Quantifying mammographic changes in temporal HRT sequences

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Abstract. In this paper we introduce a novel method for assessing mammographic (density) changes in sequences of patients on HRT. The temporal sequence of mammograms is represented using the h_{int} representation of interesting tissue and subsequently registered. The % change in h_{int} (non-fatty tissue) in the registered pair is a good approximation of the fibroglandular change in the composition of the breast tissue. The expert's description of the changes in the HRT sequences of our data set was used as the gold standard for evaluating our quantitative measure.

1 Introduction

Today, more than ever, the administration of HRT (Hormone Replacement Therapy) to postmenopausal women is controversial especially as its effects are hard to characterise and quantify [1]. On one hand beneficial effects include improvements to the cardiovascular system, osteoporosis, troublesome menopausal symptoms, vasomotor symptoms, and Alzheimer's disease. On the other hand there is some evidence for increased breast cancer risk (especially in long-term therapy) that has caused some concern. Additionally to date, efficient alternatives to HRT are still not available.

Describing and measuring HRT induced tissue changes is a part of almost every clinical study that examines data obtained before and during therapy. The clinical aim is to correlate such changes to an increased risk of cancer or to the type of therapy used, and to assess the possible influence on breast diagnosis. The latter consideration, means that increased glandular density induced by the therapy can decrease mammographic sensitivity, since the observed "brightening" of the film can make diagnosis of lesions more difficult.

The most usual change observed on a mammogram is regeneration or increased density in fibroglandular tissue but it is not uncommon to observe the opposite or no change at all. A simplified mechanism explaining the variability in the observed changes would consist of the indigenous drive to reduce hormone production competing with the induced (exogenous) hormones, combined with the different hormonal uptake between individuals.

In order to accurately quantify changes in HRT image sequences, we first normalise the intensities using the h_{int} representation [2] (discussed in the next section) and then register the images to the same co-ordinate frame. To compensate for differences in compression, Marias et al. [3] demonstrated a registration method based on boundary points to approximate the changes in compression. A recently improved method [4] that takes into consideration internal landmarks calculated using multi-scale analysis is summarised in section 2.2. In section 3, we define a quantitative measure of HRT effects and present some results before concluding with the discussion in section 4.

2 Methods used

2.1 The h_{int} representation of interesting tissue

Because of the relatively weak control over the image acquisition process, it is difficult to eliminate variability in image characteristics, such as contrast and brightness. The differences in imaging conditions lead to a non-rigid transformation between the intensities of temporal pairs of mammograms. For this reason, it becomes even more difficult to compare temporal mammograms, consequently to assess changes due to HRT. In addition, the existence of intrinsic degrading factors (scattered and extra-focal radiation) reduce the diagnostic value of each mammogram.

The h_{int} representation of interesting tissue, introduced by Highnam and Brady [2], is a robust method to normalise mammograms since in the resulting h_{int} image, each pixel represents the thickness of 'interesting' (non-fat) tissue between the X-ray source and the image. This effectively provides objective quantitative

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information about the breast structure. Using the h_{int} representation, Highnam and Brady modelled and removed the effect of scattered, extra-focal radiation as well as image glare [5] thus creating a general framework for mammogram normalisation.

Particularly in the case of HRT sequences, the objective is to assess local changes in the composition of the breast tissue. By using the h_{int} representation as a first step in our analysis, one can achieve a more accurate comparison of a mammogram with previous ones, as mammogram matching and registration do not factor out variations in the pair due to imaging conditions. Since the imaging conditions often vary temporally, even if a pair of images is very accurately aligned, differences in the intensity of corresponding points inevitably remain. For that reason, we combine the two sources of information in order to develop a robust technique for assessing HRT changes.

2.2 Mammogram registration

We register the temporal sequences using our improved multi-scale algorithm [4]. First, we calculate the location of the nipple and the points between the breast, the rib cage and the axilla by separating positive and negative curvature portions of the breast edge and locating curvature peaks as shown in figure 2.1. Next, we sample the breast edge between these points and partially register the images using thin-plate spline interpolation. By using a non-linear wavelet scale-space we isolate significant regions of interest. Based on these regions, a set of internal landmarks is defined by using a matching algorithm that includes the partial transformation (induced by the boundary alignment) in conjunction with scale, size and orientation information of the candidate matches. The matching algorithm provides the weights (the inverse of the variance σ_i^2) in order to characterise the uncertainty in the localisation of the landmarks. In the final registration step, both the boundary and the detected internal landmarks control a thin-plate spline approximation technique [6], by minimising the following functional:

$$J_\lambda(\mathbf{t}) = \sum_{i=1}^{n} \frac{|\mathbf{q}_i - \mathbf{p}_i|^2}{\sigma_i^2} + \lambda \cdot J_2^2(\mathbf{t})$$

where $\mathbf{q}_i$ and $\mathbf{p}_i$ are the landmark pairs, $J_2(\mathbf{t})$ is the bending energy of the transformation $\mathbf{t}$ and λ is a regularisation parameter that controls the trade-off between the smoothness of the transformation and adaptation to the local transformations induced by the data. The boundary points are weighted with the maximum matching score (after normalisation) ensuring that the global transformation smoothly transforms the boundary while local deformations occur on the inside according to the importance of the internal matches. The number of internal landmarks detected depends on the number of significant regions that propagate in the scale-space stack and are consistent in both images in the pair. The registered h_{int} images can now be compared more effectively in order to estimate changes in breast composition as is discussed in the next section.

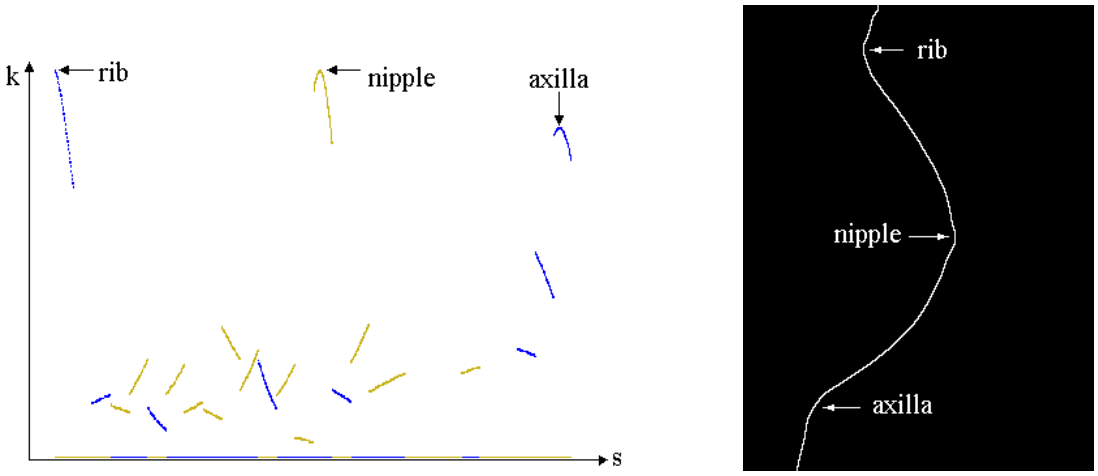


Figure 2.1: The curvature profile along the breast boundary k (*s*), consisting of the 2 peaks near both ends of the boundary (darker colour) and the peak corresponding to the nipple in the middle.

3. Results

After normalising the HRT sequences using the representation of interesting tissue and registering the mammograms, we compute the following measure to describe changes in the composition of the breast:

$$\Delta h_{\text{int}}\ (\%) = \sum_i \sum_j \frac{(h_{\text{int}}^{A_1} - h_{\text{int}}^{A_2})}{(h_{\text{int}}^{A_1} + h_{\text{int}}^{A_2})}$$

Where the superscripts A_1, A_2 indicate that the sum of interesting tissue values in each image needs to be divided to the total area of the h_{int} surface in order to account for the (usually small) difference in the number of pixels. By using an expert's opinion as the gold standard for characterising change between the HRT sequences we used the rule shown in Table 1 to evaluate our method for a total of 50 HRT sequences:

To date, using the rule described in Table1 we have achieved a 90% agreement between our measure and the expert's opinion. The measure continues to be refined in more images and we are validating other quantitative measures based on the h_{int} values in normalised-registered mammogram pairs.

% Change in interesting tissue	Corresponding change in breast composition due to HRT between the mammograms
$\Delta h_{\text{int}} \geq 0$	Fibroglandular to fatty or no change
$\Delta h_{\text{int}} \leq 0$	Fatty to gladular/stromal or no change

Table 1: The rule to assess mammographic changes due to HRT, from measuring the % normalised difference in "interesting" tissue between the HRT sequences.

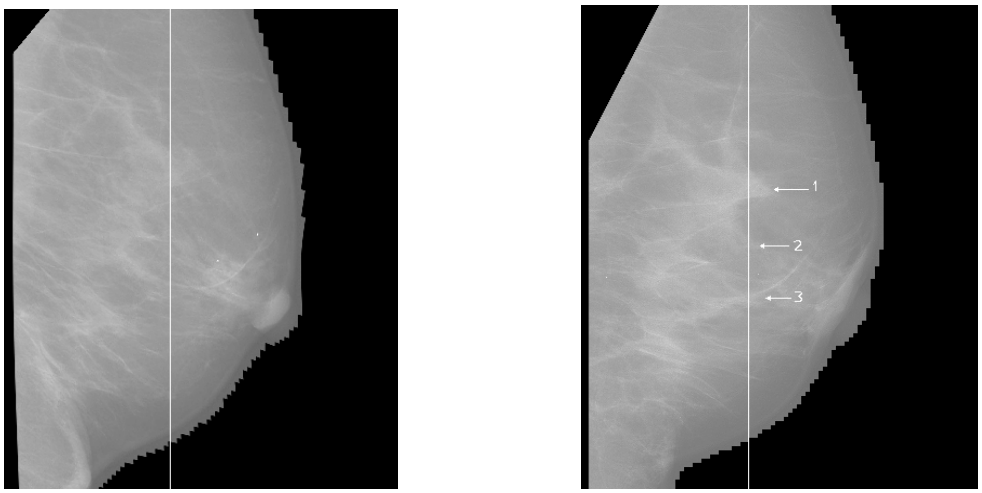
4. Discussion

The measure described in section 3 would not have yielded a significant result if the mammograms had not been normalised, since the pixel intensities would be related to the accumulated x-ray attenuation through a combination of fibroglandular and fatty tissue inside the breast. By using the h_{int} representation, we relate each pixel value to the fibroglandular composition of the breast. Registration of the images accounts for global differences in scale and the non-rigid transformation in the mammograms due to the differences in compression.

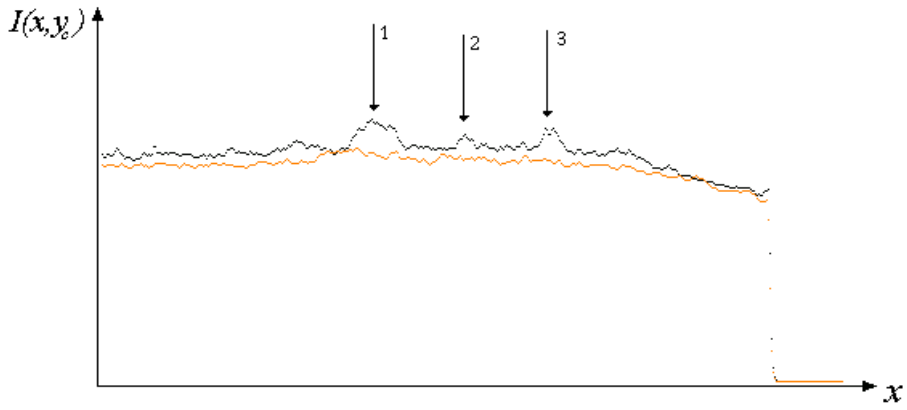
Correlation between the changes in breast anatomy due to HRT and changes in the digitised mammogram pairs is not easy. When a fibroglandular element has the same spatial extent in a sequence of HRT mammograms but its intensity is higher, it can be safely concluded that the glandular element became denser due to HRT. Similarly, it is possible to observe a small change in the intensity, but a larger spatial extent reflecting regeneration of glandular tissue, or a new growth. To be able to assess automatically and classify such changes, accurate registration and intensity normalisation is needed.

Although the measure presented in this paper describes global changes in tissue composition, our ultimate goal is to be able to assess local changes in tissue density. Figure 4.1 (a) and (b), shows a registered and normalised mammogram sequence of a patient on HRT. It is obvious in the second image that there is a "global" increase of glandular tissue. The line-intensity profile in figure 4.1 (c) shows that there is indeed a small increase in the overall intensity with some "larger" local variations (numbered 1,2,3) that correspond to the three areas of glandular tissue regeneration indicated in figure 4.1 (b).

The quantitative description of changes in mammograms of HRT patients and our objective to eventually be able to locally describe these changes are not only destined to assist the clinician to visualise change, but to help to classify changes in the breast as well. For example, a breast of a patient on HRT who is starting to develop cancer, may possibly exhibit a different (and sometimes even the opposite!) response to therapy. To automatically detect regions of differential response to HRT between the breasts would be a beneficial tool for early detection of breast cancer in patients treated with HRT.



(a) (b)



(c)

Figure 4.1: (a), (b): A sequence of mammograms showing increase in fibroglandular tissue (in (b)), due to HRT. The images have been normalised (using the in h_{int} representation) and registered, (c) The line-intensity profiles showing the intensity distribution along the same bright line indicated in (a) and (b). The darker one corresponds to (b) and comes in agreement with the observed increase of glandular tissue in (b). "Larger" local variations (numbered 1,2,3) correspond to the 3 areas of glandular tissue regeneration marked in (b).

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