Interactive lesion segmentation on dynamic contrast enhanced breast MR using a Markov Model

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ABSTRACT

The purpose of this study is to develop a method for segmenting lesions on Dynamic Contrast-Enhanced (DCE) breast MRI. DCE breast MRI, in which the breast is imaged before, during, and after the administration of a contrast agent, enables a truly 3D examination of breast tissues. This functional angiogenic imaging technique provides noninvasive assessment of microcirculatory characteristics of tissues in addition to traditional anatomical structure information. Since morphological features and kinetic curves from segmented lesions are to be used for diagnosis and treatment decisions, lesion segmentation is a key pre-processing step for classification. In our study, the ROI is defined by a bounding box containing the enhancement region in the subtraction image, which is generated by subtracting the pre-contrast image from 1\textsuperscript{st} post-contrast image. A \textit{maximum a posteriori} (MAP) estimate of the class membership (lesion vs. non-lesion) for each voxel is obtained using the Iterative Conditional Mode (ICM) method. The prior distribution of the class membership is modeled as a multi-level logistic model, a Markov Random Field model in which the class membership of each voxel is assumed to depend upon its nearest neighbors only. The likelihood distribution is assumed to be Gaussian. The parameters of each Gaussian distribution are estimated from a dozen voxels manually selected as representative of the class. The experimental segmentation results demonstrate anatomically plausible breast tissue segmentation and the predicted class membership of voxels from the interactive segmentation algorithm agrees with the manual classifications made by inspection of the kinetic enhancement curves. The proposed method is advantageous in that it is efficient, flexible, and robust.

Keywords: Dynamic Contrast-Enhanced breast MRI, lesion segmentation, kinetic curve, morphological feature, region of interest (ROI), subtraction image, Markov Random Field, MAP estimate

1. INTRODUCTION

Breast cancer is the most common cancer and the second leading cause of cancer death for American women today. The key to increasing the survival rate is early detection and treatment. Medical imaging is essential to breast cancer screening and diagnosis. Currently, x-ray mammography is the primary screening modality for breast cancer. Unfortunately, 10-30\% breast cancers are not detected on mammography\textsuperscript{1-3} and the positive predictive value (PPV) of mammography is less than 35\%\textsuperscript{4}. The use of Dynamic Contrast-Enhanced (DCE) breast MRI is increasing and it is recommended as an adjunctive breast screening modality to mammography. DCE breast MRI, in which the breast is imaged before, during, and after the administration of a contrast agent, provides a noninvasive assessment of the microcirculatory characteristics of tissues in addition to traditional anatomical structure information in 3D.
MRI primarily images the Nuclear Magnetic Resonance (NMR) signal from the hydrogen nuclei of the tissue. By applying a 3D encoded magnetic field, MRI enables a truly 3D examination of breast tissues (Figure 1). But even 3D structural information is insufficient to reliably distinguish between abnormal and normal tissues. The need for functional data is the driving force behind the development of dynamic contrast-enhanced MRI. Functional imaging is required in order to recognize the distinctions between tumors and normal tissues that exist at the molecular level, such as differences in cellular composition, permeability, and microvessel density. The use of contrast agents in MRI enables the visualization of functional changes, particularly angiogenesis, when sequential MRI scans are acquired. In a DCE MRI exam, a contrast agent such as Gadolinium diethyltriaminepentaacetic acid (Gd-DTPA) diffuses into the extravascular extracellular space (EES) via the capillaries and accumulates in tissues with high vascularity and subsequently leaks back into the vascular space and is eventually excreted from the body. The diffusion process is governed by the kinetic properties of the target tissues. The concentration of contrast agent alters the relaxation time of water protons in the surrounding tissue; thus, the accumulated amount of contrast agent around the targeted tissue will be reflected in the MR image intensity (Figure 2). As there is contrast agent uptake and washout over time, dynamic images are produced during sequential MRI scans. In DCE MRI, pulse sequences can be chosen so that the resulting images are selectively sensitive to different vascular and kinetic characteristics. Essentially, the dynamic image intensities reflect the physiological nature of the targeted tissue. For any location in the image, the dynamic image intensities can be viewed as a multi-dimensional signal, usually referred to as the kinetic enhancement curve (Figure 2).

Figure 1. Axial, coronal, and sagittal views of a T1-weighted pre-contrast 3D breast MRI (512*512*64) of an anonymous patient.

The interpretation of breast MR images is a challenging task. Traditional manual interpretation of breast MRI is time-consuming and tedious and can lead to oversight error due to the large size of four-dimensional data sets (three spatial dimensions plus time). Manual interpretation is also subject to inter- and intra-observer variability, with some lesion characteristics (e.g., internal enhancement) showing considerably more observer variability than others (e.g., margin).
There is a great need for Computer-aided Detection and Diagnosis systems capable of increasing the efficiency, accuracy, and consistency of breast MRI interpretation.

Figure 2. Pre-contrast and five post-contrast images of a breast in axial views of the same patient in Figure 1 along with an image intensity curve for the voxel centered by the red circles.

2. LESION SEGMENTATION

2.1 Background and previous methods

Interpreting breast MRI efficiently and accurately is essential. To this end automated feature extraction and classification have been pursued. In order to compute morphological features and kinetic curves for use in making diagnosis and treatment decisions, the lesion must be accurately segmented out from the ROI. Specifically, the goal of lesion segmentation is to group those voxels in ROI that share similar kinetic enhancement curves. Manual or semi-automated segmentation have been used in previous studies. Although it would be most beneficial to automate this step so as to eliminate human interaction entirely, better semi-automated segmentation methods would also be valuable.

Due to motion and breathing during image acquisition, the same coordinates in the image across time may not correspond to the same physical object, thus registration is a necessary pre-processing step for segmentation. Registration is a challenging task itself and is beyond the scope of this paper. In our work, the volumes are assumed to be registered. The registered volumes can be treated as a single volume where each voxel holds an n-dimensional vector of intensities, or intensity curve; image processing techniques can then be adopted to perform segmentation on this volume.
Few previous publications are directly related to lesion segmentation on breast MRI. The two-level-thresholds method uses one threshold to segment out the enhancing region from the background image and a second threshold to segment the suspicious lesion from the enhancing region. The segmentation in Hayton’s work is also based on thresholding the enhancement between two images in the image series. Since the signal intensity depends on the particular MRI instrumentation and contrast agent used in data acquisition, there is no general approach for selecting threshold values and thus these methods require careful user interaction. Gihuijs et al. develop a seeds-based region-growing algorithm to segment the lesion from the ROI using thresholds derived from the image histogram. However, the user needs to manually select the seeds. In addition, the same tissue may not behave uniformly to the contrast agent, which also decreases the accuracy of threshold-based methods. Since each of the kinetic enhancement curves is an N-D vector, efforts have been made to cluster those curves such that the resulting clusters are the representatives of the partitioned sub-regions in the ROI. Petroudi et al. propose a Gaussian mixture model for dynamic breast MRI data, in which the mixture parameters are iteratively updated based on K-means initialization. However, K-means initialization is not stable and not recommended in general.

Kuhl et al. point out that kinetic time curves needed to evaluated in full time course, thus makes dynamic breast MRI segmentation a n-D segmentation problem essentially. Efficient and automatic high dimensional segmentation/classification is still a challenging research topic in general.

2.2 Interactive segmentation and Bayesian theory

Since there are many variations between different imaging centers, acquisition protocols, etc., we do not attempt to develop an algorithm applicable for all image acquisition settings. Instead of automatically segmenting out the lesion from the whole breast MR imaging data, we develop interactive segmentation given an identified Region-Of-Interest (ROI). The ROI includes the suspicious lesion, which is characterized by significant enhancement on the subtraction image. After compensating for motion between pre-contrast and post-contrast images, subtracting the pre-contrast image from the 1st post-contrast image generates a subtraction image on which significant enhancement of the abnormality is obvious (Figure 3). The ROI can be defined by placing a bounding box that completely contains the enhancement within the breast region and chest wall, so that the ROI is of limited size so to reduce the segmentation complexity. Within the ROI, the lesion region needs to be accurately delineated, and a binary segmentation scheme is adopted to segment the ROI into lesion vs. non-lesion regions.

Our segmentation method is based on the Bayesian theory of maximizing the posterior probability. The likelihood distribution is assumed to be Gaussian. The prior distribution of the class membership is modeled as a Pott’s model, a Markov Random Field (MRF) model in which the class membership of each voxel is assumed to depend upon its nearest neighbors only. The multi-level logistic model will be detailed in section 2.3. A maximum a posteriori (MAP) estimate of the class membership (lesion vs. non-lesion) for each voxel is obtained using the Iterative Conditional Mode (ICM) method.

2.3 Markov Random Field and Pott’s model

Let $S = \{s = (i,j,k) | 1 \leq i \leq M_1, 1 \leq j \leq M_2, 1 \leq k \leq M_3\}$ denote a three-dimensional $M_1 \times M_2 \times M_3$ lattice with a neighborhood system $N = \{N_s, s \in S\}$. In our experiment, we only consider a second order neighborhood system (26 neighbors in 3D). Let $Y$ be a $p$-dimensional random field defined on $S$, that is $Y = \{y_s | s \in S\}$, where $Y$ is the observation of $Y$ and $y_s = [y_{s1}, y_{s2}, \cdots, y_{sp}]$ is the observed random vector $y_s$. Let $X = \{x_s | s \in S\}$ be a 1-D random field defined on $S$, and let $X$ be the realization of $X$ and $x_s$ be the realization of $x_s$. We can assume that $X$ is an MRF respect to the neighborhood system $N$ and this MRF is with a probability distribution $p(X)$. Let $c$ be a pair-wise clique that is a subset of $S$ with two sites such that each site in $c$ is a neighbor of the other site, and let $C$ denote the set of all cliques. According to Hammersley-Clifford theory, the joint
probability of the MRF \( X \) also obeys Gibbs distribution which takes the following form
\[
p(X) = \frac{1}{Z} \exp\left[ U(X) \right]
\]
where, \( Z = \sum_x \exp\left[ U(X) \right] \) is a normalizing constant called the partition function, and \( U(X) \) is an energy function taking the form
\[
U(X) = \sum_{c \in C} V_c(X)
\]
which is a sum of the potential of all the pairwise cliques. The potential function adopted in our experiment is so called multi-level logistic (MLL) model \(^{14}\), taking the form
\[
V_c(X) = \begin{cases} 
\beta & \text{if } x_s = x_{s'}, \ \forall s, s' \in c \text{ and } s \neq s' \\
0 & \text{otherwise}
\end{cases}
\]

This isotropic MLL model depicts blob-like regions. In our experiments, we empirically set \( \beta = 10.0 \) to achieve the smooth segmentation maps.

### 2.4 Class conditional probabilities

With the aid of our visualization system, the kinetic curves of the voxels can be viewed, thus making available the membership of those voxels manually selected as representative of the class. Based on those curves, the initial parameters of Gaussian, the mean vector \( \mathbf{m}_x \) and covariance matrix \( \mathbf{S}_x \), can be estimated based on those voxels manually labeled of two classes: lesion or non-lesion. And class conditional probabilities for each voxel then can be estimated according to the following Gaussian
\[
f(y_s|x_s) = \frac{1}{(2\pi)^{p/2}} \exp\left[ -\frac{1}{2} (y_s - \mathbf{m}_x)^T \mathbf{S}_x^{-1} (y_s - \mathbf{m}_x) \right] \quad x_s \in \{1,2\}.
\]

### 3. RESULTS AND DISCUSSION

The segmentation results demonstrate anatomically plausible breast tissue segmentation. Figure 3 and Figure 4 visualize the segmented lesion in 2D and 3D respectively. To confirm the segmentation results, the mean kinetic curves of segmented lesion region and non-lesion region are plotted in Figure 5. The mean kinetic time curves of the resulting lesion region and non-lesion region agree with the curve patterns of previous studies \(^{12}\).

Although there is a recommended breast MRI image acquisition protocol, in practice acquisition of breast MRI varies from imaging center to center. Unfortunately, it is difficult to develop a generalized lesion segmentation method applicable for all acquisition settings. The segmentation algorithm presented in this study is advantageous in that it should be robust to differences in image acquisition settings since the parameters are based on manually selected seed points.

A CAD system must be designed to enable efficient human-computer interaction since the system is intended to aid, not replace, the physician. Toward this goal, the segmentation results in our experiment can be simply revised by the operator by selection/deletion of additional seed points, so that the final segmentation results are to the satisfaction of the radiologist. Finally, the proposed method could be efficiently implemented for real-time segmentation in a clinical environment. For example, it takes less than one minute on a moderate workstation to perform the segmentation using MATLAB\textsuperscript{®} (The MathWorks, Natick, MA) for a fairly large ROI (86\*51\*22).

Although we have tested this method on only five cases, all of the segmentation results are encouraging. Due to space limitations, we present the segmentation results and the kinetic time curves of one case in this paper, but the results of the other four cases are provided on our website (www.bme.utexas.edu/research/informatics).
Figure 3. (a) Pre-contrast image, (b) Post-contrast image, (c) Subtraction (a) from (b), and place a bounding box (red) to define ROI, (d) Segmented lesions (denoted in white).
Figure 4. 3D rendering of a segmented lesion (in yellow) superimposed on the pre-contrast 3D MRI raw image.

Figure 5: The mean kinetic time curves of the lesion (solid) and non-lesion (dashed) in the ROI area of Figure 3. The mean curve of the lesion is a typical kinetic enhancement curve of the malignant lesion (quick washout following sharp uptake).
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