are not used during the learning phase[32].

A common subclass of classification is *probabilistic classification*. Algorithms of this type involve statistical tools to define the best class for a given instance[42]. Probabilistic algorithms output a probability that the instance is a member of each of the possible classes. The best class is normally then selected as the one with the highest probability. Classification can be also divided into two separate problems - *binary classification* and

multi-class classification. In binary classification, only two classes are involved, whereas multi-class classification considers the problem of assigning an object to one of several classes. Since many classification methods have been developed specifically for binary classification, multi-class classification often requires the combined use of multiple binary classifiers.

2.3.3 Binary Classification

Binary classification is the task of classifying the members of a given set of objects into two groups on the basis of whether they have some property or not[49]. Medical testing is a typical binary classification task (i.e. to determine if a patient has certain disease or not). In traditional statistical hypothesis testing, the tester starts with a null hypothesis and an alternative hypothesis, performs an experiment, and then decides whether to reject the null hypothesis in favor of the alternative. Hypothesis testing is therefore a binary classification of the hypothesis under study [36]. A *positive* result is one which rejects the null hypothesis. Rejecting the null hypothesis when it is actually true - a False positive (FP) - is a **type I error**; on the other hand, when the null hypothesis is false results in a True positive (TP). A *negative* result is one which does not reject the null hypothesis. Accepting the null hypothesis when it is actually false - a False negative (FN) - is a **type II error**; on the other hand, when the null hypothesis is true results in a True negative (TN). How the number of TP, FP, TN and FN can be used to assess the performances of a classification algorithm is treated in Section 3.5.

2.3.4 Binary Classifiers

An algorithm that implements a classification, is defined a **classifier**. The term also refers to the mathematical function, implemented by a classification algorithm, that maps input data to a category (i.e. *class*). A great amount of algorithms has been developed for classification purposes, in particular for computer vision tasks [34]. Some methods suitable for learning binary classifiers include[59]:

- Naive Bayes classifiers
- Bayesian networks [60]
- Decision trees [4]
- Random Forests (RFs) [22]

- Support Vector Machines (SVMs) [25]
- Hidden Markov models
- Neural Networks (NNs) [45]

In our work we focused on two types of classifiers: *Support Vector Machines* and *Random Forests* which are widely used in computer vision classification problems (e.g. [52] and [7]).

2.3.5 Software Tools

Classification tasks can be accomplished by a large amount of software tools. Here we mention the ones that we consider to be the most relevant ones.

Weka [15, 19] is a **FLOSS** general purpose data mining software tool developed by the Waikato University ⁵ which allows to implement a great variety of classifiers [59]. It also has an interface with **R** ⁶ [24].

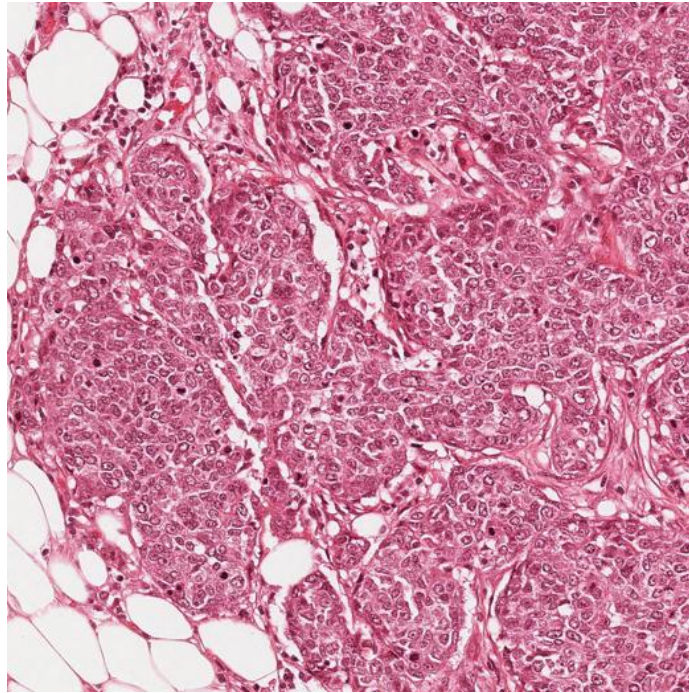
MATLAB can perform classification task by means of some of its toolboxes (i.e. Bioinformatics ⁷ and Statistics ⁸).

⁵<http://www.cs.waikato.ac.nz/ml/weka/>

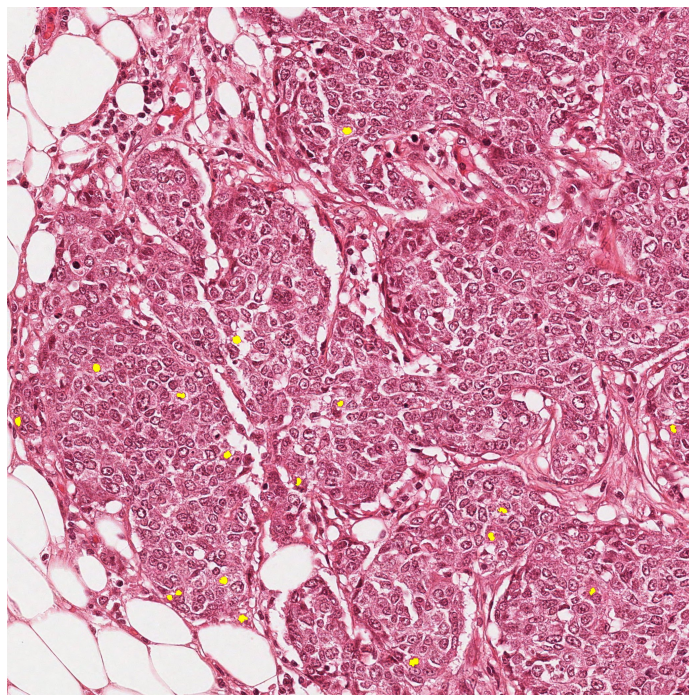
⁶<http://cran.r-project.org/>

⁷<http://www.mathworks.com/products/bioinfo/>

⁸<http://www.mathworks.com/products/statistics/>



(a) source image



(b) mitoses

Figure 2.4: Example of image with highlighted mitoses (yellow)

Chapter 3

Problem Definition

“πάντες ἄνθρωποι τοῦ εἰδέναι ὀρέγονται φύσει”
(All men naturally desire knowledge)

Ἀριστοτέλης(Aristotle, Met. 1.980a)

In our work we focused on two types of classifiers: *Support Vector Machines* and *Random Forests* which are widely used in computer vision classification problems (e.g. [52] and [7]). We also mention Convolutional Neural Networks (CNNs) because they played a relevant role in the definition of our dataset [REF].

3.0.6 Feature Extraction

Curse of dimensionality and PCA

[SNIPPET] In most computer vision applications it is not sufficient to extract only one type of feature to obtain the relevant information from the image data. Instead two or more different features are extracted, resulting in two or more feature descriptors at each image point. A common practice is to organize the information provided by all these descriptors as the elements of one single vector, commonly referred to as a feature vector. The set of all possible feature vectors constitutes a feature space. A common example of feature vectors appears when each image point is to be classified as belonging to a specific class. Assuming that each image point has a corresponding feature vector based on a suitable set of features, meaning that each class is well separated in the corresponding feature space, the classification of each image point can be done using standard classification method.

3.1 From Detection to Classification

The process of detection and classification....

3.2 Definition of Classification

Definition of classification:

- input
- output
- classes

3.3 Classification Assessment

3.3.1 Algorithms

The role of features and classifiers

3.3.2 Humans

Experience, agreement...

3.4 Performance

Definition of performance

[SNIPPET] The general appearance of a mitosis results in the fact that automatically detecting mitoses is very challenging. Different to other pattern recognition tasks, mitotic cells essentially are irregular shape objects. As a result, there is no simple way of extracting the features of mitotic cells. Benchmarking of different detection algorithms and comparison with human performance.

3.5 Benchmarks

3.5.1 Humans

Agreement between different histologists

3.5.2 Algorithms

The technique of *thresholding* is often used to analyze the performance of an algorithm that outputs probabilities in

Chapter 4

Design of a Mitosis Detection algorithm

*“Ab uno
disces omnis”*
(Learn everything from one)

Publius Vergilius Maro (Aeneis II, 65-66)

4.1 Structure

General structure of a Mitosis Detection algorithm.

4.2 Feature Extraction

(Qui o prima bisogna esplicitare che utilizziamo un subset di immagini)

4.3 Classifiers

Chapter 5

Design of a User Study

“O”

Πρωταγόρας (Protagoras)

5.1 Test Design

5.1.1 Dataset

(NB: il set di immagini usate deve esser già stato descritto)

5.1.2 User Interface

Description of the website used to collect data from users.

5.2 Data collection

Description of the data collected by the website

Chapter 6

Experimental Results

“Quote 6”

Author 6

6.1 Accuracy of the Detection Algorithm

6.2 Accuracy of Humans

6.3 Accuracy of Algorithms

(rif. paper)

Chapter 7

Conclusions

“Quote 7”

Author 7

Bibliography

- [1] National Comprehensive Cancer Network (NCCN) guidelines Breast Cancer Version 2.2011. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf, 2011.
- [2] Assessment of mitosis detection algorithms. <http://amida13.isi.uu.nl>, 2013.
- [3] ALBERTS, B., JOHNSON, A., AND LEWIS, J. E. A. *Molecular Biology of the Cell*. Garland Science, 2007.
- [4] AMIT, Y., AND GEMAN, D. Shape quantization and recognition with randomized trees. *Neural computation* 9, 7 (1997), 1545–1588.
- [5] BISHOP, C. M., ET AL. *Pattern recognition and machine learning*, vol. 1. springer New York, 2006.
- [6] BLOOM, H., AND RICHARDSON, W. Histological grading and prognosis in breast cancer: a study of 1409 cases of which 359 have been followed for 15 years. *British Journal of Cancer* 11, 3 (1957), 359.
- [7] BOSCH, A., ZISSERMAN, A., AND MUOZ, X. Image classification using random forests and ferns. In *Computer Vision, 2007. ICCV 2007. IEEE 11th International Conference on* (2007), pp. 1–8.
- [8] BRO-NIELSEN, M. Rigid registration of ct, mr and cryosection images using a glcm framework. In *CVRMed-MRCAS'97* (1997), Springer, pp. 171–180.
- [9] CANNY, J. A computational approach to edge detection. *Pattern Analysis and Machine Intelligence, IEEE Transactions on PAMI-8*, 6 (1986), 679–698.
- [10] DAMJANOV, I., AND FAN, F. *Cancer grading manual*. Springer Science+ Business Media, 2007, ch. 11, pp. 75 – 81.

- [11] DUNNE, B., AND GOING, J. Scoring nuclear pleomorphism in breast cancer. *Histopathology* 39, 3 (2001), 259–265.
- [12] ELICEIRI, K. W., BERTHOLD, M. R., GOLDBERG, I. G., IBÁÑEZ, L., MANJUNATH, B., MARTONE, M. E., MURPHY, R. F., PENG, H., PLANT, A. L., ROYSAM, B., ET AL. Biological imaging software tools. *Nature methods* 9, 7 (2012), 697–710.
- [13] ELSTON, C., AND ELLIS, I. Pathological prognostic factors in breast cancer. i. the value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology* 19, 5 (1991), 403–410.
- [14] FORSYTH, D. A., AND PONCE, J. *Computer Vision: A Modern Approach*. Prentice Hall Professional Technical Reference, 2002, ch. 10.
- [15] FRANK, E., HALL, M., TRIGG, L., HOLMES, G., AND WITTEN, I. H. Data mining in bioinformatics using weka. *Bioinformatics* 20, 15 (2004), 2479–2481.
- [16] GENESTIE, C. Mammary pathology. http://ipal.cnrs.fr/doc/projects/MammaryPathology_CatherineGenestie_2011.pdf, 2011.
- [17] GENESTIE, C., ZAFRANI, B., ASSELAIN, B., FOURQUET, A., ROZAN, S., VALIDIRE, P., VINCENT-SALOMON, A., SASTRE-GARAU, X., ET AL. Comparison of the prognostic value of scarff-bloom-richardson and nottingham histological grades in a series of 825 cases of breast cancer: major importance of the mitotic count as a component of both grading systems. *Anticancer research* 18, 1B (1998), 571.
- [18] GUICAN, M., BOUCHERON, L., CAN, A., MADABHUSHI, A., RAJPOOT, N., AND YENER, B. Histopathological image analysis: A review. *Biomedical Engineering, IEEE Reviews in* 2 (2009), 147–171.
- [19] HALL, M., FRANK, E., HOLMES, G., PFAHRINGER, B., REUTEMANN, P., AND WITTEN, I. H. The weka data mining software: an update. *ACM SIGKDD Explorations Newsletter* 11, 1 (2009), 10–18.
- [20] HARALICK, R. M., SHANMUGAM, K., AND DINSTEN, I. H. Textural features for image classification. *Systems, Man and Cybernetics, IEEE Transactions on*, 6 (1973), 610–621.
- [21] HARTLEY, R. I., AND ZISSERMAN, A. *Multiple View Geometry in Computer Vision*, second ed. Cambridge University Press, ISBN: 0521540518, 2004.

- [22] HO, T. K. Random decision forests. In *Document Analysis and Recognition, 1995., Proceedings of the Third International Conference on* (1995), vol. 1, pp. 278–282 vol.1.
- [23] HONEYCUTT, C. E., AND PLOTNICK, R. Image analysis techniques and gray-level co-occurrence matrices (glcm) for calculating bioturbation indices and characterizing biogenic sedimentary structures. *Computers & Geosciences* 34, 11 (2008), 1461–1472.
- [24] HORNIK, K., BUCHTA, C., AND ZEILEIS, A. Open-source machine learning: R meets weka. *Computational Statistics* 24, 2 (2009), 225–232.
- [25] HSU, C.-W., CHANG, C.-C., AND LIN, C.-J. A practical guide to support vector classification. Tech. rep., Department of Computer Science, National Taiwan University, Taipei 106, Taiwan, 2010.
- [26] HUANG, C.-H., AND LEE, H.-K. Automated mitosis detection based on exclusive independent component analysis. In *Pattern Recognition (ICPR), 2012 21st International Conference on* (2012), pp. 1856–1859.
- [27] HUANG, C.-H., VEILLARD, A., ROUX, L., LOMÉNIÉ, N., AND RACOCÉANU, D. Time-efficient sparse analysis of histopathological whole slide images. *Computerized Medical Imaging and Graphics* 35, 7 - 8 (2011), 579 – 591. `jc:title;Whole Slide Image Processj/ce:title;`
- [28] JÄHNE, B., AND HAUSSECKER, H. *Computer vision and applications: a guide for students and practitioners*. Academic Press, 2000.
- [29] KHAN, A., EL-DALY, H., AND RAJPOOT, N. A gamma-gaussian mixture model for detection of mitotic cells in breast cancer histopathology images. In *Pattern Recognition (ICPR), 2012 21st International Conference on* (2012), pp. 149–152.
- [30] KHAN, A., SIMMONS, E., EL-DALY, H., AND RAJPOOT, N. Hymap: A hybrid magnitude-phase approach to unsupervised segmentation of tumor areas in breast cancer histology images. *Journal of Pathology Informatics* 4, 2 (2013), 1.
- [31] LINDBERG, T. *Scale-Space*. Wiley Online Library, 2008.
- [32] LIU, J., SUN, J., AND WANG, S. Pattern recognition: An overview. *IJCSNS International Journal of Computer Science and Network Security* 6, 6 (2006), 57–61.

- [33] LOWE, D. Object recognition from local scale-invariant features. In *Computer Vision, 1999. The Proceedings of the Seventh IEEE International Conference on* (1999), vol. 2, pp. 1150–1157 vol.2.
- [34] LU, D., AND WENG, Q. A survey of image classification methods and techniques for improving classification performance. *International journal of Remote sensing* 28, 5 (2007), 823–870.
- [35] MANAVALAN, R., AND THANGAVEL, K. Evluation of textural feature extraction from grlm for prostate cancer trus medical images. *International Journal of Computer Applications (0975-8887) Volume 36-No.12* (December 2011), pp.33 – 39.
- [36] MITCHELL, T. *Machine Learning*. Mc Graw Hill, 1997.
- [37] NIXON, M., AND AGUADO, A. S. *Feature extraction & image processing*. Academic Press, 2008.
- [38] OJALA, T., PIETIKÄINEN, M., AND MÄENPÄÄ, T. A generalized local binary pattern operator for multiresolution gray scale and rotation invariant texture classification. In *In: Advances in Pattern Recognition, ICAPR 2001 Proceedings* (2001).
- [39] OJALA, T., AND PIETIKÄINEN M & MÄENPÄÄ, T. Multiresolution gray-scale and rotation invariant texture classification with local binary patterns. *IEEE Transactions on Pattern Analysis and Machine Intelligence* 24(7) (2002), 971 – 987.
- [40] PALIWAL, J., JAYAS, D., VISEN, N., AND WHITE, N. Quantification of variations in machine-vision-computed features of cereal grains. *Canadian Biosystems Engineering* 47 (2005), 7–1.
- [41] PAPAGEORGIOU, C. P., OREN, M., AND POGGIO, T. A general framework for object detection. In *Sixth International Conference on Computer Vision* (1998), IEEE, pp. 555–562.
- [42] RASMUSSEN, C. E. *Gaussian processes for machine learning*. Citeseer, 2006.
- [43] RAVEN, P. H., AND JOHNSON, G. B. *Biology 9th edition*. Mc Graw Hill, 2010.
- [44] ROUX, L., TUTAC, A., LOMÉNIE, N., BALENSI, D., RACOCEANU, D., VEILLARD, A., LEOW, W.-K., KLOSSA, J., AND PUTTI, T. A

- cognitive virtual microscopic framework for knowledge-based exploration of large microscopic images in breast cancer histopathology. In *Engineering in Medicine and Biology Society, 2009. EMBC 2009. Annual International Conference of the IEEE* (2009), pp. 3697–3702.
- [45] RUSSELL, S. J., NORVIG, P., DAVIS, E., RUSSELL, S. J., AND RUSSELL, S. J. *Artificial intelligence: a modern approach*, vol. 2. Prentice hall Englewood Cliffs, 2010.
 - [46] SAEYS, Y., INZA, I., AND LARRAÑAGA, P. A review of feature selection techniques in bioinformatics. *Bioinformatics* 23, 19 (2007), 2507–2517.
 - [47] SCHINDELIN, J., ARGANDA-CARRERAS, I., FRISE, E., KAYNIG, V., LONGAIR, M., PIETZSCH, T., PREIBISCH, S., RUEDEN, C., SAALFELD, S., SCHMID, B., ET AL. Fiji: an open-source platform for biological-image analysis. *Nature methods* 9, 7 (2012), 676–682.
 - [48] SCHNEIDER, C. A., RASBAND, W. S., AND ELICEIRI, K. W. Nih image to imagej: 25 years of image analysis. *Nat Methods* 9, 7 (2012), 671–675.
 - [49] SCHÖLKOPF, B., AND SMOLA, A. J. *Learning with kernels: support vector machines, regularization, optimization and beyond*. the MIT Press, 2002.
 - [50] SERTEL, O., KONG, J., SHIMADA, H., CATALYUREK, U., SALTZ, J. H., AND GURCAN, M. N. Computer-aided prognosis of neuroblastoma on whole-slide images: Classification of stromal development. *Pattern Recognition* 42, 6 (2009), 1093–1103.
 - [51] SMITH, S. M., AND BRADY, J. M. Susan - a new approach to low level image processing. *International Journal of Computer Vision* 23, 1 (1997), 45–78.
 - [52] SOMMER, C., FIASCHI, L., HAMPRECHT, F. A., AND GERLICH, D. W. Learning-based mitotic cell detection in histopathological images. In *Pattern Recognition (ICPR), 2012 21st International Conference on* (2012), IEEE, pp. 2306–2309.
 - [53] THEODORIDIS, S., AND KOUTROUMBAS, K. Pattern recognition. *Academic Press, Boston MA, USA* (2008).
 - [54] UNSER, M., AND ALDROUBI, A. A review of wavelets in biomedical applications. *Proceedings of the IEEE* 84, 4 (April 1996), 626–638.

- [55] UNSER, M., AND BLU, T. Wavelet theory demystified. *IEEE Transactions on Signal Processing* 51, 2 (February 2003), 470–483.
- [56] VIOLA, P., AND JONES, M. Rapid object detection using a boosted cascade of simple features. pp. 511–518.
- [57] VIOLA, P., AND JONES, M. Robust real-time object detection. In *International Journal of Computer Vision* (2001).
- [58] WANG, B.-H., WANG, H.-J., AND QI, H.-N. Wood recognition based on grey-level co-occurrence matrix. In *Computer Application and System Modeling (ICCASM), 2010 International Conference on* (2010), vol. 1, IEEE, pp. V1–269.
- [59] WITTEN, I. H., FRANK, E., AND HALL, M. A. *Data Mining: Practical Machine Learning Tools and Techniques*, 3 ed. Morgan Kaufmann, Amsterdam, 2011.
- [60] YIN, Z., BISE, R., CHEN, M., AND KANADE, T. Cell segmentation in microscopy imagery using a bag of local bayesian classifiers. In *Biomedical Imaging: From Nano to Macro, 2010 IEEE International Symposium on* (2010), pp. 125–128.
- [61] YOGESAN, K., JØRGENSEN, T., ALBREGTSEN, F., TVETER, K., AND DANIELSEN, H. Entropy-based texture analysis of chromatin structure in advanced prostate cancer. *Cytometry* 24, 3 (1996), 268–276.

Mitosis

Description of the Mitosis phases. [3, 43]

Mitosis is the process by which an eukaryotic cell separates the chromosomes in its cell nucleus into two identical sets, in two separate nuclei.

Documentazione della programmazione

Documentazione della programmazione in piccolo dove si mostra la struttura ed eventualmente l'albero di Jackson.

Listings

Il listato (o solo parti rilevanti di questo, se risulta particolarmente esteso)
con l'autodocumentazione relativa.

Website Implementation

Manuale utente per l'utilizzo del sistema

Use case

Un esempio di impiego del sistema realizzato.

Datasheet

Eventuali Datasheet di riferimento.