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Development and Application of a Suite of 4-D Virtual Breast Phantoms for Optimization and Evaluation of Breast Imaging Systems

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Abstract

Mammography is currently the most widely utilized tool for detection and diagnosis of breast cancer. However, in women with dense breast tissue, tissue overlap may obscure lesions. Digital breast tomosynthesis can reduce tissue overlap. Furthermore, imaging with contrast enhancement can provide additional functional information about lesions, such as morphology and kinetics, which in turn may improve lesion identification and characterization. The performance of these imaging techniques is strongly dependent on the structural composition of the breast, which varies significantly among patients. Therefore, imaging system and imaging technique optimization should take patient variability into consideration. Furthermore, optimization of imaging techniques that employ contrast agents should include the temporally varying breast composition with respect to the contrast agent uptake kinetics. To these ends, we have developed a suite of 4-D virtual breast phantoms, which are incorporated with the kinetics of contrast agent propagation in different tissues and can realistically model normal breast parenchyma as well as benign and malignant lesions. This development presents a new approach in performing simulation studies using truly anthropomorphic models. To demonstrate the utility of the proposed 4-D phantoms, we present a simplified example study to compare the performance of 14 imaging paradigms qualitatively and quantitatively.

Index Terms

Breast phantom; contrast-enhanced breast imaging; four-dimensional (4-D) breast phantom; system evaluation; system optimization; virtual breast phantom

I. Introduction

Breast cancer is the most common cancer among women worldwide. According to the world health organization, early detection remains the cornerstone of breast cancer control for better prognosis [1]. Currently, mammography is the most widely utilized tool for screening and diagnosis of breast cancer [2]. However, the sensitivity of mammography is reduced in dense breast tissue, even in the newer technique of digital mammography [3]. Digital breast tomosynthesis has demonstrated the capability to reduce tissue overlap and lesion obscurity by providing depth and morphology information [4]. But even so, there is still a tremendous potential for improvements to the sensitivity and specificity of these imaging modalities via design and use optimization, as well as the incorporation of new contrast mechanisms. Among those, either mammography or digital breast tomosynthesis can make use of contrast agents for high-risk screening and diagnostic purposes. The process of angiogenesis of blood vessels with abnormally increased permeability in tumor development and growth has motivated the application of contrast agents to increase lesion detectability [5]. In the case of X-ray imaging, contrast agents are often iodine-based solutions that are injected to the patient with a volume of about 1 ml per kg patient weight.

To further improve lesion visibility, contrast enhancement techniques have been introduced that involve multiple acquisitions at one or more energies before and/or after administration

of the contrast agent [6]. There are two different techniques for contrast-enhanced breast imaging to be implemented with X-ray imaging. One technique is temporal subtraction, which involves subtracting images acquired before and after the administration of the contrast agent. The principal behind this technique is that after the administration of the contrast agent, the areas with most blood perfusion show the highest contrast. Hence, when the two images are subtracted, most of the anatomy is subtracted out and only the lesions are remained. The other technique, dual-energy subtraction, involves acquiring two images after the administration of the contrast agent at mean beam energies below and above the k-edge of iodine (33.2 keV). After logarithmic transformation, the images are weighted and subtracted, yielding an image with cancelled anatomy and a substantial iodine signal due to the increase in the iodine attenuation at the k-edge. Because of the increased blood flow in tumors and leakage from their highly permeable vessels, malignancies would enhance more relative to surrounding parenchyma. Both techniques can be implemented in mammography or tomosynthesis.

As a result of angiogenesis in malignant lesions, contrast agent absorption in malignancies is different from normal tissue. Most of the lesions following a plateau (Type II) or a washout (Type III) contrast kinetic pattern have been reported as malignant, whereas most benign lesions follow a constant enhancement pattern (Type I) [7], [8]. Therefore, a combination of morphological features analysis and contrast agent kinetics can provide an augmented technique to characterize lesions.

To optimize an imaging system that incorporates contrast agent administration, it is crucial to take into account: 1) the dynamics of contrast agent propagation in the breast tissue and lesions, and 2) the variability of breast composition across the patient population, which can significantly change the detectability of lesions. To the best of our knowledge, a breast phantom that possesses these features and can be used for simulations resulting in optimization and evaluation of imaging systems has not yet been developed. There have been a few studies on system optimization for contrast-based breast imaging including clinical trials and simulations; however, most of these studies only rely on either a limited population of patients or an overly simplistic model of the breast [9]–[13].

This work focuses on the development of a suite of 4-D virtual breast phantoms capable of modeling the temporal kinetics of contrast agent propagation in tissue over a wide range of patients. The phantoms were designed to be used as a virtual platform for optimization of the design and the use of both noncontrast and contrast-enhanced breast imaging systems. The phantoms were developed by incorporating contrast agent propagation kinetics into the extended cardiac torso (XCAT) breast phantoms [14]–[16]. The XCAT breast phantoms combine empirical human subject data with the flexibility of mathematical methods to provide a realistic simulation of breast anatomy. They have recently been used with novel transformation methods to generate a large suite of simulated human subject models covering a wide range of patient types [16].

II. Methods

The proposed 4-D breast phantoms were developed based on XCAT breast phantoms derived from human subject data. The XCAT phantoms were generated from dedicated breast computed tomography data of several different human subjects by postprocessing and segmenting them into skin, adipose tissue, and three classes of fibroglandular tissue according to density, which can be compressed to various thicknesses [14]. Fig. 1 shows axial and coronal slices through compressed volumes of two phantoms with different breast densities (fraction of fibroglandular tissue in the breast volume). These phantoms combine empirical data from real human subjects with the flexibility of mathematical models to include a detailed anatomy and create additional phantoms from different breast data. They are available both in voxelized and mesh formats. In order to incorporate the fourth dimension of time into the phantoms, the different tissues in the breast were modified to contain a time-varying fraction of contrast agent-blood mixture as well as the tissue material. In the particular case of X-ray imaging, the phantom tissues are associated with the corresponding attenuation coefficients of their different constituting elements. The effective attenuation coefficient of each tissue T was modeled by

$$\mu_{T,eff}(t) = P_T \mu_T + (1 - P_T) (P_{c,T}(t) \mu_c + (1 - P_{c,T}(t)) \mu_b) \quad (1)$$

where P_T is the mass fraction of the tissue made of tissue T , corresponding to attenuation coefficient μ_T , and $P_{c,T}(t)$ is the mass fraction of the contrast agent in contrast agent-blood mixture at time t for tissue T , and μ_c , and μ_b are the attenuation coefficients of the contrast agent and blood, respectively. By targeted selection of the fractions over time and material based on previous contrast enhancement studies, these phantoms can represent the flow of contrast agent into the breast tissue [17]–[20]. Combined with the inherent capability of the phantoms to model different patients, changes in the contrast agent-blood fractions may further add to the utility of the phantoms to model different anatomical and physiological representations. The fractions used for various materials in the breast were estimated based on the relative vascularization of various tissues with the same trends reported in the literature [22], but were modified to better illustrate the properties of the phantom. These phantom parameters can be readily modified to reflect other clinical situations. These values are shown in Table I.

Assuming that the average weight of a person is 70 kg with 5L of blood, injection of ISOVUE300 (an FDA approved iodine-based contrast agent with 300 mg iodine per mL) with a dosage of 1.5 mL/kg will result in maximum 6.3 g/L iodine concentration in blood. Considering the density of blood (1.06 g/mL) and ISOVUE300 (1.339 g/mL), and a dosage of 1.5 mL per kg of patient weight, the maximum fraction of iodine in iodine–blood mixture amounts to approximately 0.0058. Reasonable temporal enhancement patterns were estimated based on data from magnetic resonance (MR) breast imaging of four patients at four arbitrary time points (T_0 : pre-contrast, T_1 , T_2 , T_3 : post-contrast) for normal tissue, benign tumors (Type I), and malignant tumors including both plateau (Type II) and washout (Type III) patterns. The estimated values of $P_{c,T}(t)$ based on relative signal intensity for the four different patterns are presented in Fig. 2.

In order to illustrate the utility of the developed phantoms with realistic breast anatomy and contrast agent uptake kinetics, a simplified example study is presented. The 4-D breast phantoms were used to evaluate 14 mammography and tomosynthesis imaging paradigms listed in Table II at clinically relevant spectra. A 9%, a 28%, and a 44% dense (by volume) breast phantom were picked from the available number of breast phantoms for this study to represent a range of the population (Fig. 3). Each breast phantom was compressed to 50% of its pendant diameter by applying a mathematical transformation preserving the volume of the breast. Six mathematically generated lesions with a dense center and gradually fading boundaries were then added to these phantoms at the mid-depth of the compressed volumes. The same lesion model as in [23] was used.

A ray-tracing algorithm implemented for a graphic processing unit (GPU) cluster simulated projection images by including an X-ray source spectrum and the geometry of a prototype¹ MAMMOMAT Inspiration tomosynthesis unit (Siemens, Erlangen, Germany). Anode/filter combination of W/Cu with 300 μm filter thickness at 49 kVp (high-energy: HE) and W/Rh with 50 μm filter thickness at 28 kVp (low-energy: LE) were used. When operating in tomosynthesis mode, 25 images were acquired over a 50° arc centered at the normal position of the X-ray tube to the detector. A filtered back-projection algorithm based upon previous studies with a cosine filter was then used on a GPU cluster to reconstruct these images into the compressed breast volume with 1 mm slice separation [24], [25]. A complete simulation framework may also include additional physical aspects of the image formation process such as patient motion, scatter, quantum and electronic noise, image processing, etc. To introduce these new phantoms, this preliminary study demonstrates their use in a simplified environment that did not include these elements.

Temporal subtraction was performed by subtracting the image at T_0 from the image at T_1 . The dual-energy subtraction was performed by logarithmically subtracting the weighted low-energy image from the high-energy image both at T_1 . In practice, this can either be achieved through the use of energy selective detectors (e.g., photon counting or dual-layer sensors) or by rapid sequential acquisition of low and high-energy images of the compressed breast. The weight factor was empirically optimized to result in the least contrast between adipose and fibroglandular tissues to reduce the anatomical noise and increase the lesion detectability according to measured signal-difference-to-noise ratio (SDNR) values.

A numerical comparison of the 14 paradigms was made by calculating SDNR as a first-order figure of merit. A circular region of interest (ROI) was selected inside each lesion at half the radius of the lesion. Signal was measured by taking the average of the mean values of ROIs in all the lesions. In addition, a number of circular ROIs were selected in the background (internal areas of the breast farther from the edges and excluding the lesions). Assume that the number of ROIs in the background is N . Anatomical noise was measured by taking the average of the mean values of these N ROIs in the background. The difference between the signal and anatomical noise was divided by the standard deviation of the mean values of the ROIs in the background. This process was repeated for every value of N .

¹The use of this device for tomosynthesis is preliminary in the U.S. The safety and effectiveness of the device have not been established. The device is under development and not commercially available in the U.S., and its future availability cannot be ensured.

between 1 and the maximum of nonoverlapping ROIs that could be fit in the background (50 in the 9% and 28% dense phantoms and 30 in the 44% dense phantom). The calculated SDNR values for $N > 20$ (steady state) were then averaged and reported (Fig. 4). We examined the effect of the size of ROIs in the background and observed that as long as they are larger or equal to the size of the ROIs in the lesions, it has a minimal effect on the stability of the reported SDNR values (Fig. 5). Therefore, the area of the ROIs in the background was selected to be 1.5 times the area of the ROIs in the lesions.

Instead of the traditional concept of local lesion detectability, this SDNR reflects a global measure of how well lesions can be distinguished from overall anatomical heterogeneity. This measure was devised to address the very different detection paradigm in subtraction imaging, where the lesion often stands out well, but it is challenging to rule out other bright areas that may result from normal anatomy or artifacts.

III. Results

To illustrate the quality of simulated mammographic projection and tomosynthesis reconstruction of the phantoms, a 28% dense breast phantom is presented in Fig. 6. Notice the distinct structures visible in the slice through the reconstructed volume compared to the more indistinct superposition of all tissue structures in the projection image. Also, notice the advantage of 3-D information in lesion visibility in the tomosynthesis reconstructed slice. Both images were generated at the same spectrum.

To present the contrast kinetics incorporated in the phantoms, Fig. 7 shows simulated mammographic projection images of a 28% dense breast phantom with lesions following a washout pattern acquired at low-energy over four time points. Notice how the lesions are most visible at the peak of the contrast at T_1 .

High-energy acquisition seemed to only offer slightly better image quality in contrast-enhanced images (T_1). Every other single-energy imaging paradigm under examination seemed to offer better image quality at low-energy. Fig. 8 compares the low-energy and high-energy conventional, contrast-enhanced, and temporally subtracted mammograms of a 28% dense breast phantom.

Fig. 9 presents the results of the eight paradigms of conventional, contrast-enhanced, temporally subtracted, and dual-energy subtracted mammography and tomosynthesis on a 9% dense, 28% dense, and 44% dense phantom. The results appear to suggest that tomosynthesis can outperform mammography in terms of lesion visibility. Furthermore, it seems that temporal subtraction can be of critical importance to enhance image quality in mammography, whereas in tomosynthesis the contrast-enhanced images (T_1) seem to have sufficient image quality. Due to the absorption of contrast agent in normal breast tissue as well as the malignancies, there is more anatomical noise present in dual-energy subtracted images compared to temporally subtracted images.

The measured SDNR values for all the examined acquisition paradigms are shown in Figs. 10 and 11 for comparison. Temporal subtraction seems to outperform dual-energy subtraction both as visually perceived and as numerically calculated. As presented,

compared to low-energy contrast-enhanced acquisition at T_1 , temporal subtraction on average provided a sevenfold increase in SDNR in mammography and a four-fold increase in SDNR in tomosynthesis. This can be explained by the fact that in temporal subtraction, the difference is between a contrast-containing image versus the mask image that contains no contrast at all. In comparison, for dual-energy subtraction, both images contain the same amount of contrast agent, and subtraction reflects only the *differential* absorption of the contrast-agent at two energies.

The results suggest that in mammography, the performance can generally be expected to be more dependent on the particular anatomy of the breast, as compared to tomosynthesis, possibly due to the 3-D nature of tomosynthesis. In mammography, as a result of temporal subtraction, we measured a 10-fold increase in SDNR in a denser breast, compared to about a four-fold increase in a less dense breast, with respect to low-energy contrast-enhanced mammography at T_1 . In tomosynthesis on the other hand, about the same four-fold increase is observed in the three breast phantoms.

Both dual-energy subtraction and tomosynthesis are techniques to reduce anatomic noise. The results suggest that in tomosynthesis, dual-energy subtraction may not be as advantageous due to the inherent noise enhancement in dual-energy subtraction; SDNR was decreased on average by 10% compared to low-energy contrast-enhanced acquisition at T_1 . Conversely, mammography, which does not have the luxury of tomosynthesis's 3-D nature, may benefit more from the dual-energy subtraction; SDNR was increased on average by 40% compared to low-energy contrast-enhanced mammography at T_1 .

IV. Discussion

In this paper, we presented our development of 4-D breast phantoms by incorporating the contrast agent uptake kinetics in various tissues. Realization of these 4-D breast phantoms extends upon previous work by including dynamic effects, paving the way to performing several design and optimization studies. Those may include the evaluation of new imaging techniques and technologies, and the evaluation of new reconstruction algorithms. These phantoms provide the ground truth in performing observer studies, enabling creating matched virtual and physical phantoms to be used for system calibration and quality assurance, and eventually to realize virtual clinical trials relevant to dynamic imaging.

In order to illustrate the utility of these phantoms, in this work, we presented a first simplified example study where 14 potential imaging paradigms were selected and simulated by incorporating three breast phantoms representing a range of patients. The paradigms represented a combination of 2-D and 3-D, conventional and contrast-enhanced, dual-energy and temporal subtraction, and low- and high-energy breast examinations. The paradigms were quantitatively compared in terms of SDNR as a first-order figure of merit. As an additional sanity check, the fully mathematical breast phantom in [23] was also incorporated with the contrast agent uptake kinetics and used for comparison. The performance of the 14 imaging paradigms applied to the 4-D mathematical phantom were in agreement with the results of this study.

Based on the results of the numerical and qualitative comparisons, 3-D imaging is generally expected to result in better detectability. It is also apparent that temporal subtraction outperforms all the other paradigms. In fact, it seems necessary to perform temporal subtraction in 2-D imaging in order to have comparable performance to 3-D paradigms. It should be noted that these phantom studies essentially represent the ideal situation with perfect compensation of patient motion. Currently, most clinical protocols favor dual-energy subtraction, presumably because temporal subtraction requires longer scan times and is more prone to motion artifacts. The effect of patient motion in these new breast imaging paradigms is a complex issue that has already been reported in previous studies [12]. Dual-energy subtraction seems to be somewhat advantageous but only in 2-D imaging. However, the use of optimized spectra based on breast thickness and density can potentially enhance the image quality in dual-energy subtraction. Beam optimization can be carried out using these phantoms. It also seems that in general the performance of 2-D paradigms is more dependent on the specific anatomy involved, whereas in 3-D imaging the performance is less anatomy-dependent. As an example, the uniformly dense fibroglandular tissue in the 44% dense breast resulted in a higher SDNR calculated for this breast compared to less dense breasts in mammography. Under our global definition, the very dense breast has higher SDNR due to the relatively more uniform background with less anatomical variability. However, it is expected that by inclusion of more breast phantoms with various densities, such trends could be reversed. Furthermore, the results support the accepted practice that acquisition at conventional mammographic energies generally maintains higher detectability than higher energies [26]; only post-contrast images acquired at higher energies show slight advantage to the lower energies due to the k-edge of iodine.

The tomosynthesis scanning can take several seconds during which the contrast agent keeps propagating. The effect of this propagation into the detection performance can only be studied by incorporating finer timing into the uptake kinetics models and spatiotemporal reconstruction algorithms. Similarly, if clinical protocols require multiple views of the affected breast or the imaging of both breasts, then during the time to take these multiple acquisitions, the contrast distribution may change even more. Studying the sensitivity of the results to various uptake kinetics and partial diffusion of contrast agent during the course of a tomosynthesis scan or multiple scans can be worthwhile in future.

Although the results were very promising, this simplified example study should further be refined by a number of enhancements before conclusive comparison of the imaging paradigms can be made. First and foremost, a larger number of these 4-D phantoms need to be used to enable statistical comparisons. The XCAT breast phantoms currently constitute the state-of-the-art in anthropomorphic breast phantoms. The number of available phantoms is currently under expansion, which in turn will capture the wide range of patients. Secondly, the projection images were created by ray tracing through the phantoms, which does not account for scattering and quantum noise. These factors should be incorporated into the simulations to enable a more realistic simulation of image quality and to further bring in the notion of dose in the comparisons. Thirdly, contrast agent uptake kinetics were modeled for normal tissue, benign, and malignant lesions based on patient MR data. The four time points considered in the kinetic patterns were based on MR imaging time stamps. The concentration of iodine in the blood was estimated based on an average population mass.

The fraction of iodine in various tissues was modeled based on the relative tissue vasculature and diffusivity. Including finer timing and patient mass dependence can further refine the uptake kinetic patterns. Lastly, the lesion model used was a mathematical rendition of a round lesion with decreasing radial density. More realistic lesion models with spiculations are under development to be used in the future generations of the phantoms.

V. Conclusion

In this work, a suite of 4-D anthropomorphic virtual breast phantoms was developed for optimization and evaluation of contrast-based imaging systems. The human subject-based breast phantoms were supplemented with contrast agent uptake kinetics in normal tissue, benign, and malignant lesions, estimated based on patient MR data. In order to demonstrate the utility of the phantoms, we employed three prototype breast phantoms to simulate and compare the performance of 14 clinically relevant imaging paradigms in lesion detection in a demonstration study. While the results are preliminary, further to be refined with Monte Carlo simulations incorporating the addition of quantum noise, scatter, and beam hardening, and further contextualized by the dose and patient variability considerations, they highlight the utility of the phantoms as useful tools for the design and characterization of breast imaging modalities. In future, we aim to increase the number of breast phantoms used to represent a population as well as incorporating more anatomic lesion models and study the sensitivity of the results to contrast agent uptake kinetic patterns. Nevertheless, the present study highlights the dramatic effect of anatomical heterogeneity on image quality, influencing different imaging modalities differently, making a clear indication that homogenous phantoms may lead to misrepresenting characterizations.

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References

1. Anderson BO, Yip CH, Smith RA. Guideline implementation for breast healthcare in low-income and middle-income countries. *Cancer*. 2008; 113:2221–2243. [PubMed: 18816619]
2. Boyle, P.; Levin, B. *Int Agency Res Cancer*. Lyon, France: World Cancer Rep. 2008.
3. Pisano ED, Gatsonis C, Hendrick E. Diagnostic performance of digital versus film mammography for breast-cancer screening. *N Eng J Med*. 2005; 353:1773–1783.
4. Niklason LT, Christian BT, Niklason LE. Digital tomosynthesis in breast imaging. *Radiology*. 1997; 205:399–406. [PubMed: 9356620]
5. Dromain C, Balleyguier C, Muller S, Mathieu M-C, Rochard F, Opolon P, Sigal R. Evaluation of tumor angiogenesis of breast carcinoma using contrast-enhanced digital mammography. *Am J Roentgenol*. 2006; 187(5):528–537.
6. Carton, AK.; Currivan, JA.; Conant, E.; Maidment, ADA. *Digital Mammography*. Vol. 5116. Berlin, Germany: Springer; 2008. Temporal subtraction versus dual-energy contrast-enhanced digital breast tomosynthesis: A pilot study; p. 166-173. *Lecture Notes Comput. Sci*
7. Kuhl CK, Mielcareck P, Klaschik S. Dynamic breast MR imaging: Are signal intensity time course data useful for differential diagnosis of enhancing lesions. *Radiology*. 1999; 211:101–110. [PubMed: 10189459]
8. Froeling V, Diekmann F, Renz DM, Fallenber EM, Steffen IG, Diekmann S, Lawaczek R, Schmitzbuerger FF. Correlation of contrast agent kinetics between iodinated contrast-enhanced

- spectral tomosynthesis and gadolinium-enhanced MRI of breast lesions. *Eur Radiol.* 2013; 23(6): 1528–1536. [PubMed: 23306708]
9. Jong RA, Yaffe MJ, Skarpathiotakis M, Shumak RS, Danjoux NM, Gunsekara A. Contrast-enhanced digital mammography: initial clinical experience. *Radiology.* 2003; 228:842–850. [PubMed: 12881585]
 10. Carton, A-K.; Li, J.; Chen, S.; Conant, E.; Maidment, ADA. *Digital Mammography.* Vol. 4046. New York: Springer; 2006. Optimization of contrast-enhanced digital breast tomosynthesis; p. 183-189. *Lecture Notes Comput. Sci*
 11. Chen S, Carton AK, Michael A, Conant EF, Schnall MD, Maidment ADA. Initial clinical experience with contrast-enhanced digital breast tomosynthesis. *Acad Radiol.* 2007; 14(2):229–238. [PubMed: 17236995]
 12. Carton AK, Gavenonis SC, Curri van JA, Conant EF, Schnall MD, Maidment ADA. Dual-energy contrast-enhanced digital breast tomosynthesis—A feasibility study. *Br J Radiol.* 2010; 83(988): 344–350. [PubMed: 19505964]
 13. Samei E, Saunders RS. Dual-energy contrast-enhanced breast tomosynthesis: Optimization of beam quality for dose and image quality. *Phys Med Biol.* 2011; 56(19):6359–6378. [PubMed: 21908902]
 14. Li CM, Segars WP, Dobbins JT III, Tourassi GD, Boone JM. Methodology for generating a 3-D computerized breast phantom from empirical data. *Med Phys.* 2009; 36(7):3122–3131. [PubMed: 19673211]
 15. Hsu CML, Palmeri ML, Segars WP, Dobbins JT III, Veress AI. An analysis of the mechanical parameters used for finite element compression of a high-resolution 3-D breast phantom. *Med Phys.* 2011; 38(10):5756–5770. [PubMed: 21992390]
 16. Hsu CML, Palmeri ML, Segars WP, Veress AI, Dobbins JT III. Generation of a suite of 3-D computer-generated breast phantoms from a limited set of human subject data. *Med Phys.* 2013; 40(4):043703–043703. [PubMed: 23556929]
 17. Kiarashi N, Lin Y, Segars WP, Ghate SV, Ikejimba L, Chen B, Lo JY, Dobbins JT III, Nolte LW, Samei E. Development of a dynamic 4-D anthropomorphic breast phantom for contrast-based breast imaging. *Proc SPIE.* 2012; 8313:83130C–83130C.
 18. Kiarashi, N.; Ghate, SV.; Lo, JY.; Nolte, LW.; Samei, E. *Digital Mammography.* Vol. 7361. Berlin, Germany: Springer; 2012. Application of a dynamic 4-D anthropomorphic breast phantom in contrast-based imaging system optimization: dual-energy or temporal subtraction?; p. 658-665. *Lecture Notes Comput. Sci*
 19. Krause W. Delivery of diagnostic agents in computed tomography. *Adv Drug Delivery Rev.* 1999; 37(1–3):159–173.
 20. Tofts PS, Berkowitz B, Schnall MD. Quantitative analysis of dynamic Gd-DTPa enhancement in breast tumors using a permeability model. *Mag Res Med.* 1995; 33(4):564–568.
 21. Brix G, Bahner ML, Hoffmann U, Horvath A, Schreiber W. Regional blood flow, capillary permeability, and compartmental volumes: Measurement with dynamic CT—Initial experience. *Radiology.* 1999; 210(1):269–76. [PubMed: 9885619]
 22. Delille JP, Slanetz PJ, Yeh ED, Kopans DB, Garrido L. Breast cancer: Regional blood flow and blood volume measured with magnetic susceptibility-based MR imaging initial results. *Radiology.* 2002; 223(2):558–565. [PubMed: 11997568]
 23. Chen B, Shorey J, Saunders RS, Richard S, Thompson J, Nolte LW, Samei E. An anthropomorphic breast model for breast imaging simulation and optimization. *Acad Radiol.* 2011; 18(5):536–546. [PubMed: 21397528]
 24. Kak, AC.; Slaney, M. *Principles of Computed Tomographic Imaging.* Philadelphia, PA: SIAM; 2001.
 25. Wu T, Moore RH, Rafferty EA, Kopans DB. A comparison of reconstruction algorithms for breast tomosynthesis. *Med Phys.* 2004; 31(9):2636–2647. [PubMed: 15487747]
 26. Huda W, Sajewicz AM, Ogden KM, Dance DR. Experimental investigation of the dose and image quality characteristics of a digital mammography imaging system. *Med Phys.* 2003; 30(3):442–448. [PubMed: 12674245]

Fig. 1.

Axial (top) and coronal (bottom) slices through a 28% dense breast phantom (left) and a 44% dense breast phantom (right). Both phantoms are compressed to 50% of the pendant breast diameter.

Fig. 2.
Contrast agent concentration over time for each type of enhancement pattern.

Fig. 3. Slice through the mid-depth of a (a) 9% dense, (b) 28% dense, and (c) 44% dense breast phantom. Notice the six lesions embedded in the mid-depth shown in dashed circles. Sizes of the phantoms are shown to scale.

Fig. 4.

Illustrating the randomized nonoverlapping background ROI selection (red, light) in the central region of the breast (blue, dark) for a total of $N = 10, 20, 30$, and 40 ROIs. Black circles point to the location of the six lesions in the mid-slice of the reconstructed tomosynthesis volume of the 28% dense breast phantom.

Fig. 5. Effect of the total number of ROIs in the background $N = 1, \dots, 50$ (left), and ROI size (right) on the measured SDNR on a sample phantom.

Fig. 6.

A 28% dense breast phantom with lesions at the mid-depth generated at low energy (W/Rh 28 kVp): (a) craniocaudal (CC) mammographic projection and (b) a slice through the mid-depth of the tomosynthesis reconstructed breast volume.

Fig. 7. Mammographic projection images of a 28% dense breast phantom with lesions following a washout kinetic pattern (Type III) acquired at low-energy (W/Rh 28 kVp) over four time points. Arrows point to the location of the lesions. Images are displayed at such window/level settings to match the backgrounds and help visualize the lesion behavior over time.

Fig. 8.

High-energy acquisitions were observed to only be slightly advantageous in contrast-enhanced images (T_1). Every other image acquisition paradigm resulted in similar or higher image quality at low-energy. Low-energy and high-energy mammograms of a 28% dense breast phantom are presented here to illustrate this result.

Fig. 9.

Comparison of low-energy pre-contrast, post-contrast, temporally subtracted, and dual-energy subtracted simulated mammograms and corresponding central tomosynthesis slices of three breast phantoms. Images were cropped for display so sizes are not to scale.

Fig. 10.

Measured SDNR values for various acquisition paradigms applied to the three breast phantoms in (a) mammography and (b) tomosynthesis. LE and HE indicate low and high energy, respectively.

Fig. 11. Measured SDNR values for various acquisition paradigms averaged over the three breast phantoms in (a) mammography and (b) tomosynthesis. LE and HE indicate low and high energy, respectively.

TABLE I

Fraction of Tissue Material in the Effective Tissue-Contrast Agent-Blood Mixture for Each Tissue

Material	Adipose Tissue	Fibroglandular Tissue	Skin	Masses
P_T	0.9	0.8	1	0.6

TABLE II

Seven Imaging Paradigms Under Comparison Applied Both in Mammography and Tomosynthesis,
Comprising a Total of 14 Paradigms

Technique		Time	Energy
Non-contrast	Single-energy	T_0	Low-energy
			High-energy
Contrast-enhanced	Single-energy	T_1	Low-energy
			High-energy
	Dual-energy	T_1	High-energy – w×Low energy
	Temporal Subtraction	T_1-T_0	Low-energy
			High-energy