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Appendix E1

The algorithm for VBD estimation works by processing DBT images to generate a 3D segmentation of the fibroglandular tissue within the breast volume. Each DBT sequence consists of two image sets: a set of source projection images and a set of reconstructed images. Both image sets are used in the developed method, which is implemented in three stages: *(a)* segmentation of projection images, *(b)* generation of a 3D density likelihood map, and *(c)* multiparametric volume refinement. Details of each stage are outlined here.

Segmentation of Projection Images

In this stage, each projection image is segmented into a dense versus nondense binary tissue mask by using a previously validated algorithm for the segmentation of dense tissue on digital mammograms (1). The original algorithm has been modified as follows to handle tomosynthesis projection images and improve computational efficiency. Specifically, each tomosynthesis projection image is processed individually in three substeps (Fig E1): *(a)* breast detection, where the breast area is detected by outlining the breast-air contour and the pectoralis muscle; *(b)* intensity clustering, where fuzzy *c*-means clustering is performed within the breast region to group image pixels according to their intensity values; and *(c)* multifeature classification, in which from the total of 86 features considered in the original algorithm (1), a subset of 16 features is selected for the segmentation of tomosynthesis projection images, including statistical and morphologic descriptors.

These features were selected by processing the whole training set and picking up those that contributed significantly to the output of the final support vector machine classifier. In addition, three focus measure operators are applied to each cluster for classification purposes (2). A support vector machine classifier specifically trained for tomosynthesis projection images is then used to determine which clusters are dense and which ones are not to yield the final segmentation.

The procedure described above is repeated for each projection image of the sequence. For additional details about this segmentation algorithm, the reader is referred to reference 1.

3D Density Likelihood Map

A 3D map of the breast volume is generated, where each voxel represents the likelihood of fibroglandular tissue. For the generation of this 3D density likelihood map, the proposed method was inspired from the "shape from silhouette" approach (3) from the research field of computer vision. Because of the limited angle of tomosynthesis, blurring artifacts are introduced in the reconstruction sections. Therefore, we aim to take advantage of the information in the source projection images to generate an initial likelihood map of the fibroglandular tissue. This map will be further refined in a subsequent stage to refine the segmentation of the fibroglandular tissue. For the sake of clarity, the generation of the 3D likelihood can be subdivided into two substeps:

(a) For each voxel of the breast volume, the density likelihood is computed by means of a voting process that involves all tomosynthesis projection images; and *(b)* to guarantee a perfect match, the generated 3D likelihood map and the reconstruction sections are then coregistered on a per-section basis by using rigid registration.

For the first step, let $\Omega_i = \{(u,v) \mid I(u,v) \text{ is dense}\}$ denote all the pixels labeled as "dense" in the previous stage of the algorithm for the i-th projection image. The dense likelihood for the voxel at coordinates *(x,y,z)* in the breast volume, namely *L(x,y,z),* is computed by means of a voting process that involves all *N* projection images as follows:

$$L(x,y,z) = \frac{1}{N}\sum_{i=1}^{N}\delta_i(x,y,z),$$

where $\delta_i(x,y,z)$ is given by

$$d_i(x,y,z) = \begin{cases} 1 & \text{if } P_i(x,y,z) \in \Omega_i \\ 0 & \text{otherwise} \end{cases},$$

where $P_i(x,y,z)$ is the projection of voxel *(x,y,z)* on the i-th projection image.

The projection of voxels of the breast volume on the projection images is determined by the acquisition geometry (x-ray source position, angle, and detector resolution) that corresponds to each projection (4,5). Specifically, the 3D coordinates of a voxel in the breast volume *(x,y,z)* are related to the 2D coordinates *(u,v)* of each pixel on the projection image by means of a series of rigid transformations $(u,v) \rightarrow (\tilde{x},\tilde{y},\tilde{z}) \rightarrow (x,y,z)$:

$$\begin{bmatrix} \tilde{x} \\ \tilde{y} \\ \tilde{z} \end{bmatrix} = [R][P] \begin{bmatrix} u \\ v \\ 1 \end{bmatrix},$$

where *R* and *P* are rotation and orthographic projection matrices, respectively, defined in terms of the resolution of the system and the angle of the x-ray source as:

$$R = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos(\alpha) & -\sin(\alpha) \\ 0 & \sin(\alpha) & \cos(\alpha) \end{bmatrix} \text{ and } P = \begin{bmatrix} \rho_x & 0 & T_x \\ 0 & \rho_y & T_y \\ 0 & 0 & 1 \end{bmatrix},$$

where α is the angle of the x-ray source, $[\rho_x, \rho_y]$ is the image resolution, and $[T_x, T_y]$ is the image size.

Finally, the 3D voxel coordinates are defined in terms of their distance from the detector, *z,* as:

$$x = x_0 + (x_0 - \tilde{x})\frac{z - z_0}{z_0 - \tilde{z}} \text{ and } y = y_0 + (y_0 - \tilde{x})\frac{z - z_0}{z_0 - \tilde{z}},$$

where $(x_0, y_0, z_0) = (0, r\cos\theta, r\sin\theta)$ is the position of the x-ray focal spot and r is the source-detector distance.

Owing to postprocessing of reconstructed sections aimed at compensating for perspective distortion, as well as deviations of the paddle angle and the projection angle from the nominal values of the acquisition geometry, the likelihood matrix *L(x,y,z)* generated previously must be registered to the reconstruction sections. This registration process allows for the computation of an accurate 3D density likelihood map without the need to explicitly know proprietary postprocessing steps applied by the vendor when generating the reconstruction sections. Specifically, each section of the 3D likelihood map must be registered to the corresponding reconstruction section. Let $C_{\mathrm{L}}(z)$ denote the breast contour of the z-th section of the likelihood map and $C_{\mathrm{R}}(z)$ denote the contour of the corresponding reconstruction section. The aim is to find the rigid transformation in terms of rotation, scale, and translation (*R, s,* and *T,* respectively) that relate these contours:

$$C_{\mathrm{L}}(z) = s\,C_{\mathrm{R}}(z)\,[R]^{\mathrm{T}} + [T].$$

The rigid transformation between $C_{\mathrm{L}}(z)$ and $C_{\mathrm{R}}(z)$ is found by means of the Coherent Point Drift algorithm (6) and is applied to each pixel of the z-th section of the 3D likelihood map to register it with the corresponding reconstruction section (Fig E2).

Multiparametric Volume Refinement

The last step for the segmentation of fibroglandular tissue from DBT images is aimed at the computation of different features for each voxel of the breast volume to refine the final segmentation. In addition to the density likelihood, a set of 19 features, including global and per-cluster features, is computed for each voxel of the breast volume to perform a support vector machine classification. These features are the same ones used for the segmentation of tomosynthesis projection images, but they are applied on a per-cluster basis (Table E1). The classification labels for training the support vector machine classifier are established by performing fuzzy *c*-means clustering of the voxels on the basis of their intensities and defining a dichotomous classification of the clusters in dense versus nondense tissue such that the resulting total fibroglandular tissue volume has the lowest error when compared with the total fibroglandular tissue volume computed from the corresponding MR imaging sequence, used as reference for training the support vector machine classifier. This training process is performed by using threefold cross-validation. In each fold, the data set is split into two independent sets: training (67%) and testing (33%). Therefore, each tested sample has not been seen by the trained classifier. The results reported in the main manuscript for the DBT VBD estimation represent the estimates obtained for each test set, thereby being a truly previously "unseen" sample.

Table E1. Features Extracted for Multiparametric Volume Refinement

Parameter	Global Features (computed on the whole breast volume)	Local Features (computed on a per-cluster basis)
Image acquisition	Patient age, breast thickness, exposure, x-ray tube current, peak voltage	3D density likelihood
Texture features	Mean, standard deviation, range, entropy	Mean, skewness, range, entropy
Focus measures	Local mean, sum of wavelet coefficients, squared frequency	Local mean, sum of wavelet coefficients, modified Laplacian filter

Note.—Details about texture features and global image acquisition–based features can be found in reference 7. Details about the focus measure operators can be found in reference 8.

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