COMPUTERIZED CALCULATION OF BREAST DENSITY: OUR EXPERIENCE FROM ARCADIA MEDICAL IMAGING CENTER

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COMPUTERIZED CALCULATION OF BREAST DENSITY: OUR EXPERIENCE FROM ARCADIA MEDICAL IMAGING CENTER (Abstract): The aim of this study was to implement a spatial fuzzy C-means algorithm for image segmentation and breast tissue density quantification and compare it with BI-RADS breast density classes determined by radiologists. Material and methods: The analysis was based on 206 mammograms performed in 111 women with various breast abnormalities. Digitized mammographic films were independently double read by radiologists certified in breast diagnosis, followed by consensus with arbitration agreement (radiological ground truth). Reporting was done using the BI-RADS mammography lexicon. Using an algorithm based on a combination of spatial fuzzy C-means clustering and binary thresholding, percent mammographic density was computed in digitized mammograms. The BI-RADS breast density readings were compared with percent breast density measurements determined by computer algorithm. Results: The algorithm was found to match the BI-RADS density classification in 90% of the cases, with an excellent agreement (κ = 0.88) between the radiological ground truth versus the algorithm breast tissue density estimates. Conclusions: Our study proposed an algorithm that can be applied both to digitized and digital mammograms, which proved to be effective in breast density estimates. The method can accurately determine the percentage density removing the human observer variability. The proposed method showed an excellent agreement with radiological ground truth. Keywords: MAMMOGRAPHIC DENSITY, SPATIAL FUZZY C-MEANS, BREAST SEGMENTATION, BINARY MASKS

Mammographic density is a risk factor for breast cancer, and it has been shown that women with high mammographic density have four to five-fold increased risk of developing breast cancer (1). Assessment of breast density may be carried out using qualitative or quantitative estimates. The most widely used clinical density estimate is the qualitative evaluation based on the Breast Imaging Reporting and Data System (BI-RADS) classes developed by the American College of Radiology (ACR) (2). However, this classification scheme is still limited by its considerable intra- and inter-reader variability.

As an alternative to qualitative evaluation, different quantitative approaches have been developed. A quantitative method for measuring breast density is supposed to be simple, accurate, reproducible, and ready to be implemented with a minimum level of operator dependency. In the assessment of
breast density from mammograms, the breast is usually segmented into distinct regions (3). There have been various approaches proposed to the task of segmenting the breast profile region in mammograms. Some of these have focused on using threshold (4), fuzzy C-means approaches (5), Gaussian mixture models (6) and statistical methods (7).

In this paper, we investigated the feasibility of quantifying breast density with an automatic approach, employing spatial fuzzy C-means (SFCM) clustering segmentation and binary thresholding.

**MATERIAL AND METHODS**

The mammographic records of 117 consecutive women (mean age, 56 years) who underwent diagnostic mammography at our facility was included in the present study. Standard cranio caudal view (CC) and medio lateral oblique (MLO) image projections of each breast were obtained. Subjects who had very poor quality mammograms were excluded. A data set of 95 cases of two-view bilateral mammograms and 16 two-view unilateral examinations (patients who had undergone mastectomy) was used in this study. No informed consent was required, as patient identification information was removed. This research protocol has been conducted according to the ethical guidelines and principles of the Declaration of Helsinki.

All mammographic examinations were performed by using a Senographe DMR unit (GE Healthcare, Milwaukee, Wisconsin, USA) with a dedicated software that convert images in Digital Imaging and Communications in Medicine (DICOM) format at a high resolution (570 dpi) of 44.5 microns and a 12-bit grayscale imaging output.

**Image segmentation.** To further process the digitized film mammograms we used public domain image-processing software, FIJI/ Image J (8), with a SFCM algorithm implemented as a plug-in.

The first step of our approach consisted in breast image segmentation. The SFCM method relies on classifying pixels into distinct regions containing a group of connected pixels (cluster) with similar properties within each group (9).

First, let \( X = (x_1, x_2, \ldots, x_N) \) be an image with \( N \) pixels to be partitioned into \( c \) clusters, where \( x_j \) is an image pixel. The identification of clusters in the image depends on a cost function that exploits the feature-based similarities between pixels, defined as:

\[
J = \sum_{j=1}^{N} \sum_{i=1}^{c} u_{ij}^m \| x_j - v_i \|^2
\]

where \( u_{ij} \) is the membership function of pixel \( x_j \) in the \( i^{th} \) cluster, \( v_i \) is the \( i^{th} \) cluster center, \( \| . \| \) is the Euclidean distance, and \( m \) is a constant which determines the amount of fuzziness of the resulting classification. The SFCM algorithm takes into account the local spatial relationship between adjacent pixels by introducing the spatial information into the membership function for clustering. SFCM algorithm can be summarized as follows: a set of integers as a parameter of the number of clusters to be allocated to the algorithm, \( c = \{3, 4, 5, 6\} \).

A weighting exponent (fuzzifier) \( m = \{1.1, 2.5\} \), and a parameter \( p \) that deter-
mines the influence of the weights, $p \in [1...\infty]$ . The spatial function it is defined as the probability that pixel $x_j$ belongs to $i^{th}$ clustering:

$$h_{ij} = \sum_{k \in NB(x_j)} u_{ik},$$

where $NB(x_j)$ is a square window centered on pixel $x_j$ in the spatial domain. The spatial function is incorporated into membership function as follows:

$$u_{ij}^* = \frac{u_{ij}^p h_{ij}^q}{\sum_{k=1}^{\infty} u_{kj}^p k_{kj}^q},$$

where $p$ and $q$ are parameters to control the relative importance of both functions, as described in detail elsewhere (10).

The SFCM method generated images of dense, adipose and whole breast tissue each one representing a cluster whose membership function $u_{ij}^*$ indicates that the pixels are toward that cluster (fig. 1).

**Fig.1.** Steps for the segmentation of the fibro glandular breast tissue using SFCM:
(A) Original digitized mammogram; (B) Segmented image of the whole breast; (C) Segmented image of the fatty regions; (D) Segmented image of the fibro glandular regions.

**Estimation of mammographic density.**
For breast tissue density quantification only the CC projections were used, as it has been previously reported that density estimates from CC and MLO views showed very strong correlation (11). Images corresponding to dense and whole breast region were transformed into binary images using the isodata thresholding algorithm implemented in Image J. The method separates the image into breast tissue and background by automatically choosing a global threshold.
that is equidistant from the average intensity of pixels below and above it:

$$\text{Threshold} = \frac{\text{average background} + \text{average tissue}}{2}$$

The area-based measurements of mammographic density were computed by recording the number of pixels that lie within the defined region (fig. 2). The percent mammographic density (PD) was then calculated as the ratio of dense area to the total area of the breast multiplied by 100.

![Fig. 2. The whole breast area delineation in CC views (1); The fibro glandular area delineation in CC view (2)](image)

**Visual interpretation of digitized mammograms.**

Each mammogram was initially independently reviewed by two trained breast imaging radiologists using the corresponding digitized screen-film mammograms. The CC and MLO views were displayed side-by-side on dedicated image displays (Totoku, Electric Co Ltd, Japan). The observers evaluated each case according to the BI-RADS mammography lexicon published by the ACR (2). After scoring the mammographic breast density in one of the four quantitative BI-RADS categories, the observers assessed the presence of associated findings such as masses, architectural distortion, focal asymmetry and calcifications. All lesions were described by using the terminology of the fourth edition of the BI-RADS lexicon and assigned to a final BI-RADS category. For cases with discordant results, a consensus reading with arbitration by a third expert radiologist was carried out, and the observers were asked to make the final assessment considered the ground truth.

**Statistics.** In order to facilitate convenient evaluation of the interobserver agreement, data readouts from the left and right breasts were pooled. Weighted kappa values were calculated to assess the level of agreement between observers. The interpretation of the kappa values was based on the criteria proposed by Landis and Koch (12): 0.20 or less indicated poor agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate
agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, excellent agreement. The Wilcoxon signed-rank test was used for comparisons between the right and left breast. The Pearson’s correlation coefficient was used to test the association between the PD area and patients age. All P values less than 0.05 were interpreted as statistically significant. All statistical analyses were performed by using MEDCALC software, version 12.5.0 (Mariakerke, Belgium).

RESULTS

Visual interpretation of digitized mammograms.

Of 206 breasts analyzed, 95 (46%) were classified as fatty, 62 (30%) as scattered fibro glandular densities, 29 (14%) as heterogeneously dense, and 20 (10%) as extremely dense. There was a total of 53 (26%) breast masses, of which 11 (5%) histologically proved malignant, and 42 (21%) presumed benign. Calcifications within breast tissue were found in 88 (43%) breasts, of which 6 (3%) were associated with malignancy. Architectural distortion and focal asymmetric densities were found in 3 (1%) and 26 (13%) breasts, respectively. A total of 69 breasts were assigned to BI-RADS class 1, 79 to class 2, 39 to class 3, seven to class 4, and nine to class 5. Interobserver agreement at the first reading varied from substantial (κ = 0.67 for breast composition, κ = 0.75 for masses, κ = 0.65 for calcifications and κ = 0.62 for BI-RADS class) to fair (κ = 0.36 for focal asymmetry and κ =0.33, for architectural distortion).

Breast density evaluation. The measured mammographic density was 36 ± 20% for the right breast and 34 ± 20% for the left breast (P=0.45). Breast density showed a statistically significant inverse relationship with age (Pearson product-moment correlation coefficient, r = -0.32, P<0.001). Based on the PD values (<25%, 25%–50%, 51%–75%, and ≥75%), each breast was assigned to the corresponding BI-RADS density class. When compared with the results of the consensus reading, overestimation occurred in 6% of the cases and underestimation in 4%. Agreement between the consensus reading versus algorithm PD estimates was excellent, with weighted kappa values of 0.88 (tab. I).

| TABLE I | Visual classification and the software analysis of the breast composition categories (N=206 breasts). |
|----------------|-------------------------------------------------|-------------------|------------------|------------------|
|            | Consensus reading | Algorithm estimates | Observer 1 | Observer 2 |
| Almost entirely fat | 95 (46%) | 94 (46%) | 77 (37%) | 110 (53%) |
| Scattered fibro glandular densities | 62 (30%) | 63 (31%) | 73 (36%) | 49 (24%) |
| Heterogeneously dense | 29 (14%) | 29 (14%) | 36 (17%) | 25 (12%) |
| Extremely dense | 20 (10%) | 20 (10%) | 20 (10%) | 22 (11%) |
| Correct classification | - | 186 (90%) | 175 (85%) | 169 (82%) |
| Classification overestimated | - | 12 (6%) | 27 (13%) | 14 (7%) |
| Classification underestimated | - | 8 (4%) | 4 (2%) | 23 (11%) |
| Weighted kappa- κ | - | 0.88 | 0.84 | 0.80 |
DISCUSSION

In this study we propose an automatic method for breast density estimates that is fast, accurate and easy to implement at minimal costs. We used open-source software, Fiji/Image J distribution, which can be downloaded for free. All of the image-processing algorithms used in this work are available as plug-in that can be tailored to user’s specific needs. Using only open-source software, we have tried to make our results reproducible and therefore easy to replicate.

Quantitative analysis of mammographic density would provide an objective assessment of breast cancer risk (13, 14) associated with varying mammographic densities. The main advantages of the proposed method are the completely automated breast segmentation and automatic thresholding technique. The algorithm was found to be superior to single-observer visual assessments in breast density measurements, matching the ground truth density classification in 90% of the cases.

The method has its disadvantages, because it is more time consuming than the visual assessment and require digitized images, but can accurately determine the percentage density removing the human observer variability. Additionally, an important limitation is that the area measurement from the 2D projection image ignores the variations in breast thickness.

Regarding algorithm optimization, a model for breast compression and thickness should be implemented and multiple comparisons between different devices (mammography systems, film scanning systems) are required, so further work is needed to implement this algorithm in routine practice.

CONCLUSIONS

Our study proposed an algorithm which proved to be effective in breast image segmentation and density estimates, with potential impact on diagnostic performance. The method is more time consuming than visual assessment, but can accurately determine the percentage density removing human observer variability. The main advantages of the proposed method are completely automated breast segmentation and automatic thresholding technique. The algorithm was found to be superior to single-observer visual assessments in breast density measurements. The proposed method showed an excellent agreement with radiological ground truth.

REFERENCES

ELASTIN-LIKE POLYPEPTIDE -COLLAGEN HYDROGELS

In order to minimize post-surgical infections and support wound healing, Anderson et al. studied the preparation of hydrogels with effective antibiotic release profile and better mechanical properties. The team prepared elastin-like polypeptide (ELP)-collagen composite hydrogels that showed a higher elastic modulus in comparison to the collagen hydrogels. The release behavior of the collagen and ELP-collagen hydrogels loaded with varying dosages of a doxycycline hyclate was characterized. Both types of hydrogels showed a gradual time dependent release of doxycycline over a period of 5 days. The ELP-collagen hydrogels had a slower doxycycline release compared to the collagen hydrogels. The released doxycycline was effective in a dose dependent manner against strains of E. coli, P. aeruginosa, S. sanguinis and MRSA. The study concluded that ELP-collagen hydrogels have improved mechanical properties, effective drug release and may be beneficial for tissue engineering applications and drug delivery (Anderson TR1, Marquart ME, Janorkar AV. Effective Release of a Broad Spectrum Antibiotic from Elastin-Like Polypeptide-Collagen Composite. J Biomed Mater Res A. 2014. doi: 10.1002/jbm.a.35219. [Epub ahead of print]).

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