Evaluation of Effects of HRT on Breast Density

Styliani Petroudi[1], Kostantinos Marias[2], and Michael Brady[1]

[1] Wolfson Medical Vision Laboratory, Oxford University, Oxford, OX2 7DD, United Kingdom
{styliani, jmb}@robots.ox.ac.uk
[2] Institute of Computer Science, Foundation for Research and Technology - Hellas

Abstract. Breast density segmentation and classification methods are combined to enable the automatic and quantitative comparison of temporal mammograms of women using Hormone Replacement Therapy (HRT). The results are based on registration and density quantification, so that potentially the clinician may be informed about substantial localised breast density changes. The measures use texture based density segmentation as well as a normalized representation of mammograms.

1 Introduction

Hormone Replacement Therapy (HRT) replaces the hormones a woman's body ceases to produce after the menopause. However, the use of HRT in post-menopausal women has created controversy, not least, because its effects are difficult to characterise and quantify. According to the Million Women Study in the UK [1], HRT use is associated with increased incidence and risk of breast cancer mortality, especially so for combined oestrogen-progesterone therapy. The risk increases with the duration of use and decreases after cessation. It seems that this may be due to *localised* increases in breast density, a known risk factor for breast cancer [2].

The response to HRT is specific to the individual. The changes due to HRT are neither necessarily homogeneous nor global, rather, they depend on the hormonal receptivity of the epithelial elements. Therefore, HRT use may result in density increases both locally, or in the breast pattern, globally. The changes can be characterised as:

- Tissue regeneration: increase in breast density over time.
- No change: no obvious change in breast density.
- Involution: decrease in breast density over time.

The type and degree of change depends on the receptivity of the hormones by the individual, and on the combination of hormones used. Localised tissue changes visible in a mammogram may signal the development of a new cancer, especially if breast cell proliferation occurs in high risk areas such as the Upper Outer Quadrant of the breast. For all of these reasons, there is broad consensus that women taking HRT should be monitored more carefully and more frequently

for breast cancer. Density segmentation, mammogram registration and local tissue density quantification can be incorporated into a clinical framework to assess the general effects of exogenous factors such as HRT.

The Standard Mammogram Form (SMF) representation of interesting tissue introduced by Highnam and Brady [3] is a method to normalise mammograms by calculating anatomical information from the mammogram image. In the resulting SMF image, each pixel represents the thickness of 'interesting' (non-fat) tissue of the compressed breast above that pixel. This effectively provides objective quantitative information about the breast anatomy. Changes of fatty to glandular tissue are precisely changes in non-fatty *i.e.* 'interesting' tissue. This information, combined with the information obtained using the texture-based approaches, can potentially provide both local and global quantitative information about density changes.

This paper describes how texture-based breast parenchymal density classification [4] and SMF may be combined with breast registration to enable automatic and quantitative comparison of temporal mammograms of women using HRT.

2 Method

Initially, the method needs to evaluate whether tissue density has changed due to use of HRT. To this end, two measures, one based on a texture-based segmented representation, the other based on the SMF representation are computed. For the texture based representation each pixel in the mammogram is replaced by the texton (texture primitive element) in the texton dictionary which lies closest to it in the texture feature space [5]. The texton value is achieved following texture classification as presented in [6]. The texton dictionary is obtained by clustering mammogram filter responses with the MR8 filter bank [6] using the following procedure: all filtered responses are aggregated over all the randomly selected training images and the k-means algorithm [7] is used to compute n cluster centres. The training test included mammograms of women using HRT and women who were not using HRT. As usual, the cases of mammograms in this training set were excluded from the test set of mammograms for which the results are presented. The measure using breast density analysis, *mean texture based difference*,

$$\Delta T_\mu = T_\mu(current) - T_\mu(previous)$$

is based on evaluating the difference between the mean texton values T_μ representing the breast area in each of the temporal mammograms. The different density classes are assigned numbers/labels T_l from 1 to n, the total number of textons used to segment the mammograms,according to the energy of the texton they represent. The mean texture based density value is given by:

$$T_\mu = \frac{1}{N_b} \sum_{i=1}^{N_b} T_l(i) \tag{1}$$

where N_b is the total number of pixels in the breast area. The second measure, *difference sum of interesting tissue*,

$$\Delta S_{int} = (S_{int}(current) - S_{int}(previous))/(S_{int}(previous))$$

is based on the normalised difference in the sum of interesting tissue S_{int} [8] in the SMF representation of the corresponding temporal pairs of mammograms:

$$S_{int} = \sum_{i=1}^{N_b} h_{int}(p_i) \tag{2}$$

where p_i corresponds to pixel i in the breast area. (Of course, the texture segmentation algorithm could also be directly applied to SMF images.) These difference measures can be used to evaluate a global increase or decrease in breast density due to use of HRT in order to recommend further investigation. The density changes are evaluated globally as either regeneration or involution, as shown in Table 1. Although "no change" in breast density is not as important as tissue regeneration, it is included in the same classification.

Table 1. Rules to assess global mammographic density changes due to HRT between temporal mammogram sequences.

Difference Measures	Corresponding Change in Breast Density
$\Delta T_\mu > 0$ *or* $\Delta S_{int} > 0$	Tissue Regeneration or No Change
$\Delta T_\mu < 0$ *and* $\Delta S_{int} < 0$	Involution

To achieve this, a two-step registration algorithm using internal landmarks and Thin Plate Splines is applied to register the SMF images and the texture segmented mammograms [9]. The resulting difference images combine registration with normalisation, and can in turn show where the changes occur and how significant they are, providing the clinician with local change information. If there is an apparent increase in breast density, the issue will need to be investigated further and monitored closely.

3 Results and Discussion

The algorithm was evaluated on a pilot dataset of 15 pairs of temporal mammograms (with a three year time interval) of women taking HRT belonging to the Screen Database collected in Oxford [10]. The ground truth was defined by a radiologist who examined the original mammogram pairs and classified global and local density changes. Seven mammograms were judged to exhibit involution, six mammograms were judged to exhibit tissue regeneration, and two mammograms were judged to exhibit "no change". The global density change evaluation

results are presented in Table 2. It must be noted that there was enough tissue regeneration to result in a global breast pattern class change in only two of the included regeneration pairs. Global density classification is followed by registration in order to evaluate local difference changes.

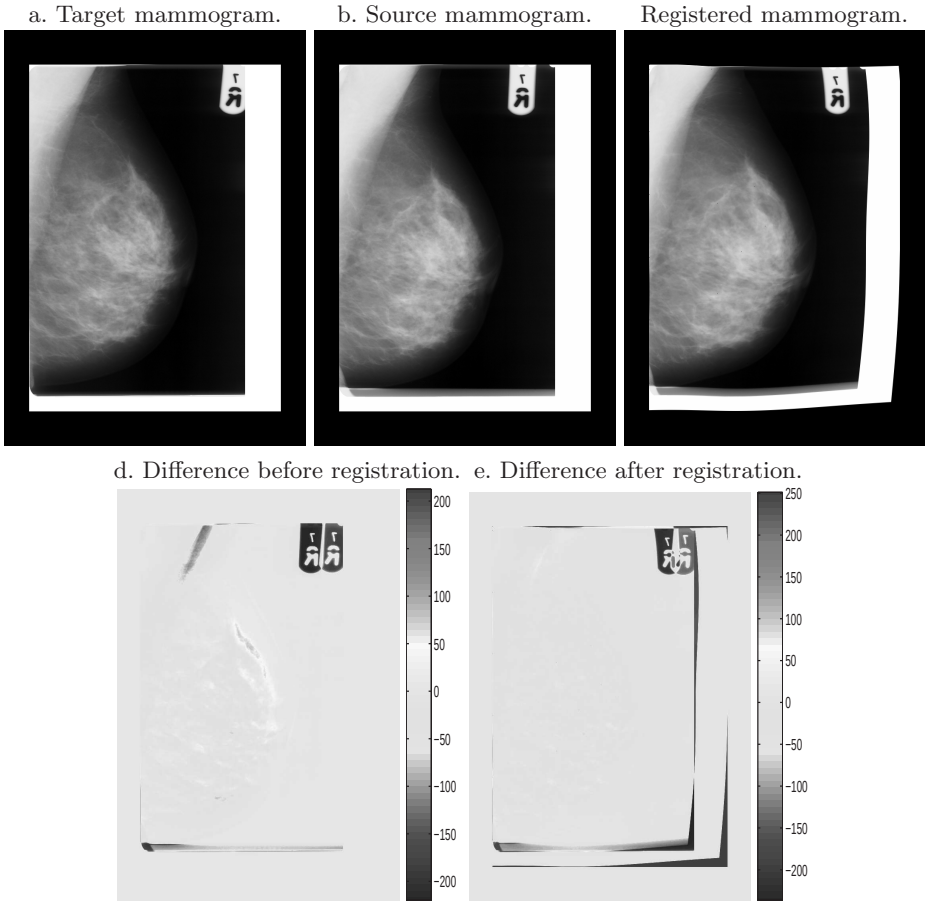
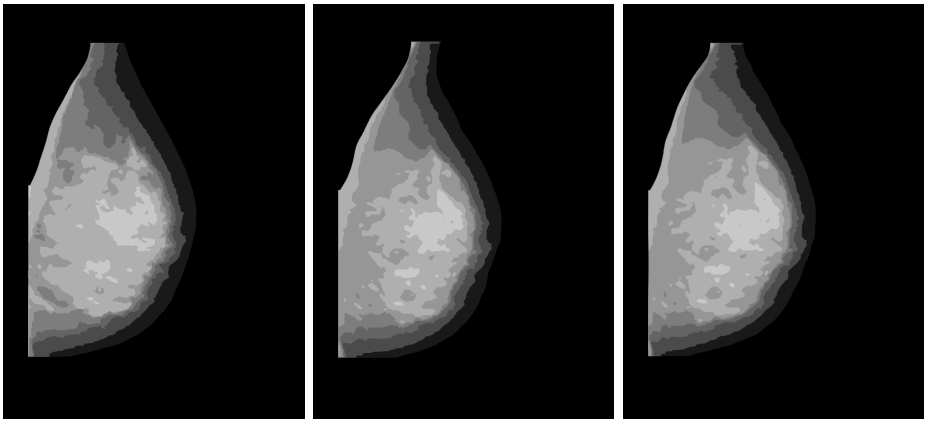


Fig. 1. A pair of right temporal mammograms of a woman on HRT exhibiting involution. Registration and differences on the original mammograms.

The example that follows corresponds to a woman who had been using HRT for a period of 4 years exhibiting tissue involution. Figures 1, 2 and 3 show the right temporal pair of mammograms of the woman exhibiting involution. As can be seen from the colour difference images after registration, the target image exhibits lower density (Figure 2 (e)) as well as lower height of non-fat tissue (Figure 3 (e)). This is especially obvious in the upper outer quadrant of the

a. Texture target image. b. Texture source image. c. Texture registered image.



d. Difference before registration. e. Difference after registration.

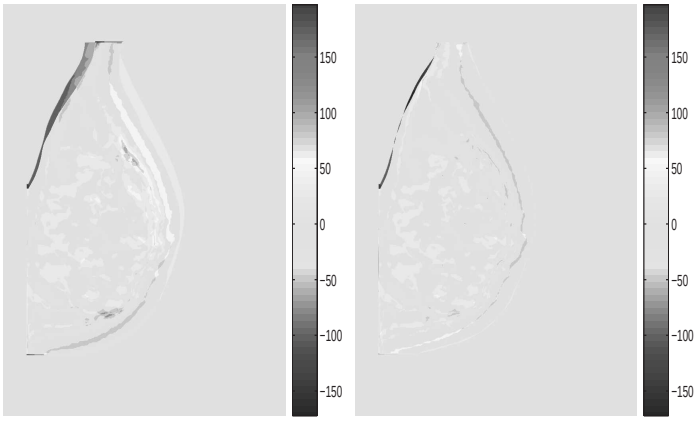
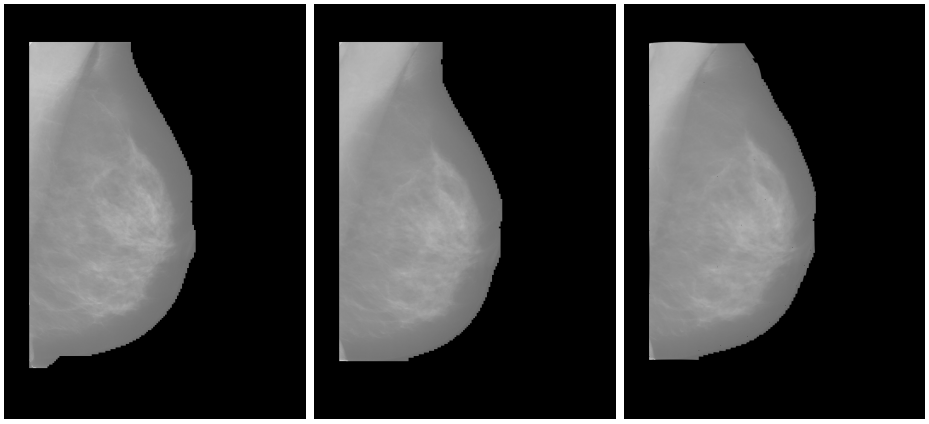


Fig. 2. The pair of right temporal texture segmented mammograms of the same woman on HRT exhibiting involution. Registration and differences on the texture segmented representation.

Table 2. Results on the agreement of the evaluation of global density changes with clinician's ground truth.

Density change measure	ΔT_μ	ΔS_{int}	ΔT_μ *and* ΔS_{int}
Agreement in regeneration and no change pairs	88%	62%	88 %
Agreement in Involution pairs	71%	85%	85%

a. SMF target image. b. SMF source image. c. SMF registered image.



d. Difference before registration. e. Difference after registration.

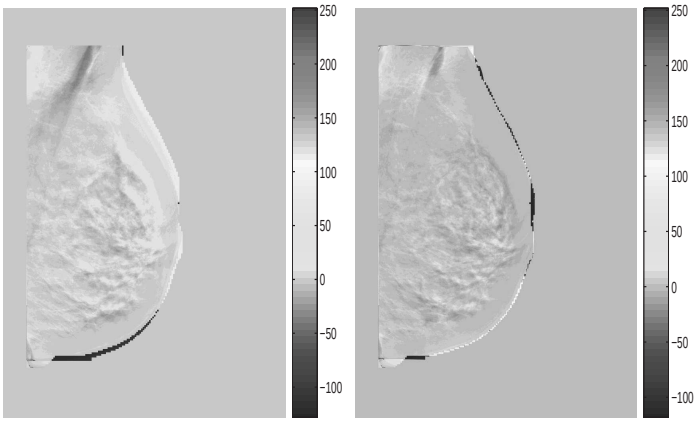


Fig. 3. The pair of right temporal SMF images of the same woman on HRT exhibiting involution. Registration and differences on the texture segmented representation.

breast. The texture difference image shows where the involution takes place and how it is distributed throughout the breast region.

4 Conclusions

The method shows that there are ways to evaluate density changes quantitatively, and enables close monitoring of any changes. The performance was evaluated by assessing the agreement with the radiologist's assessment. The results suggest how the use of texture based segmentation and density based classification may have a role to play in the clinical framework of mammographic image analysis. They are also encouraging for developing computer tools that automatically monitor changes in mammographic density between successive scans.

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