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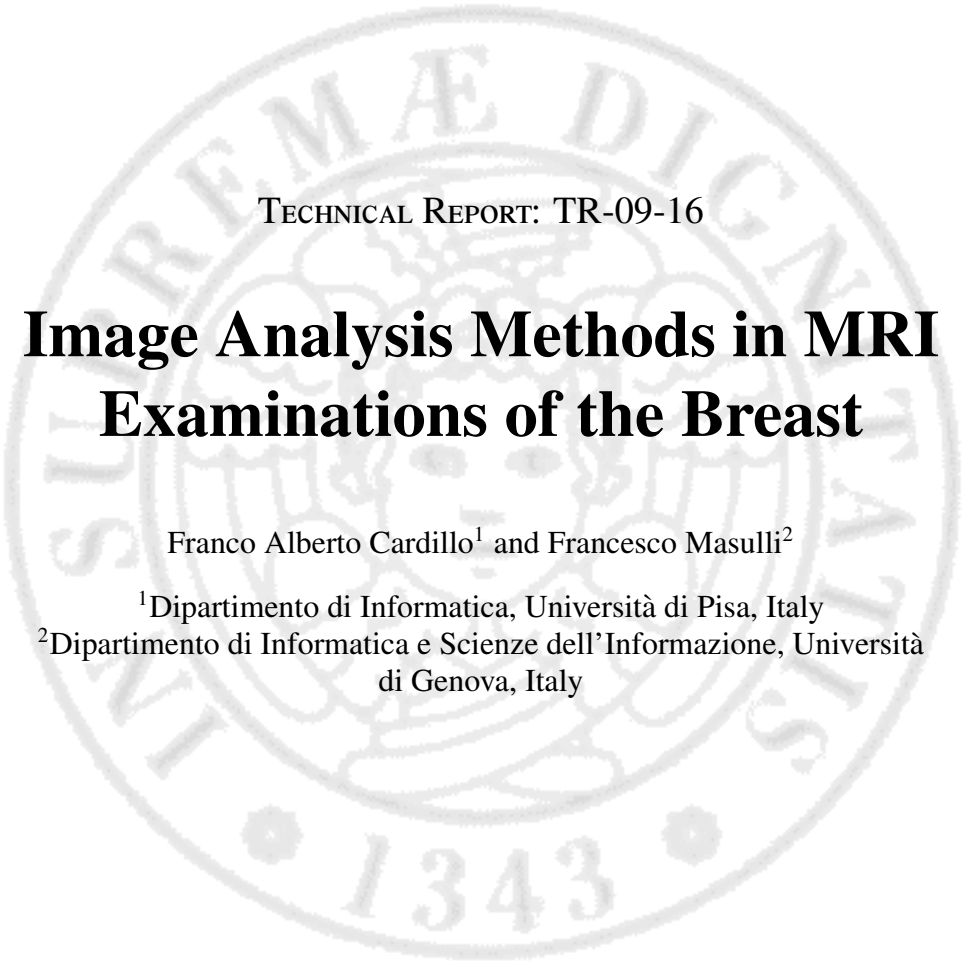

Technical Report: TR-09-16

Image Analysis Methods in MRI Examinations of the Breast

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September 28, 2009

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Abstract

Breast cancer represents a real emergency in many European and North American countries. In order to detect the diseases as soon as it starts developing, many countries have organized screening programs aimed to women monitoring. Traditional imaging modalities, like X-Ray mammography, do not provide certain and reliable results on young women or in women who underwent surgical interventions. Three-dimensional breast MRI has proven to be a valuable tool for disambiguate uncertain mammographic findings and for the pre-operative planning. However, in order for MRI of the breast to be effective, a contrast agent, highlighting areas with a high degree of vascularization, needs to be used. The full breast volume needs to be acquired once before and several times after the contrast agent injection. A contrast-enhance MR examination of the breast contains hundreds of images that must be inspected carefully. Automatic approaches to breast cancer detection can help radiologists in this hard tasks and speed up the inspection process. In this paper we present a survey of automatic approaches to breast cancer detection in MRI. We discuss both registration algorithms needed to align corresponding images acquired at different instants in time and classification algorithms able to label a suspicious area according to features automatically computed from the images.

1 Introduction

The medical diagnosis and the subsequent therapeutical planning increasingly rely upon images. Nowadays the number of imaging techniques, i.e. methods producing pictures of volumes inside the human body, is quite large and is continuously increasing. Recent image-acquisition techniques produce three-dimensional (3-D) or four-dimensional (4-D) digital datasets. The information contained in such examinations are richer than their corresponding 2-D examinations. In fact the geometry of the imaged body parts is represented with finer details. Furthermore, the imaged volumes can

be reconstructed and visualized in three dimensions, allowing the radiologists to better localize and estimate the signs of the diseases. Another advantage is represented by the possibility of studying the behaviour of the tissues over time, an information that is usually missing in older imaging modalities.

Anyway, the medical images (by themselves) do not give any hint about the diagnosis or the therapy: the collected images must be analyzed and interpreted by experts. Even if recent 3-D or 4-D acquisition modalities produce digital datasets, very often their inspection is still performed on 2-D printed films. The main limitation of such old-fashioned inspection modality is represented by its qualitative nature: the radiologists can perform only qualitative evaluations and measurements. Furthermore, printed films can show only partially the high details that modern modalities store in the single images. The use of films introduces another limitation related to the data storage. If the long-term archiving is based on films, the comparison of examinations acquired at different times may be a process too long and complicated to be performed routinely in the clinical practice. The 3-D or 4-D datasets contain hundreds of images and the number of images per examination is continuously increasing with technical advances. Since each image must be inspected, the time needed to complete the analysis of a single dataset may be very long. The full inspection process can be an error-prone process due to fatigue and habituation of the radiologist.

The problems discussed above can be partially solved by exploiting the digital format of the new data. Digital data can be stored in a centralized repository, allowing the radiologists to cross-validate their diagnosis or to access examinations acquired in the past. Furthermore, digital data can be processed by a computer. The introduction of software tools for Computer-Aided Diagnosis (CAD), able to interact with the back-end infrastructure storing the data, can alleviate the problems described above and speed up the data processing.

The use of CAD tools can help radiologists in the analysis of the hundreds of images produced by modern imaging modalities. A software program can suggest its own diagnosis or ask the radiologist to better inspect regions that the automatic analysis labels as suspicious. In some cases, in fact, CAD tools have reached or even surpassed the human diagnosis and are extensively used in routine examinations. The number of errors caused by habituation or fatigue can thus be reduced and the human performance can increase [1]. CAD tools can also be used as a valid training method for young doctors or students, by allowing them to inspect selected cases and compare their diagnosis with those provided automatically.

The present paper contains a survey of methods for the automatic or semi-automatic analysis of two specific imaging modalities: Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) of the woman breast. The paper does not tackle the issues related to archiving, sharing and communicating digital pictures. All of the methods discussed hereafter are related to the design, the implementation, and the experimentation of CAD tools able to support clinicians in the full process of analysis.

The paper is organized as follows. The section 2 discusses in more detail the benefits coming from the use of CAD systems. Section 3 briefly explains the reason why the breast cancer is considered an emergency in western countries and why a reliable software tool would be very useful. Section 4 presents the diagnostic protocol commonly used in breast cancer detection in MRI. Section 6 describes the automatic approaches

introduced so far for the automatic analysis of breast CE-MRI datasets.

2 The benefits of CAD tools

There are several motivations for introducing digital image processing and analysis methods in the clinical practice. MR or CT examinations produce volumetric, 3-D datasets. Such datasets allow an exact reconstruction and visualization of imaged internal tissues. In particular, in breast imaging, MR examinations produce 3-D views of the uncompressed breast. A CAD tool able to reconstruct and visualize the breast in 3-D would be very helpful in locating exactly the lesions.

As previously said, the inspections based on 2-D printed films are not quantitative but only qualitative. Computer methods introduce a quantitative analysis with reproducible results. The methods can be applied in several tasks: evaluating retrospectively the diagnostic protocol or the acquisition modality, supporting the operators during their visual inspections, comparing two different diagnostic set of criteria. The previous cases represent only a few examples of the available domain of application.

CAD tools help the clinicians by reducing the time needed for the analysis of a complete 3-D or 4-D dataset. A CAD program might highlight locations discarded by the human and suggest a second analysis

So far, the inspection of medical examinations is restricted to a single modality. Anyway, better results can be obtained by a multi-modal analysis, i.e., an inspection merging information extracted by images acquired by using different techniques. Multi-modal analysis are hard to perform 'manually', but become possible if the radiologist is supported by a computer.

A CAD tool would greatly improve the clinical routine especially in cases where the number of examinations is very high, like in the screening programs for the early detection of breast cancer.

3 Breast Cancer and Imaging

According to the latest American statistics [2], whose data are similar those published by other western countries, breast cancer is the most frequently diagnosed non-skin cancer in women, accounting for more than one out of four cancer cases. Furthermore, breast cancer is the second leading cause of death among women, second only to lung cancer.

The early detection of a breast cancer represents the only way to ensure affected women a high survival rate. 5-year relative survival rate is close to 100% for localized disease, i.e. in its earliest stage, but the rate drops to 27% when the cancer has spread in the woman's body [2].

The earliest sign of breast cancer is an abnormality shown by an image-based examination. X-Ray mammography is a very effective method of early detection: it detects 80%–90% of breast cancers on women without any clinical symptom. X-Ray mammography is the most commonly used imaging modality in screening programs since it is able to detect a cancer several years before any evidence is detected in a clinical

examination of the breast. However, due to its projective nature, X-Ray mammography has some limitations: both dense breasts (in young women) or scar tissues (caused by surgical interventions) are opaque to X-Rays. The mammography can thus be completely negative because some tissues hide a cancer region. Furthermore, in case of pre-operative planning, the 2D natures of the mammography might prevent from localizing exactly multiple foci of the disease [3, 4].

Two specific modalities are receiving a great attention: Computed Tomography and Magnetic Resonance Imaging. It is not easy to understand the role for CT in the investigations for breast cancer [5]. Various studies have reported that CT can be used successfully in the detection and characterization of breast tumors, for the local staging of breast cancer, and for the evaluation of a neoadjuvant chemotherapy. Unfortunately, the ionizing radiations delivered to the woman during a CT examination cannot be underestimated. They are estimated to be 10 times greater than a standard mammography, 20 times for a pre-contrast and post-contrast CT, 30 to 40 times for a dynamic CT [6]. CT should be used when mammographic findings are inconclusive and MR has contraindications preventing it to be executed. For the previous reasons, Computed Tomography of the breast is not used very often and is thus excluded by this paper.

3.1 Magnetic Resonance Imaging

MRI of the breast and, in particular, Contrast-Enhanced Magnetic Resonance Imaging (CE-MRI), are useful complementary methods to traditional diagnostic techniques. Some of the major benefits of breast MRI are:

- detailed 3-D representation of the full uncompressed breast. Unlike X-Ray Mammography, where the breast is compressed, during MR the woman lays prone, with the breasts suspended in the receiving coils. The possibility to determine exactly the location of the lesions is very helpful in the therapy or surgical planning.
- The dense breast of young women is opaque to X-Rays and some lesions might be hidden by opaque tissues. Breast MRI is not affected by dense tissues and produces images of any soft tissue in the breasts.
- Even if modern equipments use low levels of radiations, X-Ray Mammography uses ionizing radiations, which can be an obstacle to its application for screening purposes for young women. MRI (CE-MRI) of the breast does not use dangerous waves or agents.

Anyway, plain MRI is not very useful for the investigation of the breast. There is a significant overlap between the signal coming from benign and malignant tumors. In order to be effective, breast MRI requires the use of a paramagnetic contrast agent. When used in combination with the contrast agent, the examination is called Dynamic-MRI (D-MRI) or contrast-enhanced MRI (CE-MRI). The contrast-agent has no contraindications and is tolerated better than the radiations absorbed during a single mammography [7].

Even if CE-MRI is being performed by several years, there is a wide variety of acquisition protocols and interpretations schemes. In the next section, the examination will be described:

- using the terminology defined in the standard DICOM for what concerns the acquisition of the images and their logical structure in digital format.
- Using the lexicon proposed in [8] for what concerns the image inspection and the final reporting.

3.2 Contrast-Enhanced MRI

In CE-MRI studies of the breast, the full volume of the breast is imaged once before and several times after the injection of a contrast-agent. Each acquisition produces the same number of images, such set of images is called a series. The series are ordered in a set or study. The images in the study have the same dimensions, i.e. the same number of voxels[1] and the same color depth, i.e. the same number of gray levels.

In CE-MRI the first series, acquired before the injection of the contrast agent, is called the pre-contrast or morphological series. It corresponds to a plain (without contrast agent) MRI examination. The series acquired after the injection of the agent are called post-contrast. The number of the post-contrast series and the time lapse occurring between two consecutive series depend on the particular protocol used in the clinical centre and on the specific acquisition procedure. The ordered set of the acquired series is called study.

All the series have the same number of cross-sectional views, each one called a slice. The resolution, i.e. the number of voxels, is the same in all the images. It depends mainly on the acquisition device, but also on the particular acquisition sequence. Older devices produce images with 256×256 voxels, current devices offer 512×512 or 1024×1024 slices. Typically, there is no gap between consecutive slices. The physical dimension of the volume whose signal is stored in a single voxel depends on the device, on the actual volume being acquired, and on the specific image acquisition technique used.

4 Diagnostic Protocol in breast CE-MRI

In order to establish the presence of lesions, either malignant or benign, each slice in the study must be analyzed. Two different sets of criteria can be used in order to characterize a suspicious lesion: morphological and dynamical criteria [9].

Morphological criteria, which correspond to the criteria used also in other examinations, such as, for example, mammography, study the shape and the internal texture of the lesion. Dynamic criteria are related to the diffusion of the contrast agent in the tissues. The rationale behind the second set criteria relies on the fact that tumors are characterized by a different (increased) angiogenesis and vascular permeability with respect to normal tissues. Malignant and benign tumors thus present both a different

[1] Voxel stands for volume element.

morphological appearance and a different dynamic behaviour. The final diagnosis is made by combining the results of the morphological and dynamic analysis according to specified schemes [3, 9].

4.1 Dynamic criteria

Dynamic criteria concern the diffusion and the concentration of the contrast agent in the tissues. Both the diffusion and the concentration are studied at different times in the acquisition process. Basically, normal tissues do not enhance, their gray level does not change between the pre-contrast image and a post-contrast one. Lesions, both benign and malignant, present an enhancement. The first step in the interpretation of a CE-MRI examinations is in fact the search for enhancing regions in every image in post-contrast series. Such search is performed in subtracted images, i.e. images obtained by subtracting from a post-contrast image the corresponding pre-contrast one. The subtraction is often performed voxel-by-voxel, even if there are works proposing alternative and more complex algorithm to obtain subtracted images [10].

One of the most common dynamic criterion is the relative enhancement, first introduced in [11]. This method requires the computation of the following ratios:

$$E_n = \frac{I_n - I_{pre}}{I_{pre}} \cdot 100 \tag{1}$$

where I indicates an image at a specific index in the series (the index is not shown in order to simplify the notation), I_n corresponds the post-contrast belonging to the n-th series and I_{pre} is the corresponding pre-contrast image, and the index n ranges over the post-contrast series. For example, if the j-th image in some series contains a suspicious lesion, I_pre corresponds to the j-th image in the pre-contrast series, while $I_1, \ldots, I_{k-1}$ correspond to the j-th images in the $k-1$ post-contrast series. In practice, such subtracted images are not computed for the whole image but only for user selected regions, called Region of Interest (ROI).

The second criterion is the steepest slope calculation, first introduced by [12], and later modified by [13] in the initial slope:

$$Slope_i = \frac{E_{peak}}{T_{peak}} \tag{2}$$

where E_{peak} is the maximum percent enhancement in the ROI and T_{peak} is the time (series index) elapsed from the injection of the contrast agent till the peak in enhancement.

The washout ratio, described in [13], is one of the established quantitative criterion. It describes the downslope of the time-intensity curve:

$$W_{peak-k} = \frac{I_{peak} - I_k}{I_{peak}} \cdot 100 \tag{3}$$

where k is the index of a post-contrast series and *peak* corresponds to the index of the image with the maximum signal intensity.

Relative-enhancement values, computed according to eq. 1, are usually used to plot time-intensity curves. Such curves offer a good qualitative criterion to discriminate among enhancing regions.

One of the most used criterion has been described by [14]. It classifies suspicious areas in three different categories, depending on the shape of the associated relative-enhancement curve (figure 1):

- Type I. Steady curves, where signal intensity increases persistently with time.
- Type II. Plateau curves. After an initial increase, the signal remains constant over time.
- Type III. Washout curves. After an initial increase, the signal decreases over time.

Type II and type III curves (usually) show early peak enhancement in the first two minutes, then the signal does not increase.

The dynamic criteria based on curve analysis are very useful in discriminating between cancer and non-cancer regions. Quite often, by using dynamic criteria only, it is possible to reach a correct diagnosis. For example, a type III time course is a strong indicator of malignancy and is independent of other criteria [14].

Unfortunately, since there is some overlap between the dynamic behavior of malignant and benign lesion, in some occasions other types of criteria must be applied. Figure 2 shows real curves extracted from enhancing regions: it is clear that there is a significant overlap between the two types of curves.

4.2 Morphological criteria

The original set of criteria and the rules for interpreting them was introduced by [15] and later updated in [16]. One of the major results that should be achieved in breast MRI is a common acquisition protocol and a common lexicon. With a common framework and terminology, the results and the diagnosis obtained in different clinical trials or research groups can be compared in order to refine the diagnostic protocol. We do not present the complete morphological classification scheme, in the following some criteria, proposed in [8] with the aim of defining a common lexicon, are briefly presented.

Lesions may present basically three different appearances:

- foci, small enhancing regions;
- mass, larger enhancing regions;
- non-mass, linear, patchy, diffuse or segmentai enhancement.

Once an enhancing region has been segmented, its shape margin can be classified according to the morphological criteria listed above. The shape is classified as smooth (round or oval), lobulated, irregular, spiculated. For non-mass lesions, the classification, when feasible, is simpler and has three classes: smooth, irregular, clumped.

The third morphological criterion concerns the internal pattern of enhancement. A region presenting regular and homogeneous is usually classified as benign. Irregular, non-homogeneous patterns of enhancement are usually found in malignant cases and

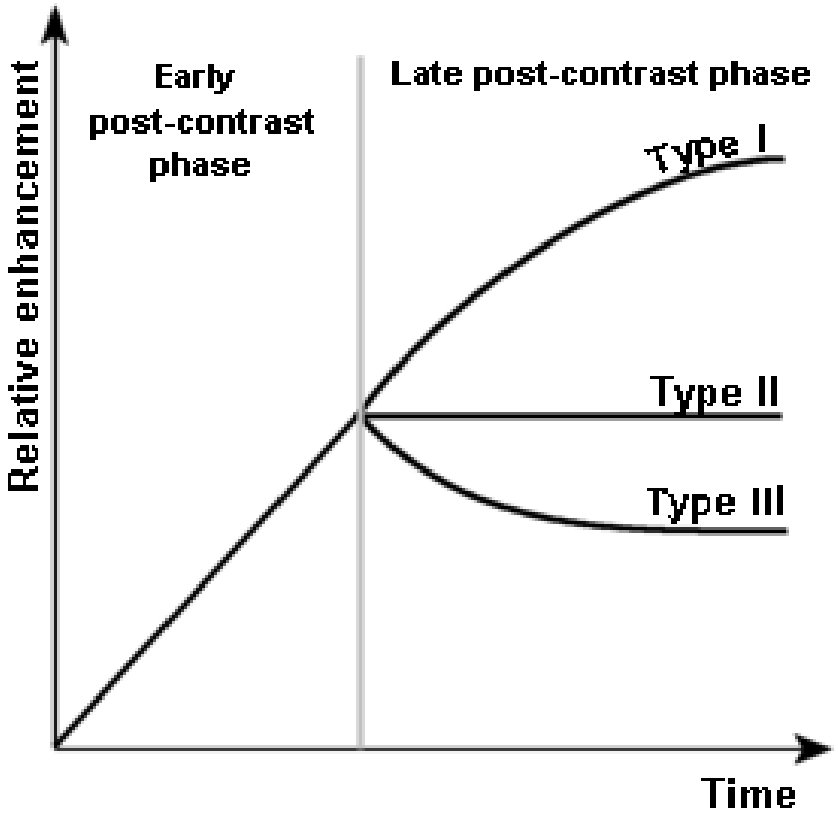

Figure 1: Ideal contrast-enhancement curves. Type I curves are usually benign. Type II curves are uncertain. Type III curves are usually malignant.

are thus classified accordingly. In the latter case the terms commonly used are: heterogeneous confluent/rim/dark septations. A detailed description of the classification scheme and a definition of the various terms can be found in [8].

Even if in some cases the only dynamic or morphological criteria are discriminative enough to obtain a correct diagnosis, an enhancing region can be classified only using both criteria. Combined classification schemes, i.e. schemes trying to relate the two types of analysis, are often used. One of the most common one is the Fischer scheme, discussed in [17].

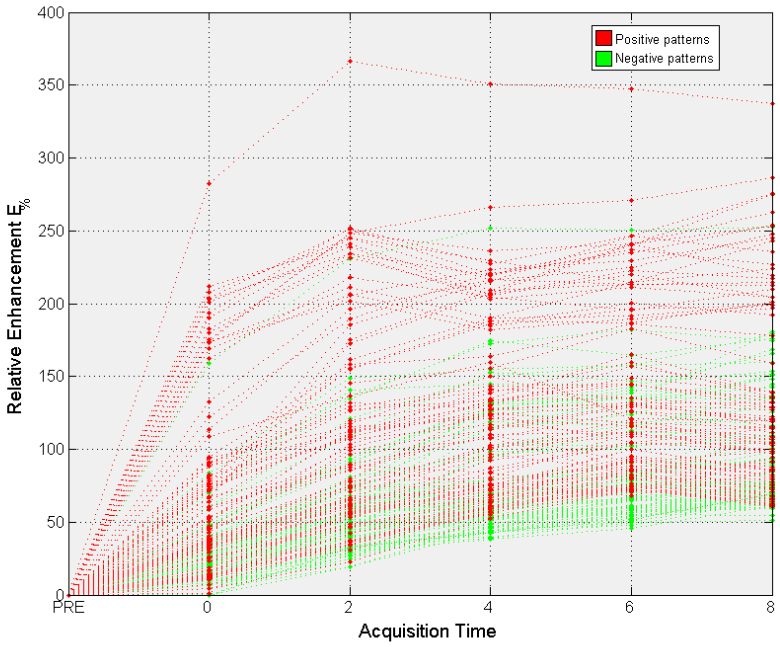

Figure 2: Real relative-enhancement curves. Red curves were extracted from malignant regions. Blue ones were extracted from benign regions.

5 Image registration

As discussed in the previous section, the dynamic criteria rely on a set of values extracted from the same region in images acquired at different instants in time. In order to obtain significant and correct results, the ROI must be placed exactly on the same spatial coordinates in the examinations.

Corresponding images in different series might not be aligned. In fact, during the acquisition, the patient might move. Even if the patient is able to stay completely still, the heartbeat and the breathing deform the volume being acquired resulting in misaligned images. Such movements need to be corrected before extracting the intensity values used to compute dynamic criteria.

More specifically, the image in a given post-contrast series must be aligned to the corresponding image in the pre-contrast series. The task of overlying two (or more) images taken at different times (or from different viewpoints or in different imaging modalities) is called image registration and represent a widely studied research field in image processing [18, 19, 20, 21].

In case of breast MRI registration, image registration refers to the spatial alignment of a post-contrast image with the corresponding image in the pre-contrast series. The

goal of the registration step is the elimination or the reduction of the differences in the two images introduced by the patient's movements or by the heartbeat. The differences introduced by the contrast-agent in the post-contrast images must be obviously preserved.

According to the terminology and the taxonomy of the methods first introduced in the survey [20], breast MR image registration can be classified as an intrinsic, voxel-based, non-rigid and local registration task. It is intrinsic because it relies only on information that can be extracted from the images. Since the breast does not contain any landmark, i.e. salient points that can be reliably located and identified by the radiologist, registration algorithms are voxel-based due to being limited to use exclusively information extracted by the voxels.

However, breast image registration in CE-MRI is very difficult to correct. In fact, the changes in gray levels caused by the diffusion of the contrast agent must not be corrected by the registration algorithm. Many intrinsic algorithms, in fact, assume that the gray levels in corresponding regions of the two images do not change over time. The differences are considered a sign of a movement and corrected in order to reach a correct match. The basic assumption characterizing most of the algorithm for breast MR registration is that the differences due to enhancing regions are much smaller than the entire breast. Since the differences caused by the movement affect a larger area (and volume), the algorithms simply ignores small enhancing areas. Since the major goal of automatic breast MR processing is the early detection of (small) suspicious areas, that assumption can be considered reasonable.

In [22], the authors propose a registration algorithm that minimizes the ratio of variance between a pre-contrast and the corresponding post-contrast images. Since their registration algorithm only accounts for global and rigid transformations, the algorithm first separates the breast from the chest, register the entire volume by applying the registration step in a pair-wise fashion, and finally reconstruct the volume. This algorithm cannot correct elastic deformation caused by compression or other movements, but the author claim that rigid registration is good enough to correct for the major movements. However, other authors report that breast movements cannot be corrected by rigid and global models [23].

In [24, 25], the authors present a method for registering bidimensional MR breast images based on a modified Self Organizing Map (SOM) [26]. Before the actual registration algorithm starts, the images are preprocessed and a set of features is extracted for every voxel in the images. Each voxel is then described by the partial derivates in its coordinates along the x and y axes and by the mean gray value in its neighborhood. Voxels lying in a plateau, i.e. a region with a constant gray level, are not used to drive the registration process. A SOM network is first overlaid on the source image, with a node for each voxel in the image. The artificial neural network is then trained using a modified version of the original algorithm able to correct local and elastic deformations. The training set corresponds to descriptions of relevant voxels in the target images. Once the network has been trained, a new image is built by interpolating the values of each node in the network. Also in this second algorithm, the basic assumption is that the number of voxels affected by the contrast agent is less than the number of voxels whose gray level has changed due to patient's movements.

In [27], the authors present a non-rigid registration algorithm based on an optical-

flow method. Their method first estimates a global affine transformation in a hierarchical fashion, by using a pyramid of images. In the second stage, they use an optical-flow method to take into account local and elastic deformations that cannot be corrected by the initial step.

In [23, 28], the authors present a novel two-stage registration algorithm for elastic registration of MR images. First, a global and affine transformation is estimated in three dimensions. Second, local and elastic deformations are corrected using Free Form Deformations based on B-splines. The degree of alignment between the post-contrast and the pre-constrast images is computed using normalized mutual information. Mutual information measures image similarity using the entropy computed on image histogram. In normalized mutual information, the measure accounts for overlap between the two images. The method modifies the two images in order to maximize the normalized mutual information. The deformation is computed on a set of control points in a multiresolution fashion in order to reduce the computational cost. The second paper [28] contains a quantitative evaluation of the registration results. Such results show that the non-rigid transformations are able to reach better results than rigid or affine models. This method, however, might cause volume changes in regions containing enhancing areas [29]. Such drawback can be overcome by introducing a regularization term in the cost function used during the registration [30]. The registration is accomplished by including in the cost function a regularization term modeling the local incompressibility constraint. Such term is motivated by the assumption that breast tissues are incompressible in small deformations and for short time periods. The experimental results show that the improved method improves the intensity based correction of MR examinations by reducing the shrinkage of structures in the images.

In [31], the authors propose a registration algorithm based on control points (landmarks). Unlike previous algorithms, the algorithm does not use the entire image content. It selects a set of locations in the two images and determines the transformation by identifying corresponding coordinates in the two images. The approach uses Elastic Body Splines (EBS) and includes constraints for modeling the physical properties of the tissues. The algorithm exploits the 3-D nature of the data considering deformations along the three axes. The algorithm can obviously work with manual or automatic landmark selection. The experimentation includes registration using random points in the two images (in specific breast areas) or automatically-extracted control points using a correlation measure.

In [32], the authors present a new method based on mutual information, Bayesian estimation of similarity among image patches, and optic flow to correct the differences caused by movements. In order to better distinguish changes in gray levels caused by patient's movements or by the paramagnetic agent, the model includes a model of the agent diffusion in the breast tissues. The computation of the similarity between two image patches takes into account the model of the agent. Once the mutual information has been computed, the likelihood of a movement is studied in a Bayesian framework, where local deformations are accounted for. Since local deformations are computed for a subset of image points, the result of the correction is an interpolated image. The authors propose a multiscale method based on optic flow where the global deformation, i.e. affecting the entire volume, is estimated on a fewer number of points. The method has been tested on a limited sample (examinations from three patients only) and relies

on the assumption that the enhancement model is reliable, which is not always the case.

In [33], the authors propose a method where the two images being corrected are first represented by a set of features and then registered. The approach is similar to [24] and does not involve an image-based similarity measure like mutual information. The edges are extracted by applying classical image filters (e.g. median filter) and morphological operators like opening and closing. Egde images are binarized and used for the actual computation of the transformation. Registration is performed on 2-D images by looking for corresponding structures in the binarized maps.

MR breast image registration is a very complex task due to the nature of the breast tissues and the specific imaging modality. The deformations affecting the tissues are not rigid or global. In general, they are a combination of a global rigid motion and local elastic deformations. Furthermore, there is not anatomical structure that could guide the registration process, at least for the global and rigid motion component. Registration algorithms can thus only rely on gray values, but those values cannot give a good estimate of the motion since they change due to the contrast agent even if the patient does not move. Any registration algorithm can thus mistake a tumor for a region subject to motion and delete the enhancing voxels. Some algorithms try and accommodate for enhancing regions by introducing a pharmacokinetic model of the contrast agent in the similarity computations. Obviously, a pharmacokinetic model cannot correctly evaluate the enhancement in any situation. However, there is not a general agreement as to whether or not use a registration algorithm. Several studies have in fact reported that a voxel-based registration algorithm (i.e. algorithms developed so far for MR breast images) can modify enhancing regions or delete them[34, 35, 36].

6 Automatic approaches for cancer detection

As discussed in the Introduction, CE-MR examinations of the breast are composed by several series, each one containing several images. As technology advances, the number of images in the series increases and the time needed to perform a complete analysis of the full dataset may become very long.

A CE-MR examination is usually performed in order to disambiguate the lesions detected on X-Ray mammograms and to detect small lesions that could be hidden by dense tissues in the 2-D images. In order to obtain a reliable diagnosis each image must be inspected and automatic methods can be very useful if they are able to reduce the time needed for the full analysis and speed up the entire diagnostic procedure.

Automatic methods can be subdivided in two categories: fully-automatic and semi-automatic algorithms. Fully-automatic algorithms require little or no human intervention. A key requirement for these algorithm is the ability to automatically locate the image regions that need to be analyzed. For example, a fully-automatic algorithm must be able to locate the breast regions and ignore the chest. Semi-automatic algorithms require a certain degree of interaction with the user. Usually they need the user to select the regions to be analyzed or can be guided in the breast segmentation process.

Hereafter we do not distinguish between automatic and semi-automatic approaches, but classify the relevant works in model-based and data-driven algorithms. Model-based approaches use compartmental models with one or more compartments to de-

scribe the flux of the contrast agent. The basic assumptions in this class of algorithm is that the parameters of the model describe physiological processes. However, there is not a single model able to fit data extracted from any type of tumor.

Data-driven models do not use compartmental models or other models whose components are claimed to be in a one-to-one relation with biological and physiological parameters. They use mathematical models, at various degrees of complexity, to fit the data extracted from the examinations. A relevant characteristic of the algorithms in this latter class concerns the nature of the features used in the analysis. Some algorithms use human-readable features and provide a human-readable classification of a region. Others do not allow an easy interpretation of their computations and their results. Even if the comparison among the algorithms is usually accomplished by looking at the degree or reliability of the final results, algorithms that are easily interpreted by the radiologists are better suited for being used in the real-world practice.

6.1 Model-based analysis

Model-based approaches to cancer detection describe the dynamic of the contrast agent diffusion, i.e. the intensity change in the signal, by a non-linear parameters compartmental model. The parameters of the model are estimated from a sample dataset by fitting a non-linear function to the observed data.

The compartmental models have one or more compartments corresponding to the blood flux and the extracellular extravascular space. The models also include constants corresponding to known physiological processes [37, 38].

In [39], the authors present a model-based CAD tool able to perform breast segmentation, image registration and automatic analysis of signal-time curves describing dynamic criteria. The segmentation algorithm has been developed specifically for the images included in their dataset: breast MR images acquired along the sagittal plane. The breast is identified by locating the breast-air boundary and the chest wall. The algorithm starts by finding the external border of the breast, where the signal increase is strong and very easy to detect. Once the external border has been detected, it is eroded by applying a series of erosion operators according to the Mathematical Morphology theory. The finding of the chest wall is then reduced to the problem of detecting the most likely boundary with the same shape as the eroded breast boundary. The authors propose a combination of a graph search algorithm and dynamic programming technique to locate the optimum profile. The quantitative evaluation of enhancing regions is a based on a pharmacokinetic compartmental model. There are two compartments, the first one modeling the blood plasma and the second one modeling the extracellular space of the breast tissue. Each compartment is described by coupled differential equations whose solution gives different rise functions that can be associated to the different types of enhancement. The model includes equations to simulate the slow administration of the contrast agent and to take into account noise. The same pharmacokinetic model is used by the registration algorithm to ignore differences in the images not caused by movements, as described in the previous section.

In [40], the authors propose a model-based method using a Bayesian estimation of the parameters. Their single-compartment model describes the diffusion of the contrast agent from the arterial flux into the extracellular extravascular space and its venous

efflux. They introduce a spatial-based estimation of the parameters estimation. In fact, in other models the estimation procedure evaluate a single voxel or all of the voxels in a ROI: in both cases they produce a single set of parameters describing the analyzed region. In [40], each voxel is associated to a set of parameters, but the estimation is based on information coming from voxels in their (2-D or 3-D) neighborhood. The Bayesian estimation produces an a posteriori distribution of probability which is later used for an accurate computation of standard errors and confidence intervals. The authors show that the Bayesian approach with a spatial-based estimation procedure allow better morphological and functional statistics of the analyzed regions.

Another one-compartment approaches can be found in [41], where parameters are estimated using a simplex minimization procedure. A different two compartments model is described in [42]. A more complex model is described in [43], where the authors clearly show that a more realistic simulation of the physiological processes needs more info in order to produce reliable results. Such information is not usually available in the normal clinical practice, thus limiting the applicability of more sophisticated approaches.

6.2 Data-driven approaches

Data-driven approaches use more or less complex mathematical models to classify regions of enhancement without using any physiological or biological constraint. The features can be related to the dynamic behaviour of the contrast agent or to the morphology of an enhancing region.

Approaches using soft computing techniques do not rely upon any hypothesis about the behavior of the contrast agent. Usually, approaches in this class try to infer the signal characteristics from the available data. In some cases, for example when using Artificial Neural Networks (ANN), the knowledge acquired about the signal enhancement or the morphology of the lesion is not expressed in an clear symbolic form, but remains hidden in the network weights. The major pro of such approach is the independence from any prior knowledge about both the morphological appearance of the tumor and its dynamic behavior. Obviously a minimum understanding of the domain, even if only partial, is needed in the feature extraction step. The works discussed below represent part of the works that have been recently published. Most of them use neural network due to their capability to learn from noisy data.

In [25], the authors present Mammalyzer, one of the earliest CAD systems proposed by a research group. The system uses the SOM Matcher algorithm (described in section 5) for performing the image registration and a simple threshold-based classification scheme for voxel labeling. The classification simply compares the value of a voxel in a post-contrast image with a single voxel in the corresponding pre-contrast image. The voxel is labeled as suspicious if the percent increment in value (brightness) exceeds a given threshold (90% in the paper). Besides the very basic classifier used, the main limitation of the Mammalyzer system is represented by the fixed-value parameters. The authors set the parameters and developed the analysis procedure targeting only the particular images they had available. Mammalyzer II. Mammalyzer

II [44] is an extension of Mammalyzer within the Cyclops [2] expert system framework. The authors claim that Cyclops is able to choose optimal image operator sequences and parameter sets. Within this framework, the original Mammalyzer algorithms can be applied to a wider class of MR examinations.

In [45], the authors present an automatic approach for the extraction and classification of 3-D morphological features. They computed margin descriptors and radial gradient analysis on 3-D volumes corresponding to enhancing regions and on single 2-D slices extracted from the 3-D volumes. The features were represented as functions of time and space and approximated using multiple regression from data. Classification is performed using linear discriminant analysis. A Receiver Operating Characteristic (ROC) analysis of the classification results show that the combination of the radial enhancement and margin sharpness represent a good feature for distinguishing between benign and malignant enhancing regions both in 2-D and in 3-D, with better results on 3-D data.

In [46], the authors discuss the application of ANNs for the classification enhancing regions. The authors used 14 features extracted from time-intensity values describing the dynamic of the contrast agent diffusion in the wash-in and in the wash-out stages. For each examination, a single time-intensity curve is extracted by placing a free-size ROI on the most enhancing region. In case of inhomogeneous enhancing regions, the curve with the maximal enhancement is kept. The 120 elements dataset is then used for training a Multi-Layer Perceptron (MLP) with 14 input nodes, five hidden units and one output element for the binary classification into the two categories benign or malignant. The neural network has been trained with the backpropagation with momentum learning algorithm for 100000 epochs. The experimental results have been obtained with a leave-one-out experimentation and report a 89% accuracy, which is comparable to the one obtained by experienced radiologists (91%) and significantly grater than that reached by low-experience radiologists.

In [47], the authors report a detailed experimentation of multilayer perceptrons for the classification of time-intensity curves. They experimented 3-layers MLPs with a different number of units per layer on a dataset constructed from 162 malignant and 102 benign CE-MRI examinations. The dataset is constructed in three steps. First, a the parameters of a pharmacokinetic two-compartment model [48] are estimated for each voxel in the images. Second, the parameters of the model are used to color-code suspicious enhancing region. Third, the time-intensity curves are extracted by manually placing on one of the color-coded enhancing regions a ROI covering the larger part of the lesion. The time-intensity curves are computed by averaging the voxels value over the entire ROI in the 32 images in the series. The dataset is expanded with with 105 time-intensity curves extracted from normal breast tissues by placing a ROI in the ductal areas far from suspicious lesions. The final dataset contains 340 time-intensity curves: 162 malignant, 73 benign, and 105 corresponding to normal parenchyma tissue. The dataset was split in a training set and a test set and all the networks were trained for 20 epochs. The authors made various tests in order to establish the number of units performing best, the input space dimension allowing the network to reach a better performance, and the network discriminative power with two categories (be-

[2] http://www.cyclops.ufsc.br/

nign/malignant) or more (lesion type). The most interesting results concern the ANN behaviour versus the number of categories. The authors report that the ANN is able to distinguish between a lesion and normal breast tissue with 87% correct classifications. The largest 28-4-3 (28 input nodes, 4 hidden nodes, 3 output nodes) reaches a good performance on discriminating between malignant and benign curves. The performance decreases when the network is trained to distinguish among different lesion types.

In [49], the authors propose a method based on decision trees constructed by using features extracted from ROIs selected by a human expert. The goal of their study was to establish whether or not qualitative criteria, like those based on relative enhancement curves, allow a better diagnosis. They built a first decision tree using morphological features only and a second one using both morphological and dynamic criteria. By experimenting on a 100 cases dataset with balanced benign and malignant classes, the authors reported that enhancement curves were the most predictive kinetic features.

In [50], the authors describe an experimentation of several methods for the classification of time-intensity curves and other dynamic criteria. They used CE-MRI examinations acquired using T2* weighted sequences, that provide a higher specificity than T1-weighted according to some reports [51, 52]. They experimented the following classifiers: minimum enhancement threshold, Fisher's linear discriminant function, probabilistic ANN, MLP trained with the backpropagation algorithm, and a criterion based on a Correlation Coefficient (CC) between the input curves and a target function. All of the classifiers were trained and tested on time-intensity curves or dynamic features extracted from those curves computed as an average over the voxels in the ROIs. The minimum enhancement threshold and the CC were tested also on a dataset including curves and features computed on single voxels. The ROIs were extracted in semi-automatic fashion: voxels were labeled according to their CC with a target curve extracted from malignant data, while regions were formed using a region growing approach. When the automatic segmentation failed, the ROIs were extracted manually. All of the classifiers were trained with a leave-one-out cross-validation method. The authors used 127 examinations, 70 of which containing a malignant region. They found that the minimum enhancement threshold provides the best results among the tested classifiers. In order to reach performance similar to the threshold-based classifier, the other approaches, in particular the two ANNs, required a detailed fine-tuning step to learn and avoid overfitting. The threshold-based classifier was found to be robust with respect to the choice of the threshold value.

In [53], the authors study the performance of three-layer MLPs using a ROC analysis. They used 76 cases with the goal of establishing quantitatively the importance of features commonly used by radiologists. The network used in the test had an input layer with a variable number of nodes, a hidden layer with five units and an output layer with a single output unit for the binary classification in benign/malignant categories. They established the importance of the features by training the network using different subsets of the available input features and training the networks with a jackknife method with early stopping. They found that the ANN trained on the dynamic features perform almost as well as the the radiologists participating to the research work. The inclusion of morphological features made the network performance decreases. The authors did not experiment their algorithm in combination with an image registration step.

In [54], the authors compare the multilayer perceptron (described in [47]) against the pharmacokinetic model described in [48] on a dataset including examinations from 15 women. Both the models were trained to classify time-intensity curves composed by 28 measurements points (corresponding to CE-MRI series of images of the entire imaged volume). The results were evaluated visually by color-coding the images according to the output label of the ANN or the parameter values in the pharmacokinetic model (which are not directly related to a category). The two models correctly classify malignant and benign lesions, with the ANN classification resulting in a higher rate of false positive cases on benign lesions presenting a strong enhancement. The benefits of the ANN, that does not use any a priori knowledge, over the pharmacokinetic model are related to the higher computational speed and the final labeling into direct categories. Obviously, the architecture of the ANN, in particular its input field, is related to the imaging protocol: an ANN must be used on data with the same characteristics of the training dataset.

In [55], the authors discuss the discriminating power of textural features, i.e. properties of the distribution of gray levels inside selected ROIs, and show how they can be used in discriminating between benign and malignant lesions. The ROIs were selected by expert from images in 79 CE-MRI examinations. For each ROI, the number of gray levels is decimated to 32 and are represented using Gray Level Co-occurrence Matrices (GLCM). The statistical analysis, using Logistic Regression Analysis, proved that there are significant statistical differences in the GLCM of benign and malignant lesions. In particular, features like entropy, sum entropy, and variance are the best indicators to test for a correct classification.

In [56], the authors used a MLP trained with the backpropagation learning algorithm to classify static features in CE-MRI of breast. The set of features include pre- and post-contrast signal intensities, mass margin descriptors, mass shape, mass size, and mass granularity by texture analysis. They did not include dynamic features related to the signal behaviour over the acquisition time. The used dataset includes 14 patients. The static region descriptors were extracted via thresholding and binary image processing by morphological operators. The features were used to build a dataset used in a 10-fold cross-validation testing of the MLP. The final sensitivity, specificity, and accuracy were higher than 90%. Their results are somewhat contrasting with other research papers, such as [53], reporting a greater discriminating power of dynamic features.

In [57], the authors experimented an improved neural network, called "Temporal Associative Subjective Memory with Bimodal Activation" to study both dynamic and morphological features extracted from 604 histologically proven cases of contrast-enhanced lesions. Furthermore, they used an automatic input variable selection method. Such method trains a population of ANNs using different input features and selects the best networks using genetic algorithms. Their improved ANN shows a sensitivity of 94% and a specificity of 92% in predicting the correct diagnosis. By using that complex training strategy, they report that the best neural network is able to outperform a trained and experienced radiologist.

In [58], the authors present the results of an extensive experimentation aiming at evaluating the discrimination power of kinetic and morphological features by training a MLP with backpropagation. They used a dataset containing 105 lesions (75 malignant

and 30 benign), divided in a training set with 59 lesions and a test set with 46. For each lesion, the morphological features (margins, homogeneity, rim enhancement, and septation) were assessed by a trained radiologist via visual inspection. Dynamic (kinetic) features were computed from ROI positioned on the region (in each lesion) presenting maximal early enhancement. They performed a cross-validation procedure 10 times, by splitting the training set in two halves for training and validation (in order to avoid overfitting). Several MLPs have been tested by varying the number of input features (from 3 to 26) and the number of hidden units (from 2 to 13). The importance of the input features was estimated by automatic relevance determination, that is a method for evaluating the importance of the features by studying the variance of the weights on the ANN connections. Several combinations of features were used in the experimentation and the results were evaluated with ROC analysis. The authors report that the highest diagnostic accuracy is reached by the minimized model using only the most important features evaluated on the maximized model, that is the MLP using the entire set of input features (both morphological and dynamic). The most important features were the margin descriptor, time to maximum enhancement, two features related to the washout-ratio and the type of the curve. The maximized MLP and MLPs based on dynamic features ranked among the best performers. MLPs using morphological features only was the worst. Their results confirm that dynamic criteria give a correct diagnosis on a large number of cases. However, there is an overlap in the dynamic behaviour of benign and malignant patterns. In this case, the most valuable morphological criterion appear to be the margin descriptor. Unfortunately, the evaluation of the margins is not always possible: on small lesions, the spatial resolution of CE-MRI is not enough to distinguish between a smooth and an irregular border.

In [59], a five-parameter logistic equation is fitted to signal value in order to characterize the dynamic behaviour of the contrast medium. They experimented their method on six cases presenting different pattern of enhancement, with type I, type II, and type III curves. The logistic equation was able to fit those curves and suggested that the most valuable dynamic features are related to the presence of a plateau, to the maximum slope, and to the washout stage.

In [60], a fully automated method for detecting suspicious lesions in CE-MRI axial images is presented. First, non-relevant regions, like the thoracic cavity or the lungs, are removed by applying a Cellular Neural Network (CNN) without using any a priori information about the breast anatomy. CNNs are composed by a N-dimensional array of units which are able to receive multiple inputs from neighboring units and have a single output. Each cell has an internal state which is usually hidden from neighbouring cells. CNNs are often applied for performing morphological operations on 2-D images. In the current method, two CNNs are applying for performing gray level thresholding and removal of small object. Once the breast has been segmented, Maximum Intensity-Time Ratios (MITR) are computed and a new image is constructed with the resulting values. A 3-D template is then applied to the images in order to highlight spherical 3-D regions which are likely to correspond to enhancing regions. It must be noted that this method does not classify the detected regions: it just shows the enhancing regions reaching an impressive 100% sensitivity with a low rate of false positives. Anyway, the method was experimented on a very limited dataset (39 lesions) and uses some non-adaptive thresholds that can strongly influence the performance on extended datasets.

In [61], the authors propose an Empirical Mathematical Model (EMM) of the contrast agent diffusion. The model is based on a single equation with five parameters whose initial values strongly influence the computational time for the fit to be computed or failure to converge. Other diagnostic features were not computed on the data but manipulating the model equation. The method was experimented on 22 cases with malignant, benign, and no lesions. The authors report that they obtained a very good fit on data from all of the lesions. It should be noted that the acquisition protocol used in the current experimentation was different from the clinical one. In particular, they acquired complete series of images at very long time delays (up to 30 minutes) after the contrast agent injection. By using the modified protocol, they were able to study accurately the washout ratio, which represents a very reliable dynamic criterion.

7 Conclusions

In this survey we have discussed how contrast-enhanced MRI studies of the breast can be automatically processed by computer programs. Breast MRI is becoming an important tool able to disambiguate uncertain mammographic findings. A typical CE-MRI examination of the breast produces hundreds of images and each image must be inspected. A CAD tool would provide a great benefit in the clinical practice. It could simply speed up the inspection or it could be used as a second expert reading the examination. Furthermore, recent acquisition devices produce images with more details than the older devices. The diagnosis relies upon two different sets of criteria: morphological and dynamic. Dynamic criteria require the comparison of values extracted from different images. A registration step is thus required by which images must be spatially aligned in order to get a reliable comparison. There are several methods that can be used to bring the images in spatial alignment, but the best suited methods are those able to correct elastic, local deformations. In CE-MRI the use of the contrast agent further complicates the correction since gray levels change in the various images. The methods try to compensate these differences by using models of contrast-enhancement or algorithms based on mutual information.

Once the movements have been corrected, the analysis can proceed. Morphological criteria require the application of digital image processing operators to build a representation of enhancing areas. Texture-based methods are used to study the internal pattern of enhancement. Dynamic criteria require the application of classification techniques for the categorization of the curves and the values extracted from the images. Methods can be roughly subdivided into model-based algorithms and data-driven approaches. In the former case a model of the contrast agent diffusion is used to classify a region, in the latter case a training set of images is used and the extraction of a model for the enhancement is delegated to an inductive classifier. Since it is quite hard to build a reliable model of the enhancement, inductive classifier and statistical techniques are suited for the classification task. Even if many authors report quite good results, this subject lacks a standard corpus of images that could be used as a benchmark to compare and validate the various approaches. Every author uses their own dataset, some authors present results obtained on only few cases. Another problem is breast segmentation. Even if the segmentation would improve the results of the registration and of

the classification modules, especially when fully automatic approaches are used, only few methods have been experimented.

From this survey the following priorities can be listed as emerging:

- the importance to set up a collection of a large number of examinations to be used as benchmark;
- the necessity to experiment and validate the registration methods. The methods should be experimented on images with great movements and should be validated in order to be sure that they do not remove small lesions;
- the challenge to develop new digital image processing algorithms and inductive classifier for the two distinct set of criteria, may be by cross-fertilization of both the areas;
- the importance of statistical techniques that should find, if any, relationships among the various features that could be used in the description of the lesions.

8 Acknowledgements

The work was partially supported by grants of the University of Genova and of the University of Pisa. Franco Alberto Cardillo has been supported by a Post-Doc fellowship of the University of Pisa.

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