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Three-Dimensional In Silico Breast Phantoms for Multimodal Image Simulations

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Abstract

Anatomic simulators have provided researchers with the realistic objects needed to develop and evaluate medical imaging approaches. Today we have new insights into the cellular biology of breast tissues that is driving many new targeted diagnostic and therapeutic approaches, including molecular imaging. We report on our initial efforts to build a scalable framework for the construction of realistic 3-D *in silico* breast phantoms (ISBP) capable of leveraging existing knowledge and yet adaptable to fully integrate future discoveries. The ISBP frames are developed with scalable anatomical shapes and morphologic features as adapted from a rich literature on this topic. Frames are populated with tissue subtypes essential for imaging and object contrast functions are assigned. These data can be resampled to match the intrinsic scales of various imaging modalities; we explore mammography, sonography and computed tomography. Initial comparisons between simulated and clinical images demonstrate reasonable agreement and provides guidance for future development of a more realistic ISBP. An end-to-end simulation of breast images is described to demonstrate techniques for including stochastic variability and deterministic physical principles on which image formation is based.

Index Terms

Breast imaging; computed tomography (CT); mammography; modeling; ultrasound

I. Introduction

Our numerical models of the adult female breast build upon prior software [1]–[4] and hardware [5], [6] model forms and recent discoveries on mammary tissue morphology. [7]–[16] The goal is to provide an *in silico* breast phantom (ISBP) for the development of medical imaging systems that reflects current knowledge of normal tissues and provides a

framework for integrating future knowledge at all relevant spatial and temporal scales, eventually including the dynamics of disease formation and progression.

Imaging methods are often evaluated using simple physical models (test objects) that abstract anatomical or functional features central to the diagnostic process [6], [17]; e.g., breast mass shape, blood flow patterns, or microcalcification density. Test objects allow for quick assessment of feature visualization performance that may be directly related to important engineering metrics such as spatial resolution and detective quantum efficiency. The principal strength of the test-object approach to imaging system evaluation is that object features are known exactly. Weaknesses include fixed and unrealistic properties that are modality specific.

In contrast *in silico* tissue modeling is an economical route to improving imaging technologies by including realistic and stochastic multimodality features with exactly known properties. Since image data recordings depend on interactions between modality energy and breast structures, *in silico* models are developed from an anatomical frame to which physical properties are assigned that define energy absorption and scattering interactions. Modeling is complicated by there being few known physical principles for defining tissue structures and natural stochastic variations. The ideal model includes structures at all length scales that interact with imaging systems, person-to-person variations, and physiological transformations associated with menstrual cycle, aging, pregnancy, and disease.

Organs of the body consist typically of parenchymal cell structures providing function that are arranged within stromal tissues and regulated by mesenchymal cells to provide form. There have been two approaches to generating software breast phantoms that preserve function and form. The first method assigns cell types to voxels of segmented image data [18]. This method has the advantage of being derived directly from human data [19], [20], but it is limited by the types of structures that the host imaging modality can observe, the resolution and coverage of the modality, and it is difficult to accumulate an ensemble that represents natural diversity.

The second approach is to generate mathematical models that simulate breast structures in a manner consistent with anatomical observations, then sample the results at appropriate intervals, and assign object contrast properties to voxels [1], [3]. This is the ISBP method that enables scalable dimensions and sampling intervals as required for multimodality imaging simulation and for user adjustment of tissue composition, structure size, and randomization. ISBPs provide a means for precise registration of multimodality images even if the characteristic dimensions are very different. Our model differs from other approaches in that it is derived entirely from statistical observations of tissues leading to mathematical equations that permit modeling at all scales and with intrinsic randomness. Stochastic model elements facilitate generation of ensembles to represent a population of patients for analysis. The principal objective of this report is to describe our ISBP approach. However, we have also demonstrate some of the medical images that can be generated from ISBP using simple X-ray and sonographic image simulators.

II. Methods

Parameters selected in this section to describe breast anatomy are selected from a vast literature on this topic [8], [9], [11]–[13], [15], [22]–[25]. When published parameters were unavailable, we selected reasonable numbers.

A. Breast Boundary

The outer breast boundary, e.g., Fig. 1, can be defined by fitting geometrical functions to the overall observed breast shape. Hence, we begin the simulation process by defining the outer shape in Cartesian coordinates. The depth dimension of the breast is defined by the z axis, where the chest wall is located in the coronal plane at $z = 50$ mm while the nipple terminates in the coronal plane at $z = 0$ mm. The vertical dimension of the breast is defined by the y axis, where smaller and larger values of y indicate inferior and superior anatomical points, respectively.

The breast shape is defined in this framework by an ellipsoid and series of second degree polynomials designed to fit user defined reference points on the outer surface. The ellipsoid defines the lower part of the breast and polynomials define the upper part. These reference points are determined using available anthropomorphic measurements and breast curvature information [9], [10], [13]. To define the lower part of the breast, the six spatial reference points listed in Table I are determined to fit the ellipsoid shown in Fig. 2. An additional constraint is that the slope of the ellipsoid at the nipple point, z/y , equals zero to ensure the nipple becomes the outermost point of breast.

The upper part of the breast is simulated using second degree polynomials that join an upper attachment-point set to the lower ellipsoidal-point set as shown in Fig. 3(a). In this example, the lower part of the breast is defined by the ellipsoid for $y < 20$ mm and the upper part is defined by polynomials for $y \geq 20$ mm, Fig. 3(b). The upper attachment-point set is defined as a line segment in the chest wall plane at $z = 50$ mm at height $y_{\text{upper}} = 160$ mm. It extends along the x axis to either side, as shown in Fig. 3(a). The ellipsoidal-point set is defined by points on the ellipsoid that lie in the xz plane at $y_{\text{lower}} = 20$ mm. This is taken to be approximately the same height above the nipple as the lower breast point is below to maintain curvature [15]. The ellipsoidal-point set is shown in Fig. 3(a) as the lower curved segment. Polynomials are defined by point pairs and the corresponding slopes.

B. Subcutaneous Fat Layer and Fibroglandular Region

The fibroglandular region and subcutaneous fat layer are defined by a similar, yet smaller inner boundary located inside the outer boundary of the breast model. The inner boundary is defined by the same number of spatial reference points but their locations are selected based on anatomical data that describes the thickness of the subcutaneous fat layer. Our simulations are based on a report of the average axial thickness of subcutaneous fat being approximately 23% of the breast at the chest wall and approximately 7.5% near the nipple [14]. The inner boundary is fit to an ellipsoid-polynomials set in the same manner as the outer boundary with the ellipsoidal attachment point set plane remaining at $y_{\text{lower}} = 20$ mm.

The retromammary fat layer extends along the pectoral muscle, posterior to the fibroglandular region, and has a relatively constant thickness. Here, the retromammary fat layer (Fig. 1) is assigned a constant thickness of 4 mm and is incorporated into the subcutaneous fat layer [14]. Thus, the *subcutaneous fat layer* is designated as the volume between the outer and inner boundaries (including the retromammary fat layer) and is assigned as adipose tissue, while the *fibroglandular region* is designated as the volume inside the inner boundary and is assigned as fibrous tissue.

C. Subcutaneous–Fibrous Surface

The subcutaneous–fibrous surface refers to the boundary interface between the subcutaneous fat layer and fibroglandular region. Several breast imaging modalities have shown that this surface is highly irregular. To simulate this irregularity in physical phantoms, Madsen used molds formed on a surface indented spherically at random depths and locations [5], [6]. Our

study incorporates a similar approach where 8-mm-diameter adipose spheres are added to the phantom simulation near the subcutaneous–fibrous interface [6]. The sphere centers are placed at random locations 0–4 mm below the surface within the subcutaneous fat layer. An illustration of this method is shown in Fig. 4. Fibrous tissue within the fibroglandular region that is overlapped by a sphere is replaced by adipose tissue, while the subcutaneous fat layer is unchanged. Any volume outside the outer boundary is neglected. The newly added adipose tissue is incorporated into the subcutaneous fat layer. Fig. 4 shows a partial ISBP with the subcutaneous–fibrous surface. Typically, 1000 spheres are used in the simulation.

D. Intraglandular Fat

Intraglandular fat regions are simulated within the fibro-glandular region. They are small elongated adipose streaks often orientated along ductal structures. These intraglandular adipose compartments are modeled as small elongated ellipsoids of varying sizes with equatorial radii A and B between 1–3 mm, and polar radii C between 4–12 mm. The ratios A/C and B/C are maintained at $1/4$. Their tilt angles, θ and ϕ , are calculated to orient the polar radius along a line connecting the ellipsoid center point and the nipple point. To slightly randomize the orientation, polar radii are varied from this line by a randomly selected angle from 0° to 30° . Center points are selected to be randomly located within the fibro-glandular region. Fibrous tissue overlapped by the ellipsoid is replaced by adipose tissue, while the subcutaneous fat layer and volume outside of the outer boundary are left unchanged. Adipose compartments satisfy an overall adipose fraction of the breast [Subcutaneous Fat Volume + Intraglandular Fat Volume]/[Total Breast Volume]. The examples in Fig. 5 show the volumes of four partial phantoms generated with different adipose percentages.

E. Cooper's Ligaments

Cooper's ligaments are fibrous ligaments that are interwoven within the subcutaneous fat layer and function to connect the fibroglandular region to the skin and pectoral muscle. In histological images, they appear as thin fibrous compartments surrounding adipose tissue [1], [3]. In ISBP, Cooper's ligaments are modeled as elongated ellipsoidal shells of varying sizes that exist within the subcutaneous fat layer. The equatorial radii, A and B , are each calculated to be between 6–13 mm and the polar radius, C , is calculated to be 40 mm. Sizes were selected from observations on clinical breast computed tomography (CT) images and to be consistent with the adipose sphere sizes. The thickness of each shell is approximately 2 mm. The ellipsoidal shell center points are randomly distributed on the outer boundary surface and maintain greater than 26 mm distance between each center to avoid overlapping. Their tilt angles, θ and ϕ , are calculated to orient the polar radius along a line extending from the ellipsoid center point to a central point within the breast to ensure each shell extends towards and terminates at the subcutaneous–fibrous surface [Fig. 6(a)]. The ellipsoid thickness is designated as fibrous tissue and replaces the adipose tissue within the subcutaneous fat layer that it overlaps. Volumes within the fibroglandular region and outside of outer boundary remain unchanged [Fig. 6(b)].

F. Ductal Structure

The functional unit of breast tissue is the ductal structure lined by epithelial cells, which is responsible for the production and transport of milk. There are typically 15–25 ductal trees in a breast [7], [14], [15]. The trees begin close to the nipple and branch out into a root like growth, or lobes, that ends in terminal ductal lobular units. The lobes from different primary ducts are intertwined [11], [12], [25]–[27]. Hence, in our simulation, each ductal tree is simulated as a nodal network following a random binary tree model [2], [4]. Each branch of the binary tree is represented as a node. The nodal network begins at a single *root node*. Every node, including the root node, branches or “bifurcates” into two other nodes. Thus,

each node is a *parent node* and has two *children nodes*. The exception to this is a *terminal node* which does not branch but is terminated by a terminal ductal lobular unit. Each node also has an associated *node order* and *biorder*. The node order is a particular value which is indicative of level or height of the node in the nodal network, with a high number being closer to the root and a low number being closer to the terminal branches. The biorder of a node is the two node orders of the associated children nodes. Terminal nodes have a node order equal to 1. The root node has the highest node order, s , and is the start of the nodal network.

To generate a random binary tree from a ramification matrix, one can use the probability elements in the ramification matrix to calculate the biorder of the root node and generate a new pair of nodes. The biorder of these new nodes can be calculated using the ramification matrix elements as well, and so on, until terminal nodes are reached. After rounding to the nearest hundredth, the measured matrix from Bakic *et al.* [4] is

$$R(s=4)=\begin{bmatrix} 0.36 & 0.64 & 0 & 0 \\ 0.35 & 0.29 & 0.36 & 0 \\ 0.29 & 0.28 & 0.23 & 0.20 \end{bmatrix}. \quad (1)$$

For our simulation, we designed a ramification matrix that allows the ductal tree to branch a few additional node orders as it is very difficult to differentiate between branches as they get closer to lobules in galactograms. Hence, we generated ductal trees using the following ramification matrix:

$$R(s=6)=\begin{bmatrix} 0 & 1.0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1.0 & 0 & 0 & 0 \\ 0 & 0 & 0.36 & 0.64 & 0 & 0 \\ 0 & 0 & 0.35 & 0.29 & 0.36 & 0 \\ 0 & 0 & 0.29 & 0.28 & 0.23 & 0.20 \end{bmatrix}. \quad (2)$$

This causes the binary tree to branch with the parameters in (1) but to have two additional degrees of branching when normally the tree would terminate. An example of a ductal tree generated using the ramification matrix in (2) is shown in Fig. 7. Additional details about the ductal structure can be found in Appendix.

G. Lobules

Lobules are positioned at the end of terminal ductal branches and are typically made up of 10–100 acini that are approximately 0.15 mm in diameter [7]. In our simulation, lobules are modeled as a cluster of three spheres where one sphere is placed at the end point of the terminal branch and two others are placed 0.5 mm from the terminal branch end point in stochastically varied directions. Spheres have a random diameter between 1–2 mm. Fig. 8 shows a simulated ductal tree with lobules as well as close-up view of the lobular structure. The complete ductal structure can be seen in Fig. 9.

H. Phantom Overview and Image Simulation

The complete phantom is the compilation of all of the developed structures: breast boundary, subcutaneous fat layer, fibroglandular tissue region, subcutaneous–fibrous surface, intraglandular fat, Cooper’s ligaments, and ductal structure. We have added a microscopic level of detail that stops at the functional level of histologic structures.

Resampling the properties of the ISBP produces a 3-D voxel matrix. The level of detail we considered was that each voxel contain a specific tissue subtype as shown in Fig. 9. Since three subtypes are generally recognized to be important for whole-breast imaging, we simplified the resampled voxels to contain the tissue types used in our ISBP. For image simulation, voxel values are converted from integers representing tissue type to biophysical values that form the contrast mechanism of the imaging modality being simulated. The phantom is then processed using image acquisition simulators for each modality to produce simulated images.

III. Results

A. Mammography Simulation

Complete ISBPs are produced with dimensions $100 \times 200 \times 50$ mm in the x , y , and z directions and resampled at $100 \mu\text{m}$ pixel size. Mass attenuation coefficient values and densities of adipose, fibrous, glandular tissues, and air are obtained from the International Commission on Radiation Units and Measurements (ICRU) [22]. Assuming uniform tissue densities, the linear attenuation coefficients at 20 keV for each tissue representing voxel can be calculated and replaced as the following: Adipose = $5.393 \times 10^{-2} \text{ mm}^{-1}$, Fibrous = $8.615 \times 10^{-2} \text{ mm}^{-1}$, Glandular = $7.036 \times 10^{-2} \text{ mm}^{-1}$, and Air = $9.3215 \times 10^{-5} \text{ mm}^{-1}$. Noise-free, scatter-free mammograms are simulated for a monochromatic incident X-ray beam of energy 20 keV and parallel beam geometry. The resampling of the ISBP to X-ray properties is performed in an uncompressed geometry.

To generate medio-lateral projected mammograms, the linear attenuation map is summed along the x axis resulting in a two-dimensional image that is 200×50 mm sampled at $100 \mu\text{m}$. The simulated relative exposure found at a detector element is assigned a gray level in the image pixel using a sigmoidal characteristic curve given elsewhere [28]. Mammograms are produced from randomized ISBPs each with different adipose tissue percentages of 40%, 50%, 60%, and 70%. Simulated mammograms and a typical clinical mammogram are shown in Fig. 10.

To validate the texture of our mammography simulations, fractal analysis was performed and compared to fractal dimension values obtained from clinical and simulated mammograms in the literature [4], [18], [23], [24]. The fractal dimension is found [29] by first calculating the 1-D, radially-averaged power spectrum of fibroglandular region in the mammogram. The fractal dimension is obtained from the slope of the linear regression fit to the linear region of the log-log power spectrum. Fractal dimensions calculated for simulated mammograms of each composition are compared to clinical and simulated mammograms reported previously by other groups, as listed in Table II. Results demonstrate fair agreement between values reported here and the range of values in the literature. Our fractal dimension values are very stable among various adipose fractions, which agrees with trends found by others [29].

B. Ultrasound Simulation

Sonograms are generated by selecting an analysis region centered on a sagittal plane passing through the center of the ISBP. The image plane was 42×25 mm in the axial and lateral directions, respectively, with an angular orientation such that an approximately flat surface perpendicular to the axial scanning direction is obtained. A $100 \mu\text{m}$ pixel size is again used for the simulation with the acoustic impedance properties at any pixel populated from the tissue subtype values as: Adipose = 1.45 MRayl, Fibrous = 1.80 MRayl, and Glandular = 1.54 MRayl [30]. Assuming a linear system, 3-D sound pulses were convolved in the 2-D image plane and integrated along the elevational plane to yield 2-D images of 3-D objects.

The Field II program [31], [32] was used to numerically generate the pulse-echo impulse response simulating properties of the VHF5–10 linear array transducer of the Siemens Sono-line Antares system (Siemens Medical Solution, Mountain View, CA). Transducer parameters include 7 MHz center frequency, 53% bandwidth, $f/2$ and 20 mm in-plane aperture. Point scatterers are added to the different tissue-type regions in proportion to their relative impedance. Interfaces perpendicular to the beam axis produce specular reflections. Radio-frequency echo signals are sampled in range at 40 Ms/s and laterally with a 0.2 mm pitch. The attenuation factor equation $e^{-\alpha_0 f d}$ is applied to echoes in range with coefficient $\alpha_0 = 0.5 \text{ dB cm}^{-1} \text{ MHz}^{-1}$, axial depth $d = ct/2$ cm and at frequency $f = 7 \text{ MHz}$. B-mode images are created from radio-frequency echo signal simulations by computing the envelope of the analytic signal, applying demodulation and time-gain compensation, downsampling in range to create square pixels, and applying a standard scan conversion algorithm [33]. Sonograms are produced from the ISBPs with the four adipose contents described previously. Final image pixel values are filtered and log compressed to simulate typical postprocessing. Simulated and clinical sonograms may be compared in Fig. 11.

C. X-ray Computed Tomography Simulation

While the two previous simulations provided implementations to address current clinical imaging modalities, X-ray CT and tomosynthesis techniques are exciting new approaches that could augment present practices. Hence, we employed the phantom and image formation simulation to provide CT images through a coronal plane of the breast phantom. In our simulation, coronal slices are taken halfway between the nipple and chest wall (25 mm depth). The slice area is $100 \times 100 \text{ mm}$ in the xy plane and $250 \mu\text{m}$ pixel size. The slice thickness was 1 mm; that is, the detector element area was $0.25 \times 1 \text{ mm}$. Because the outermost skin layer is not simulated in the phantom but does appear in CT images, an approximate 0.5-mm-thick layer of fibrous tissue was added to the breast boundary in the phantom slice. A 20 keV monochromatic X-ray beam is simulated, therefore the same linear attenuation coefficients used in mammography simulation are used to produce the 2-D linear attenuation map. Assuming parallel beam geometry, the Radon transform is used to acquire 180 projections separated by 1° from the attenuation map to create a sinogram. The CT image is reconstructed from filtered backprojection using a Ram–Lak filter. Reconstructed values are converted to gray-scale values by applying the same characteristic curve used for mammography simulations above. Images are produced from phantoms (assuming no noise or scatter) of four adipose tissue contents as in previous simulations, and the results are shown in Fig. 12.

IV. Discussion

A. Mammography Simulation

Structural features apparent in the simulated mammograms can be easily recognized. The subcutaneous fat layers can be seen as the lesser attenuating borders of the breast. Cooper's ligaments can also be identified within these fat layers as fibrous streaks. Ducts and lobules are not visible as their attenuation is very similar to fibrous tissue and do not produce enough contrast to be visible. As the phantom increases in adipose percentage, the increased adipose content leads to lower attenuation and the brightness in the images are reduced. The increased number of adipose compartments also increases the gray-scale value variance and produces random areas with varying amounts of attenuation, resulting in an image that appears to have greater texture.

Comparing simulated mammograms to the clinical mammogram in Fig. 10(e), larger scale features, and the overall contrast and texture appear similar. In the clinical mammogram, it appears as though more intraglandular fat is localized in the outer boundaries of the

fibroglandular region, while intraglandular fat is distributed randomly within our phantom. Hence, a more anatomically accurate model of locating intraglandular fat should be developed along with an accurate breast compression simulator. Also noticeable is that simulated mammograms lack the detail that clinical mammograms display when both are examined at finer resolutions. This may be due to a nonrepresentative tissue distribution or insufficient model structures at a finer scale within the phantom. Hence, a finer resolution ISBP is required to assign properties. Another area of improvement would be to simulate a polychromatic X-ray beam, cone beam geometry and implement a rheologically accurate tissue compression model. These features are required to more closely mimic clinical mammograms.

B. Ultrasound Imaging Simulation

The most noticeable difference between simulated and clinical sonograms is the speckle contrast. We have applied no spatial compounding to the simulated images in Fig. 11(a)–(d), which were applied to the clinical image of Fig. 11(e). The average speckle size appears similar in both image types, suggesting that simulated beam properties are similar to clinical values.

Both image types show hypoechoic adipose regions surrounded by the more echogenic fibroglandular regions. Interfaces separating the two tissue types that are nearly perpendicular to the beam axis yield a specular interface. It is noticeable that as the amount of intraglandular fat increases, more dark compartments within the fibroglandular region appear. Ductal branches can be identified as thin bands within the fibroglandular region that are brighter than adipose tissue and slightly darker than fibrous tissue.

The orientations of intraglandular fat differ between image types. Perhaps adipose regions adopt a predominantly horizontal orientation in clinic images when patients lie prone, as in Fig. 11(e). Consequently, as with mammograms, mechanical modeling of tissue deformation with patient orientation and under transducer compression would improve structural realism.

Examined at a smaller scale, the simulated sonogram tissue structure near internal boundaries is somewhat inconsistent with what is shown in clinical sonograms. It is possible that the model needs to be simulated at greater spatial resolution to allow for simulation of cell density and distribution at a finer scale. Anatomical knowledge at the 10–100 μm scale may help create a more accurate model. Furthermore, sonogram simulation could be used as a feedback tool to develop a more realistic model at these scales for other imaging modalities.

The effects of pulse transmission through skin layers have not been addressed in this study. Sound scattering, absorption, and reflections at these layered surfaces lowers image quality for two prominent reasons: signal loss and aberrations. Transmission through skin lowers the received signal amplitude without significantly changing noise power, and therefore echo SNR is reduced. More importantly, large transmission or reception apertures lead to reduced coherence due to wavefront distortions imposed by skin [20], [35], which lowers contrast and spatial resolutions. Adding skin layers to the simulation will have the effect of lowering image quality.

C. Computed Tomography Simulation

The presence of adipose compartments passing through the coronal CT images is clearly apparent, and it can be seen that they increase in number as the adipose percentage of the phantom is increased. Ducts and lobules are visible as small spots that appear slightly darker than fibrous tissue, contrary to mammography where ducts are difficult to visualize. The

tissue distributions in simulated and clinical images appear similar as fibroglandular and adipose “marbling” is present in both. The subcutaneous fat layers are structured similarly in both and have similar irregular surfaces. Here, the subcutaneous fat layer is the same thickness for each simulation. Changing the fat layer thickness with breast density should be considered for model refinement.

Cooper’s ligaments can be seen in the subcutaneous fat layer of the simulations, extending from the inner fibroglandular region to the outer skin. However, Cooper’s ligaments are less noticeable in the clinical image, indicating that the initial ligament model likely overestimates the thickness and density of these structures. The intraglandular fat present in the clinical image seems to be localized more on the outer areas of the fibroglandular region with some centralized fatty deposits, as opposed to distributed randomly as in our simulation. Again, a refined model of intraglandular distribution is needed.

The fine resolution detail lacking in the simulated images compared to the clinical images is evident, and can be attributed to the lack of a model to simulate accurate tissue distributions and densities at smaller scales. Improvement in CT simulation can arise from use of a polychromatic beam with an accurate scattering simulation and fan-beam illumination geometry. On the ISBP side, modeling only large to medium scale structures, and assuming uniform tissue densities, image features tend to appear more rigid and less organic. The issue once again highlights the need to develop models spanning a larger length scale than simply the one that is close to the pixel size of the imaging modality. Comparisons between simulated and clinical CT could provide valuable feedback for this future development, synergistically improving both CT simulations and ISBP development. Both object and system models can be improved individually, hence, we propose that a corresponding effort in co-developing the simulation from end-to-end is also needed.

D. Model Extensions

Cytologic structures or details within cellular domains may be added to expand to molecular imaging. ISBP is a general framework that can be extended to any level of structural detail. Once structural information is in place, each spatial location can be populated by the physical, chemical, and biological properties appropriate. ISBP detail is ultimately limited by computational resources, so the level of detail must be adjustable to fit the purpose. Hence, coarse-framed ISBP can be upsampled to the appropriate detail required for image simulations so as to optimize computation and storage requirements.

V. Conclusion

The development of 3-D ISBP is reported and image simulations are produced and analyzed for three imaging modalities. The ISBP could include dynamical scalability to desired dimensions and modality-specific information content and resolution, thus facilitating multimodality image simulation. The benefit of having a known object with adjustable contrast provides a controlled imaging environment, greater understanding of how structures appear in images, and the precise image registration of multimodality images. These benefits makes the software phantom an attractive tool to reduce the time and cost of system development with the goal of improved imaging and screening methods. Since simulation parameters are adjustable, we can produce unique phantoms by altering a small set of parameters based on clinical measurements or images that can be used to rapidly evaluate experimental parameters. This capability also lends itself towards inclusion of information from smaller scales as well as the possibility of adding more detailed anatomical structures. By iteratively comparing simulated and clinical images to improve realism, we will further phantom development. Finally, the ISBP and integrated imaging simulation provides a means to explore the role of information at different length scales, new contrast

mechanisms, including strain imaging or molecular probes, and changes in breast structure due to benign and malignant disease.

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Appendix

Details of the ductal tree structure are provided in this appendix and in [28].

Physical Characteristics

In addition to the connectivity of the nodal network, each branch has associated physical characteristics. Branches are represented as cylinders characterized by height, radius, and two sets of associated angles. The first pair are lobe angles, α and β , that define the *lobe axis*. Every branch in a lobe has the same α , β , and lobe axis. Branch angles, θ and ϕ , define

the direction of individual branches. They are calculated with respect to the lobe axis. Height, h , and radius, r , of each branch decrease with decreasing node order k according to

$$h = h_0 \frac{k}{s} \text{ where } h_0 = 8 \text{ to } 12 \text{ mm} \quad (\text{A1})$$

and

$$r = r_0 \frac{k}{s} \text{ where } r_0 = 1 \text{ to } 2 \text{ mm} \quad (\text{A2})$$

where s is the value of the root node (here, equal to 6), and h_0 and r_0 are stochastically-varying lengths selected in the ranges indicated to follow anatomical observations [11], [14], [27]. Both h_0 and r_0 are recalculated each time a branch is created to produce variability. The method of calculation in (A1) and (A2) produces dimension variability, while maintaining a relatively constant height:radius ratio for each branch.

In close proximity to the nipple, ductal branches have reduced radii of approximately 1–2 mm. Therefore, duct radii as they pass through the subcutaneous layer are set to be a stochastically-varying radius between 1–2 mm [7]. Once the starting branch has passed through the subcutaneous region, the duct assumes its originally calculated radius from (A1). The *lobe axis* determines the overall branching direction of its uniquely associated tree structure with the axis origin being located at the base of the ductal tree. α and β rotate the original Cartesian axis (x, y, z) after it has been shifted to the base of the tree to form a new lobe axis with coordinates (x', y', z'). β rotates the x axis and y axis around the z axis and α rotates the z axis around the y axis. By mapping the ductal trees on a specific lobe axis, the entire ductal tree can be oriented along a given direction.

When generating new branches, a reference lobe axis is set with origin located at the endpoint of the parent branch (or starting point of the two child branches), as seen in Fig. 13. Child branches are generated in pairs that exist within a unique plane that contains the reference lobe z' axis. This plane is rotated by angle ϕ with respect to the reference x' axis and is calculated as

$$\phi = \phi_p + \phi' + 90^\circ \quad (\text{A3})$$

where ϕ_p is the previous rotated angle associated with the parent node and ϕ' is a random angle [4] between $\pm 15^\circ$. Within this plane, the two child node branches are at angles θ_1 and θ_2 with respect to the reference lobe z' axis. When the child branch node orders i and j are equal to each other, θ_1 and θ_2 are calculated as

$$\theta_1 = 60^\circ + \theta', \quad \theta_2 = -60^\circ + \theta' \quad \text{when } i = j \quad (\text{A4})$$

where θ' is a random angle [4] between $\pm 10^\circ$. When child branch node orders i and j are not equal, we have [4]

$$\begin{aligned} \theta_1 &= (30^\circ + \theta') \frac{j}{i-1}, \\ \theta_2 &= (-30^\circ + \theta') \frac{i-j}{i-1} \end{aligned}$$

when

$$i > j. \quad (A5)$$

Ductal Tree Generation

The starting branches of the ductal trees are positioned based on anatomical data of ductal openings [16]. In the implementation here, 21 lobe starting points and lobe angles are predefined within 3 mm radius of the nipple point to ensure each tree branches radially with respect to the nipple (Fig. 14) [11], [16], [25], [27]. The starting point of each ductal tree is selected randomly from the pool of predefined points.

Each time a pair of child branches is calculated during ductal tree generation, it is checked that both branches are within the bounds of the fibroglandular region and that they are not overlapping with other existing branches. If both constraints are satisfied, the branch pairs are accepted and added to the ductal network. If at least one of the constraints is not satisfied, the node orders and physical characteristics of the child branches are recalculated in the same probabilistic manner. If after 30 recalculations the child branches are still not accepted, no branch is generated from the parent node and the parent node is designated as a terminal branch.

Here, we have developed a protocol that allows ductal trees to grow simultaneously. Between 15 and 21 starting branches are selected to begin each ductal tree, and their properties are stored sequentially in a pointer. The generation sequence begins by examining the first starting branch in the pointer and determining the appropriate characteristics of children branches. If children branches are accepted, they are added to the end of the pointer. After examination of the first starting branch is complete, the next branch in the pointer is used to generate children branches and so on. This process continues by sequentially examining each branch in the pointer, including new ones that have been accepted. The end of the process occurs once growth terminates under the constraints of the tissue above.

Fig. 1.
Normal breast anatomy. (Illustrated by and adapted from Lynch. [21]).

Fig. 2.
Ellipsoid fit to reference points.

Fig. 3. The outer boundary of the breast is defined by an ellipsoid in the lower part (dark) and by second degree polynomials in the upper part (light) where $y_{upper} = 160$ mm and $y_{lower} = 20$ mm.

Fig. 4.

a) The placement of spheres used to simulate irregular subcutaneous fibrous surfaces is illustrated. b) Example simulation of a subcutaneous–fibrous surface for an ISBP.

Fig. 5. Four simulated volumes with different adipose percentages. Displayed images are from maximum intensity projection.

Fig. 6. Volume showing fibrous tissue of Cooper's ligaments within the subcutaneous fat layer.

Fig. 7.
Example of a ductal tree generated from the ramification matrix in (2).

Fig. 8.
a) Ductal tree with lobules attached. b) Close-up of the sphere clusters that composes lobule structures.

Fig. 9.

Structures that compose the complete breast phantom. Structures include the breast boundary, tissue regions (subcutaneous fat layer and fibroglandular region), subcutaneous–fibrous surface, intraglandular fat, Cooper's ligaments, and ductal structure.

Fig. 10.

a)–d) Simulated mammograms for different adipose compositions (40%, 50%, 60%, and 70%) of the breast. e) Clinical mammogram. (Clinical mammogram used with permission from Bliznakova *et al.* [1]).

Fig. 11.

a)–d) Simulated sonograms for different adipose percentages: 40%, 50%, 60%, and 70%. e) Clinical sonogram where SK = Skin, SF = Subcutaneous Fat, G = Fibroglandular (Fibrous), IF = Intraglandular Fat, D = Ductal Tissue (Glandular), and RF = Retromammary Fat. (Clinical sonogram used with permission from Ramsay *et al.* [14]).

Fig. 12.

a)–d) Simulated breast CT images for different adipose percentages: 40%, 50%, 60%, and 70%. e) Clinical breast CT image. (Clinical CT image used with permission from Boone [34]).

Fig. 13.

Examples show orientation of branching angles with respect to the reference lobe axis. θ_1 and θ_2 are calculated with respect to the z' -axis and ϕ is calculated with respect to the x' -axis.

Ductal Opening Locations

Fig. 14.
Relative locations of each ductal opening.

TABLE I

Outer Boundary Reference Points

Label	Reference Point	Coordinates	Location (mm)
P1	Nipple Pt.	(x_0, y_0, z_0)	(50,50,0)
P2	Lower Attachment Pt.	(x_1, y_1, z_1)	(50,34,50)
P3	Left Attachment Pt.	(x_2, y_2, z_2)	(10,50,50)
P4	Right Attachment Pt.	(x_3, y_3, z_3)	(90,50,50)
P5	Lower Breast Pt.	(x_4, y_4, z_4)	(50,25,25)
P6	Upper Ellipsoid Pt.	(x_5, y_5, z_5)	(50,110,50)
P1	Nipple Tangent Slope	z/y	0

TABLE II

Fractal Dimensions Of Simulated Mammograms And Simulated/Clinical Mammograms Reported by Others.
Our Error Bars Indicate the Standard Deviation From Three Image Realizations of the Same ISBP

Simulated/Clinical	Fractal Dimensions
40% Adipose	2.504 ± 0.026
50% Adipose	2.534 ± 0.0026
60% Adipose	2.568 ± 0.001
70% Adipose	2.584 ± 0.0015
Clinical (Caldwell [24])	2.29 ± 0.06
Clinical (Byng [23])	2.39 ± 0.11
Simulated (Bakic [4])	2.39 ± 0.10
Simulated (Li [18])	2.425 ± 0.18