An Examination of Silver as a Radiographic Contrast Agent in Dual-Energy Breast X-ray Imaging

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Abstract. Silver nanoaprticles have been investigated as an alternative to iodine in dual-energy breast x-ray imaging. Dual-energy imaging involves acquiring images at two distinct energy windows (low and high). Weighting factors are then applied to create an image where the contrast between background tissues has been suppressed. Silver (Ag) represents an attractive contrast material due to its favorable x-ray attenuation properties (k-edge of 25.5 keV). Theoretical analysis using polychromatic spectra shows that silver can provide similar, if not better, contrast to iodine. Spherical Ag nanoparticles with an average diameter of 4 ±2 nm were synthesized using the Brust method in water. The particles were surface stabilized with polyethylene glycol and showed little cellular toxicity in T6-17 fibroblast cells. These results have encouraged further investigation into validation and testing in living system models. Silver nanoparticles represent an exciting avenue for the development of a novel dual-energy, x-ray breast imaging agent.

1 Introduction

Contrast-enhanced dual-energy (DE) x-ray imaging provides a technique to increase the contrast of radiographic imaging agents by suppressing the variation in signal between various tissue types. In the breast, this involves the suppression of the signal variation between admixtures of glandular and adipose tissue. By reducing the effect of this "anatomical noise", it is then possible to more accurately segment and quantify the signal from the contrast agent. Dual-energy imaging utilizes two distinct energy windows (low- and high-) to quantify the variation in attenuation with energy. To achieve a suitable contrast between imaging agent and tissue, it is therefore necessary that their respective attenuation profiles do not follow the same general trend from low- to high- energy. This can be done by using a contrast material whose k-edge lies between the two energy windows. The discrete jump in attenuation due to the photoelectric effect of the extra k-shell electrons means that the contrast material exhibits a markedly different attenuation profile to the surrounding tissue.

Currently, the majority of research that is performed in dual-energy x-ray imaging involves iodinated contrast agents. Silver (Ag) represents an attractive alternative due

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to the location of its k-edge (25.5 keV) within the range of clinically-used mammographic energies. Silver filtration is also common in the clinical setting, which could provide additional benefit with a silver imaging agent. The aim of this study is to provide an experimental argument for Ag in breast DE x-ray imaging, and to develop a prototype Ag nanoagent for testing in living systems.

2 Results (Theoretical Simulations)

Monoenergetic Analysis: A monoenergetic analysis was first performed to identify candidate combinations of low (LE) and high (HE) energies. Linear attenuation coefficients (LAC) were calculated for various admixtures of glandular and adipose tissues ranging from 0 to 100% glandular. Separately, the LAC were calculated for a 50% glandular, 50% adipose composite with increasing concentrations of contrast material. Mass attenuation coefficients needed for this calculation were obtained from the NIST XCOM online physics database [1]. Energy pairs ranging from 15 to 45 keV (in 1 keV intervals) were studied. For each energy-pair, two-dimensional maps of linear attenuation coefficients for tissue were calculated in terms of glandularity and concentration of silver (see Figure 1). Linear relationships were observed for both variables. The metric R was defined as the angular separation between these two linear fits.

An energy pair of (20, 30) keV was identified to maximize *R* (44°) using a silver contrast agent. A similar calculation for iodine showed that *R* was maximum at an energy pair of (30, 40) keV with a value of 39°. These energy pairs were further studied with polychromatic spectral analysis.

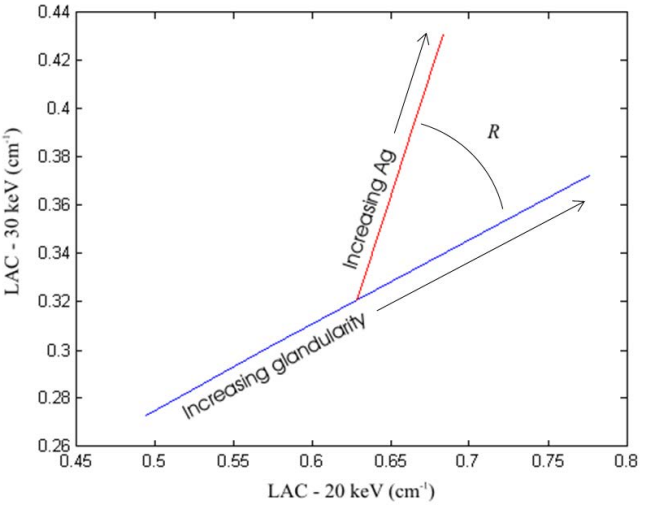

Fig. 1. Two dimensional map of LAC for variations of glandularity and concentration of silver, the metric *R* was defined as the angle between the two linear fits

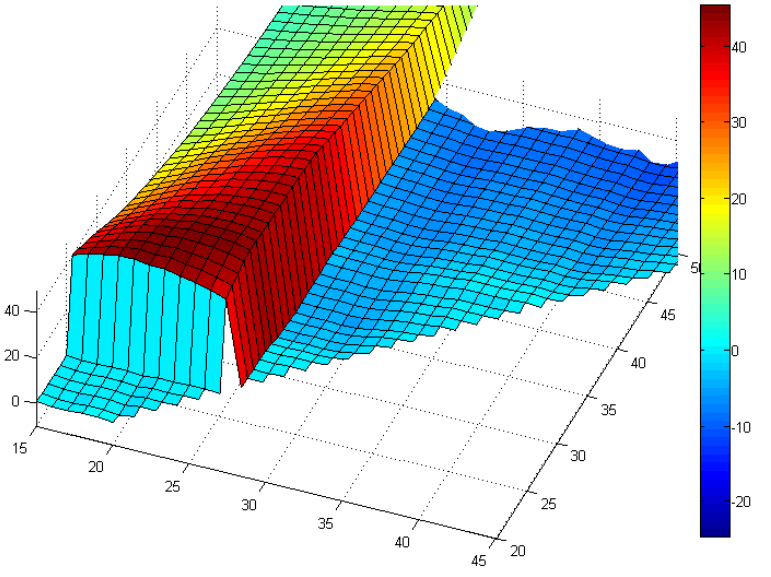

Fig. 2. Surface plot of *R* for various combinations of low- and high- energy pairs. A maximum occurs at (20, 30) keV providing an *R* of 44°.

Polychromatic Spectra: Tungsten polychromatic spectra were designed using the interpolating method of Boone et al [2]. Hundreds of combinations of kVp and filter materials were tested until three spectra with mean energies of roughly 20 (S1), 30 (S2) and 40 keV (S3) were chosen, as shown in Table 1. It is expected that a spectral pair of S1, S2 would be more beneficial to a silver contrast agent compared to iodine while a spectral pair of S2, S3 would be better suited to an iodinated contrast agent.

Table 1. Parameters used for the simulation of the 3 spectra with various average energies. Abbreviations used for the filter: Ag (silver), Al (aluminum), Cu (copper).

	kVp	Filter Combination	Average Energy (keV)
S1	32	80 μm Ag	21.6
S2	45	0.2 cm Al	30.0
S3	49	0.03 cm Cu	38.0

Weighting Factors: For each spectrum, the transmission through 1 cm of tissue of varying breast tissue composition (0% to 100 % glandular) was calculated. A thickness of 1 cm was chosen as an initial starting point for our calculations. The transmission was then converted to signal intensity (*S*) given by:

$$S = ln\left(\sum_{E=0}^{kVp} E \times I_E \times e^{-\mu_E t}\right) \quad (1)$$

Where E is the energy in keV, I_E is the incident photon fluence (photons/mm^2) at that energy, μ_E is the linear attenuation coefficient of the breast tissue composition at that energy E, and t is the thickness of tissue. This formulation assumes that an ideal energy-integrating detector is used. The dual-energy signal (S_D) was defined as the weighted subtraction of the low- and high-energy SI:

$$S_D = S_{HE} - w \times S_{LE} \tag{2}$$

For a given pair of tissue glandularities (see Figure 3, G1 and G2), a weighting factor was determined such that the DE signal from G1 was equal to that of G2.

$$S_D(\mathrm{G1}) = S_D(\mathrm{G2}) \rightarrow w = \frac{H1 - H2}{L1 - L2} \tag{3}$$

Thus, in a DE image no contrast would be observed between these two tissue types using this calculated weighting factor.

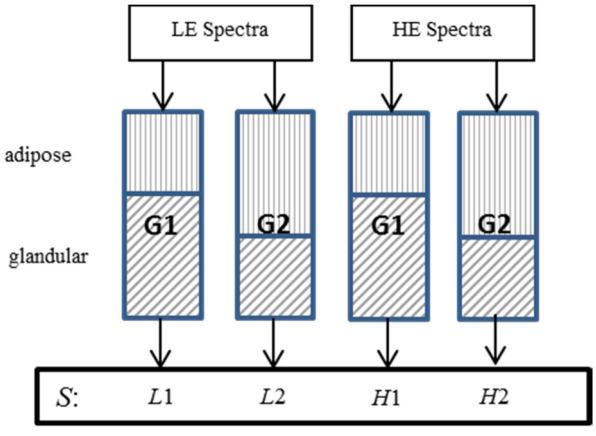

Fig. 3. Schematic setup for determining the weighting factor for a given pair of tissue glandularities (G1, G2). A weighting factor is chosen so as to equate the S_D of the two materials. S_D is given by a weighted subtraction of the high and low signal intensities.

The weighting factor needed to suppress various combinations of tissue glandularities are shown for a high/low spectral combination of S0, S1 (Figure 4) and S1, S2 (Figure 5). The weighting factor is relatively invariant with tissue composition. This would imply that for a given spectral pair of low- and high-energy beams, it should be possible to effectively null the contrast between the underlying tissue structures in the breast.

Contrast Calculation: The calculated values of w were used to determine DE signals for background tissue (50% adipose, 50 % glandular) and contrast enhanced tissue (50% adipose, 50% glandular + 1mg/mL of contrast material). The contrast (C) was calculated as the difference in S_D of tissue with and without contrast material. Values of C using silver, iodine and various low/high spectral pairs are tabulated in Table 2. The data correlates well with those predicted by monoenergetic calculations.

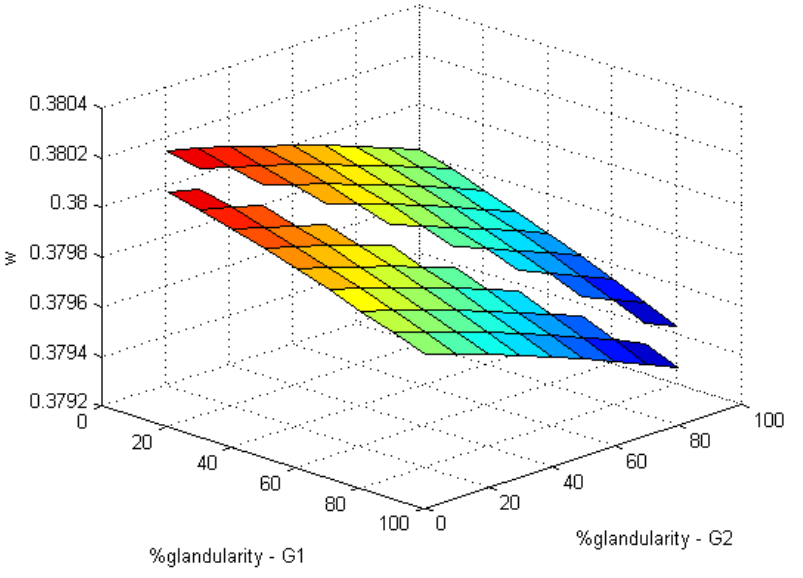

Fig. 4. Weighting factors calculated for S1 (low) and S2 (high)

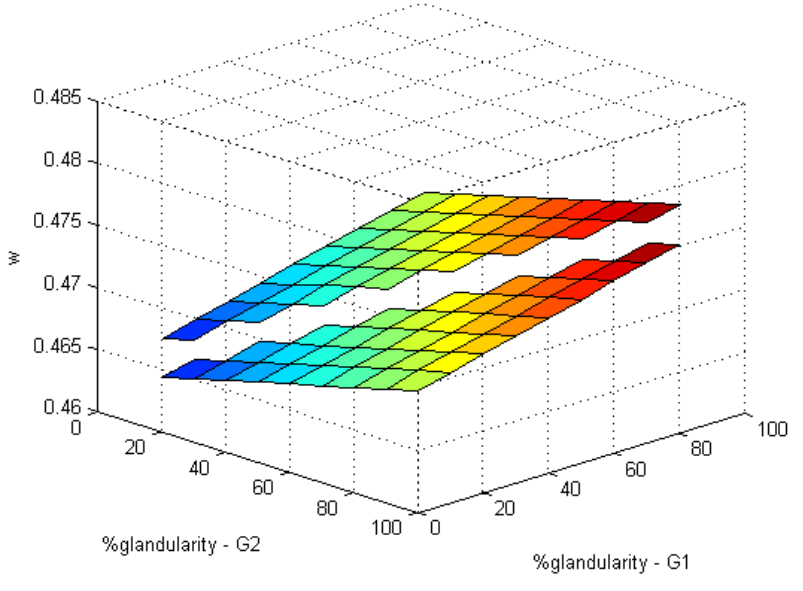

Fig. 5. Weighting factors calculated for S2 (low) and S3 (high)

1. The contrast observed for each contrast material is greater when using the spectral pair that brackets the k-edge of that material. The contrast observed for silver is greater when using the (S1,S2) spectral pair. Conversely, the contrast observed for iodine is greater when using the (S2,S3) spectral pair.

2. The maximum contrast observed for silver is greater than that of iodine. By comparing the spectral pairs that best suited each material, it was found that the contrast observed for silver was roughly twice that of iodine.

Although these results are not conclusive, they do support our initial hypothesis that silver demonstrates significant potential as a contrast material for dual-energy breast x-ray imaging.

Table 2. Signal Differences tabulated for silver and iodine using various low- and high – energy spectral combinations

C (Digital Units)	Spectral Combinations	
	Low E: S_1 **High E**: S_2	**Low E**: S_2 **High E**: S_3
Silver	20.8 ± 0.003	7.44 ± 0.08
Iodine	9.88 ± 0.004	11.70 ± 0.05

3 Results (Nanoparticle Development)

Silver nanoparticles (AgNP) have been synthesized using the Brust [3] method in water. This is preferred over the Turkevich method as it provided a more reliable size distribution of particles from batch to batch. Figure 6 shows a transmission electron micrograph (TEM) of the synthesized particles. Analysis of the size distribution yielded a mean diameter of 4 ±2 nm. Initial analysis showed two populations of nanoparticles present which accounts for the high standard deviation in mean diameter. The AgNP were surface stabilized using polyethylene glycol (PEG, M_w = 5000) to improve solubility in cell media and phosphate buffered solutions. A molar ratio of 1.5:1 was used between the PEG stabilizing ligand and silver.

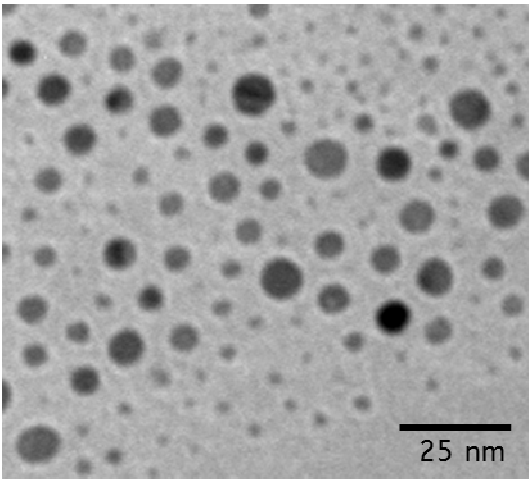

Fig. 6. TEM of the colloidal silver nanoparticles synthesized using the Brust method in water. The particles have been stabilized using a polyethylene glycol surface chain.

The cellular toxicity of the stabilized AgNP was measured in T6-17 fibroblast cells using the MTT assay. Figure 7 shows the relationship between concentration of Ag in AgNP and percent cell viability after 24 hour incubation. Compared to a sham treated control, total cell viability of 50% was maintained at an Ag concentration of 10 mM (roughly 1 mg Ag/mL). These results show marked improvement over cell viability studies using AgNP in the literature [4-5] and have encouraged us to begin analysis of the particles in living systems.

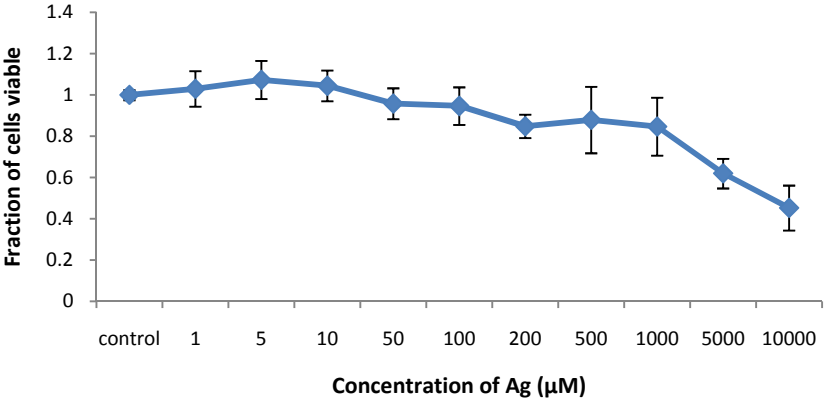

Fig. 7. Cellular toxicity of AgNP in T6-17 cells after 24-hour incubation

4 Discussion

Silver is being investigated as a novel imaging agent for dual-energy breast x-ray imaging. Monoenergetic analysis of linear attenuation coefficients showed that compared to iodine it is possible to achieve a greater separation between tissue with and without contrast when silver is used. These results were corroborated by polyenergetic spectra simulation where silver showed up to twice the radiographic contrast of iodine.

It should be noted that only a small subset of the possible spectral pairs were tested in the polyenergetic simulations. The results should therefore not be considered as conclusive as the true optimal contrast values for each material may differ slightly if a more extensive search was performed. However, both the monoenergetic and polyenergetic simulations demonstrate that there exists enormous potential for the use of silver in DE breast x-ray imaging.

Initial work has been completed on the synthesis and testing of AgNP. Spherical AgNP (d = 4 ±2 nm) were synthesized using the Brust method, and stabilized with PEG surface ligands. Little cellular toxicity was observed in cells for silver concentrations up to 1mg/mL. The testing of these particles in living systems is currently underway.

Silver nanoparticles represent an exciting avenue for the development of a novel DE breast x-ray imaging agent. Simulations have demonstrated that within the mammographic energy range, silver is able to offer comparable, if not greater DE contrast to iodine. This work provides the initial groundwork for a rich, new direction in contrast-enhanced DE breast imaging.

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