A new user - friendly visual environment for breast MRI data analysis

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Abstract

In this paper a novel, user friendly visual tool for **Bre**ast MRI **D**ata **An**alysis is presented (**BreDAn**). Given planar MRI images before and after IV contrast medium injection, **BreDAn** generates kinematic graphs, color maps of signal increase and decrease and finally detects high risk breast areas. The advantage of **BreDAn**, which has been validated and tested successfully, is the automation of the radiodiagnostic process in an accurate and reliable manner. It can potentially facilitate radiologists' workload.

Keywords: Magnetic Resonance Imaging, Mammography, Data Analysis, CDSS, Clinical decision support systems, CAD, Kinetics.

1. Introduction

Nowadays, better screening has shown that the number of breast pathology cases increases steadily and breast cancer is their main expression [1]. Therefore, accurate and timely diagnosis of breast diseases is vital for patient's treatment [2].

The protocol of breast imaging-screening involves at a first stage clinical examination and X-Ray mammography. However, numerous studies have

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shown that classical X-ray mammography has a false-negative rate of 20% [3], especially in women in the pre-menopausal period with dense breasts. X-ray mammography fails to detect: a) cancerous sites, b) all breast cancerous sites, c) infiltrating lobular carcinoma and d) ductul carcinoma in situ (DCIS). Nowadays, the answer to an inconclusive mammography or ultrasound examination is the adjunctant exploitation of the imaging method of breast MRI [4, 5].

Breast MRI is a powerful tool in breast imaging. The method, although costly, is safe without the use of ionizing radiation, thus reducing health risks for patients. Furthermore, studies have shown that the sensitivity of breast MRI, especially for the detection of cancer, is the greatest of all imaging techniques [6–14], making it very useful for the detection process [15, 16]. Reviewing related literature, breast MRI sensitivity is within the range 84-93 % while its specificity is within 37 - 97 % [3]. This can produce high false positive rate which would lead to unnecessary biopsies and discomfort to patients. In general, breast MRI is an accurate method for the visualization of the internal tissues of the breast, providing high resolution images that allow radiologists to accurately diagnose the existence of pathologies always in conjuction to X-ray mammography. Recent technological progress in software issues with the development of fast pulse sequences with good fat suppression and in hardware issues with the development of dedicated breast coils of high signal to noise ratio [17] and sensitivity encoding [18] have established breast MRI as an important, accurate and reliable imaging tool in the medical community.

The contribution of breast MRI in determining breast pathologies is revolutionary [5, 19, 20]: it can i) identify early stage of cancer in women at high risk [18], due to its high sensitivity in dense breasts [5, 8]; ii) help towards detecting cancerous sites previously underestimated by mammography [21], or determining mammography's inconclusive findings [22] of various sizes (multifocal or multicentric); iii) differentiate between pathologies; iv) determine tumor size and v) determine image adjacent chest wall and muscle. Regarding the pre-operative staging, breast MRI can determine vi) the surgical planning (performance of a radical mastectomy or a modified one) [23]. It can also, vii) assess the response to neoadjuvant chemotherapy [9, 24], where early knowledge of a response to specific scheme of neoadjuvant chemotherapy can help in adjusting it (change dose and/or frequency or even substituting it with another scheme); viii) assess any residual tumor load following lumpectomy and tumor recurrence at the lumpectomy site. However, this requires

technical and radiological experience due to the surrounding scar tissue that enhances after IV contrast medium injection causing a shining effect which can potentially hide adjacent lesions. Finally, breast MRI can detect primary cancerous sites in cases of patients with metastasis, so a therapeutic scheme can be assigned, thus avoiding radical solutions, such as whole breast radiation or mastectomy. Overall and despite the fact that there are rare cases of breast pathologies that escape MRI [5, 25], breast MRI has been incorporated into the clinical daily routine of breast imaging and has become a standard tool for breast evaluation.

The concept of breast MRI relies upon the angiogenesis of cancerous sites [26, 27]. IV administrated contrast gadolinium-based media, facilitate the imaging of those sites in an accurate and precise way. The advantage of breast MRI as a diagnostic examination is that it produces two pieces of information that help towards the differential diagnosis of pathologies. Firstly, it produces various types of planar images prior and after the administration of contrast medium. Secondly, it produces dynamic information regarding the flow of injected contrast medium within the breast tissue. Breast diagnosis incorporates both the morphological characteristics of breast tissue, as well as the kinetics of the contrast medium within breast tissue. Regarding the former, anatomical morphological characteristics of pathologies include the shape, the size and the smoothness. Spherical or oval lesions, smooth and well defined margins of homogeneously enhanced lesions correspond, usually, to benign pathologies, whereas star-like or dendrite-type lesions refer to malignancy. Enhancement imaging characteristics are not, however, conclusive by themselves for the determination of breast pathology.

The extra supplied information by breast MRI, i.e. the kinematic characteristics of the injected contrast medium, can help in conjunction with the morphological information towards the differential diagnosis and determination of type of pathology. The dynamic flow characteristics of contrast medium during the wash-in and wash-out periods demonstrate the degree (number, density) and type (leaky) of vascularity.

Cancerous sites are characterized by capillaries with pathological vessel wall architecture and leaky endothelial linings. Therefore, the effect of angiogenic activity is twofold: there is an increased vascularity, leading to a focally increased inflow of contrast material, plus increased vessel permeability, leading to an accelerated extravasation of contrast material at the site of a tumor [3]. This means that MRI signal is very intense after the contrast medium is injected to the patient, but significantly debilitates as time goes

by. Therefore, benign lesions are characterized by high signal intensities.

Considering a region of interest (ROI) of breast tissue, the signal intensity pre and post IV contrast medium administration can be followed with respect to time, generating a kinematic curve. There are three types of curves (Figure 1) [3]. The structure of these curves is very closely connected to the existance of cancer [28, 29]. Type I represents a continuously increasing curve, reflecting a wash-in process of the contrast medium through the vascularity of the ROI in a gradually increased manner. Type II is an initially increasing curve, usually faster than that of Type I, which is followed by a plateau, indicating an initial wash-in process that is followed by a saturation state. Finally, Type III is an initially increasing curve which is followed by a decreasing slope. The latter suggests an initial fast wash-in process through the angiogenesis vascularity followed by a rapid wash-out process, due to the architecture of the tumorous vascularity.

Figure 1: Three possible types of curves.

Curves of Type II, III indicate a malignancy and require the radiologists to be extra vigilant [29]. The pathology probability for all three types of curves is shown in the following Table 1.

Curve Type	Pathology Probability
Type I	8.9%
Type II	33.6%
Type III	57.4%

Table 1: Pathology probability for all types of intensity curves [29].

Various types of software have been developed and are currently used for breast MRI data analysis, i.e. *Siemens syngo-BreVis* [30], *General Electric* Func*Tool*, *CADstream* [31]. **BreDAn** is a novel visual tool that performs MRI data analysis in a fast, reproducible and reliable manner displaying anatomical images as well as kinematic information in an accurate and precise way. This process is automatic, user friendly and robust.

The structure of the present paper is as follows. In section 2, the technical characteristics of MRI images are presented. In section 3, **BreDAn** software is described in detail. In section 4, results of the clinical testing of **BreDAn**,

are illustrated, followed by its evaluation. In section 5 conclusions and future challenges are presented. Finally, section 6 concerns the mode of availability of **BreDAn**.

2. MRI protocol - data

The breast MRI protocol consists of various types of pulse sequences. They are implemented in different axes in order to locate, define extent and diagnostically differentiate pathologies. MRI generates two types of information: the imaging one, which assigns anatomical and morphological characteristics of lesions and the dynamic one, which describes the kinetics of the IV injected contrast medium within anatomical volumes [32–34]. These two types of information that are produced within a single examination help towards the differentiation of pathologies, constituting breast MRI a powerful imaging tool [3, 4]. Superior diagnostic accuracy can be achieved by combining the aforementioned types of information with other variables (including multivariate models [35] and b values [36]).

All MRI examinations were performed in a 1.5 Tesla Signa HDxt General Electric system. Patients were in the prone position. Parallel imaging techniques along with 8 channel dedicated breast coils were used. A typical breast MRI protocol consists of the following pulse sequences:

1. Axial T1 Fast-Spin-Echo (FSE) which elevates hemorrhagic cysts and facilitates the simultaneous comparison between the patient's breasts.
2. Axial T2 Fat-Saturation (FS) which pronounces cysts, pathologies, tumors.
3. Axial Diffusion-Weighted-Imaging (DWI) which pronounces solid anatomical damages and lymph nodes, through high magnetic signal.
4. Dynamic T1 Fat-Saturation (FS) which pronounces information about the wash in and wash out process of the contrast medium (+C).
5. Axial T1 Fast-Spin-Echo (FSE) after IV contrast medium injection (+C).
6. Coronal T1 Fast-Spin-Echo (FSE) after IV contrast medium injection (+C).

Typical values of the variables for the imaging information of the above pulse sequences are illustrated in Table 2. Typical values of the variables for the dynamic information of the above pulse sequences are illustrated in Table 3. At this point, it should be pointed out that there are more quantity

parameters related to the dynamic contrast-enhanced T1-weighted MRI data in the literature, i.e. [37].

	Axial T1 FSE	Axial T2 FS	DWI	Axial T1 FSE + C	Coronal T1 FSE + C
TE (ms)	16	93	94	16	16
TI (ms)	-	-	-	-	-
TR (ms)	740	5960	6300	740	480
Thickness (mm)	4	4	4	4	4
Spacing (mm)	1	1	1	1	1.5
FOV (cm)	28	28	36	28	35
Matrix	512×320	512×320	192×160	512×320	512×320

Table 2: Typical values of the parameters of the MRI imaging pulse sequences.

	Dynamic T1 FS + C
TE (ms)	2
TI (ms)	7
TR (ms)	4
Thickness(mm)	2
Spacing (mm)	0
FOV (cm)	24
Matrix	256×192

Table 3: Typical values of the parameters of the MRI dynamic pulse sequences.

The total number of images accumulated in each pulse sequence is a function of the size of the breasts to be imaged and the prescribed thickness-spacing of each slice. MRI packages all the information of every slice in a special file format, called *dicom* [38]. These files, besides the MRI image, also contain various other information such as patient data, examination date and others. In order to be processed, the MRI image has to be separated from the header information contained in the dicom file.

The current visual environment makes use of the dynamic T1 Fat - Saturation grayscale MRI images, acquired at sagittal plane. The images are of dimensions 256×256, which means that each MRI image is sustained by 256 pixels horizontally and 256 pixels vertically. Each pixel has *depth* 8, meaning that it can be assigned with intensity values belonging to the integer interval of $2^8 = 256$ elements [0, 255]. Value 0 corresponds to dark black color and value 255 to bright white. Intermediate colors correspond to intermediate integer values [39].

BreDAn normalizes the intensity values of the image pixels to the floating number interval [0, 1], with 0 corresponding to dark black and 1 corresponding to bright white. Intermediate colors correspond to intermediate floating point values. The normalization process takes place because computer arithmetic works better with floating point numbers in the interval [0, 1], minimizing floating point and rounding errors, resulting from mathematical operations.

3. BreDan: A visual tool for breat MRI data analysis

In recent years, there has been a great effort for the exploitation of powerful computer systems in order to support clinical decisions. The, so called *CDSS* (Clinical Decision Support Systems), provide useful diagnostic information in order to facilitate clinical decisions and constitute a very interesting area of research [40–49]. As a direct consequence, more sophisticated CDSS's attempt to detect suspicious areas in the different anatomies of the human body using diagnostic medical images.

CDSS can be further evolved in order to provide automated diagnosis. This is called *CAD* (Computer Aided Diagnosis) [50–52]. CAD in breast MRI imaging can improve cancer detection by increasing radiologists' sensitivity [53, 54]. The promising science behind CAD can reduce potential errors and variation of qualitative analysis [55] and improve standardization among different MRI work-stations [56].

BreDAn is a CDSS. A step by step presentation of **BreDAn** follows. The application, in practice, simulates the radiological diagnostic methodology.

3.1. Step 0: Initialization

Initially, the user loads to the application the dicom files of a chosen slice of the MRI examination, corresponding to the dynamic images before and after the IV injection of contrast medium. **BreDAn** gives the user the option of *windowing*. If windowing is omitted the application automatically proceeds to the next step, taking into consideration all the pixels of the scanned images, i.e. pixels corresponding to breast areas, pixels corresponding to background and pixels corresponding to the header. However, this is computationally time consuming and the use of windowing is recommended. In this case, the user needs to define a rectangular region of interest (ROI), containing the part of the image that represents the breast area, avoiding other information

such as header and background. Note here that the defined ROI has to cover the whole breast area, otherwise potentially pathological areas can be missed. Windowing makes the application more efficient, as the algorithms of the tool will focus only on the specific ROI (Figure 2).

Figure 2: Applying windowing.

3.2. Step 1: Intensity filter

In this step, the application requires the user to define an intensity threshold, stated as *prc* (a similar approach is illustrated in [57]). Then, **BreDAn**, for each of the input images, surrounds the areas where the pixel MRI signal intensity exceeds the value I_{thres}, where:

$$I_{thres} = I_{avg} + prc \cdot I_{avg}$$

Value I_{avg} denotes the average pixel MRI signal intensity of the current MRI image. A low *prc* value will highlight areas with low pixel intensities as well as areas with high pixel intensities. Selecting higher threshold value for *prc*, only areas with high pixel intensities will be marked, which correspond to *potentially pathological* areas. Figure 3 displays this step for $prc = 2.5$.

Figure 3: Potentially pathological areas derived for $prc = 2.5$ for the 8 consecutive pulse sequences.

The user can experiment with the value of *prc*, which acts as a sensitivity measure (low *prc* values correspond to high sensitivity, while high *prc* values to low sensitivity), until the visual result of the potentially pathological areas, are clearly pronounced. After the *prc* value is inserted, the selection of the potentially pathological areas is performed automatically, minimizing the human error.

3.3. Step 2: Intensity curve slope filter

In this step, the intensity curves of all potentially pathological areas of all images are constructed. Let SI_i be the average intensity of a potentially

pathological area in image i and SI_0 the average intensity of the same potentially pathological area in the pre-contrast medium administration image. The average intensity of the assigned area is obtained by averaging the intensity values of the pixels forming this area. Then, the percentage intensity modification in image i, with respect to the pre-contrast medium administration image, is given by the following formula (wash-in rates formula [3]):

$$\frac{SI_i - SI_0}{SI_0} \cdot 100$$

After the construction of the intensity curves for each potentially pathological area, the areas whose curves appear descending in three consecutive time points, starting from the second scan, are marked, while all other areas are ignored. The marked areas are the *high probability pathological areas*. Finally, all the high probability pathological areas are combined into a single image and displayed on the computer screen (Figure 4) Notice that the radiologist does not need to study one by one all the intensity curves, as used to be the case, since this is automatically performed by **BreDAn**.

Figure 4: High probability pathological areas.

3.4. Step 3: Color fragment filter

After demonstrating the high probability pathological areas, **BreDAn** produces color maps with respect to the maximum slope of signal increase and the maximum slope of decrease (Figure 5). Let SI_i be the average intensity of high probability pathological areas in image i, and SI_{i+1} the average intensity of the same area in image $i+1$. Then, the slope between successive pulse sequences i and $i+1$, is given by:

$$\frac{SI_{i+1} - SI_i}{(i+1) - i} = SI_{i+1} - SI_i$$

For the maximum slope of increase color map, the signal is mapped according to the rainbow color scale (Figure 6). In this scale, red color corresponds to high signal intensity, i.e. fast wash-in, whereas blue color corresponds to low signal intensity, i.e. slow wash-in. Similarly, for the maximum slope

Figure 5: Left: Maximum slope of increase, Right: Maximum slope of decrease.

of decrease color map, red color corresponds to fast wash-out, whereas blue color corresponds to slow wash-out processes.

In the sequel, the tool requests the user to define a chromatic threshold variable (T_c) representing a desired wash-in/wash-out rate metric. This variable takes values within the interval [0, 1] and each value is assigned to a color based on the rainbow palette (Figure 6). 0 is mapped to blue, 1 is mapped to red and intermediate values to intermediate colors obtained by linear interpolation [39].

Figure 6: Left: Connection between T_c value and colors through rainbow pallet.

Based on the T_c value, for each high probability pathological area, the application finds the average color of the corresponding area of the two (increase / decrease) color maps. Then, these two color averages are mapped to two scalar values (using inverse linear interpolation [39]). Let $T_{ColorMapIncrease}$ and $T_{ColorMapDecrease}$ be the two aforementioned scalar values. If the following statement holds:

$$T_c < T_{ColorMapIncrease}\ AND\ T_c < T_{ColorMapDecrease}$$

then the high probability pathological area is characterized as *diagnostically pathological area*, as it introduces wash-in/wash-out rates larger than the user selected reference value T_c, otherwise it is ignored as noise.

Finally, after T_c value is inserted, all the diagnostically pathological areas are automatically marked and displayed in red color for emphasis (Figure 7).

Figure 7: Diagnostically pathological areas with $T_c = 0.4$.

3.5. Step 4: Intensity curves display

Finally, the user can manually select multiple ROIs, and their corresponding intensity curves are automatically displayed. For example, in Figure 8 two ROIs have been chosen. The blue ROI represents pathological area, while the green ROI represents healthy tissue. The blue curve (blue ROI) has more than three consecutive descends corresponding to wash-out process. Biopsy showed that that was a case of malignant tumor. The green curve (green ROI) displays a continuous wash-in process.

Figure 8: Multiple ROIs and corresponding intensity curves (green: healthy tissue, blue: pathological tissue).

BreDAn allows the user to select any MRI breast image to process. In addition, it displays patient information and enables resulting image storage on a predefined directory of the terminal. Finally, it provides instructions on the application screen, facilitating the usage of the tool and navigating the radiologist through the environment. Concluding, **BreDAn** routines correspond to the commonly used diagnostic methodology, as indicated in Figure 9.

Figure 9: Algorithm for MRI data interpretation [3].

4. Evaluation of BreDAn

BreDAn was extensively tested and evaluated using 534 breast MRI data sets (522 F, age group 31-79 years old and 12 M sets, age group 55-68 years old). All MRI examinations had been performed on the same 1.5 T Signa HDxt GE system using the same protocol. Three characteristic clinical cases illustrate its applicability and potential.

4.1. 1st Case: Normal case

The first clinical case concerns a normal healthy case. No pathological areas were detected by the application. In addition, the intensity curves of four randomly selected areas (Figure 10 left) are of Type I (Figure 10 right). Both maximum slopes of intensity increase-decrease color maps (Figure 11) illustrate the marked areas (ROIs), with medium signal intensities reflecting a slow wash-in process and the absence of a wash-out one.

Figure 10: Left: ROIs randomly selected, Right: Their corresponding intensity curve.

Figure 11: Left: Maximum slope of increase color map, Right: Maximum slope of decrease color map.

4.2. 2rd Case: A case of benign tumor

The second clinical demonstration concerns a case of a benign tumor, according to biopsy. A pathological site was successfully detected and clearly marked by **BreDAn** (Figure 12 left). The corresponding Type II curve, displays three consecutive signal decreases reflecting a slow wash-out process (Figure 12 right). Maximum slope of increase color map (Figure 13 left) displays a marked area of high signal intensities, i.e. a fast wash-in process, while the maximum slope of decrease color map (Figure 13 right) displays a marked area with relatively high signal intensities, i.e. a relatively slow wash-out process.

Figure 12: Left: High probability pathological areas as marked by the application ($prc = 2.5$, $T_c = 0.4$), Right: Its corresponding intensity curve.

Figure 13: Left: Maximum slope of increase color map, Right: Maximum slope of decrease color map.

4.3. 3rd Case: A case of malignant tumor

The third clinical demonstration concerns a case of breasts with a malignant tumor, according to biopsy. In the following Figures, **BreDAn** detects and marks the cancerous area (Figure 14 left) and automatically displays its intensity curve (Figure 14 right) which is of Type III. A wash-out process is clearly present. Maximum slope of increase/decrease color maps are also generated and illustrated in Figure 15. Pathological areas are displayed in both color maps with high signal intensities, corresponding to fast wash-in and fast wash-out processes.

Figure 14: Left: High probability pathological areas as marked by the application ($prc = 2.5$, $T_c = 0.925$), Right: Its corresponding intensity curve.

Finally, **BreDAn** was compared and assessed with *FuncTool*, a commercial software package, developed by $GeneralElectricMedicalSystems$ and approved by the Food & Drug Administration (FDA). 534 breast MRI data sets were analyzed using both tools and the results were found to be in significant agreement, but in the case of using **BreDAn** the results were produced much faster. The nature of the data set is illustrated in Table 4 and can be used as ground truth. In Table 5, the system evaluation on the entire testing data sets, in terms of sensitivity and specificity, is presented. The information that can be extracted from the aforementioned tables is very important for the statistical evaluation of **BreDAn**. The high sensitivity (98%) of the software makes it quite reliable as a clinical decision support system.

For illustration reasons an example of a breast MRI examination (F, 55 years old), with malignant tumor on the left breast, follows. The protocol

Figure 15: Left: Maximum slope of increase color map, Right: Maximum slope of decrease color map.

of pulse sequences and parameters used was presented in section 2. In the left part of Figure 17, from top to bottom, the resultant maximum slope of increase-decrease color maps and intensity curve of a selected ROI (Figure 16), generated by *FuncTool* are illustrated. In the right part of the same Figure, the respective color maps and intensity curve for the same ROI, derived by **BreDAn** are presented. Agreement between the outputs generated by the two applications is satisfactory. Small deviations between the intensity curves of the applications are attributed to the different chromatic interval of values assigned to pixels. Dicom image chromatic interval takes values within [0, 255]. **BreDAn** normalizes pixel chromatic values to [0, 1]. *FuncTool* does not use a standard value interval as signal intensity increase, in T1-weighted MRI images, is not exactly proportional to the concentration of contrast medium accumulated within a lesion, leading to scan-by-can analysis [58] (unlike, e.g., in contrast agent enhanced CT imaging where there is a direct correlation between contrast agent concentration and Hounsfield units [59]).

In addition, **BreDAn** encapsulates the exact pathological area, through an accurate segmentation process, avoiding inaccuracies produced by the corresponding manual processes in FuncTool. This leads to slightly different signal intensity averages between the two applications.

Figure 16: ROI corresponding to the intensity curves of Figure 16 (left: *FuncTool*, Right: **BreDAn**).

Figure 17: Results of *FuncTool* (left) and **BreDAn** tool (right).

Nr Total Cases	Nr Pathological Cases (%)	Nr Normal Cases (%)
534	51 (9.55%)	483 (90.45%)

Table 4: Illustration of the nature of the data set, used for testing **BreDAn**, confirmed by biopsy.

Evaluation Matrix	Positives	Negatives	Sensitivity (%)	Specificity (%)
True	50	314	98%	65%
False	169	1	-	-

Table 5: Statistical evaluation of **BreDAn** in 534 cases.

5. Conclusions and future challenges

BreDAn is a user friendly visual environment for breast MRI data analysis that automates the process of detecting potentially pathological lesions. To achieve its purpose, the software simulates the modern methodology that is used by radiologists to detect, differentiate and stage breast pathologies. It can facilitate and accelerate the work of radiologists in an accurate and reliable manner minimizing human error. Furthermore, the **BreDAn** visual platform has been tested and assessed with 534 clinical cases and produced reliable and successful results.

A very interesting future challenge is to improve the developed software, using statistical algorithms and other analytical methods, in order to further increase the probability of correct suspicious areas detection. This will improve the detection accuracy of the tool and will help towards the assignment of a more specific and targeted therapy plan.

Finally, another future challenge would be the evolution of **BreDAn** from a CDSS to a CAD system. To this end, the increase of the specificity levels of **BreDAn** is essential. This can be made possible with the exploitation of the 534 breast MRI data sets and the usage of specified pattern recognition methods, in order to proceed to automatic classification of the findings (benign, malignant, invasive, noninvasive). The classification will lead to the diagnosis and it could be realized according to the kinetic features illustrated in [60–62] and the morphological features illustrated in [62].

6. Mode of availability

BreDAn is not an open source application. A demonstration video is available at http://graphics.di.uoa.gr -¿ Research -¿ Resources. If you are interested in obtaining **BreDAn**, please contact a.danelakis@gmail.com.

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