

# Gold Nanoparticles as Contrast Media in Dual-energy Radiography: a Monte Carlo Study

P. Jackson\* and M. Geso\*

\*Royal Melbourne Institute of Technology,  
Plenty Road, Bundoora, Australia, price.jackson@rmit.edu.au

## ABSTRACT

There has been recent interest in the use of gold nanoparticles as contrast media in cancer diagnosis. Modern dual-energy CT imaging protocols implement simultaneous scans using two X-ray sources with different tube potentials allowing the differentiation of materials on an elemental basis. This technique has been successfully employed to highlight and digitally remove the presence of iodinated contrast media and we suggest a protocol to optimize similar detection of gold. Using EGSnrc, we have investigated an imaging protocol designed to highlight gold atoms in a tissue phantom. Gold's K- and L-edges occur at 80.7 and 11.9 keV, respectively, requiring special consideration in order to remove the element's appearance from the low-kVp scan. In the investigated protocol, thin gold and copper filters are used to increase the spectral discrepancy between the low and high energy image sets. Subtraction image results show improved contrast enhancement compared to conventional imaging parameters using iodinated contrast media while still removing the appearance of confounding anatomical structures.

**Keywords:** gold nanoparticle, contrast, computed tomography

## INTRODUCTION

Contemporary trends in radiographic imaging are leaning toward material separation and identification in images. Dual-energy CT uses subtraction technique, or to be more specific an algorithm that compares voxel Hounsfield unit density between image sets, to identify materials based on their energy-dependent attenuation. To such ends, the equipment exploits the K-edges of elements to indicate the presence of bone, contrast media, or various other anatomical and pathological features that can be of diagnostic value to radiologists [1,2].

Gold, in nanoparticle form, has been identified as a likely candidate for use as some form of contrast medium in diagnostic radiography [3-6]. This is attributed to the element's high K-edge (80.7 keV) and relative biocompatibility. Research suggests that implementation may take the form of either a traditional intravenous suspension that travels indiscriminately through the bloodstream or as a directed contrast material through the addition of targeted ligands or antibodies [7-9]. In either instance, due to the element's expense and scarcity, it is

worthwhile to maximize the detection potential for such a material. That will allow its use with the smallest possible administered dosage.

In this work, we have sought to identify an improved radiographic methodology for specific detection of gold in the human body. We have used similar principles to those in dual source computed tomography (DSCT), specifically those of second generation DSCT equipment. These machines simultaneously record two image sets, one with high kVp and one with low kVp. In the case of newer equipment, a 0.4 mm tin filter is used on the high-energy source to improve the spectral discrepancy between image sets [2]. This same technique can be applied for the detection of a heavy element such as gold, but some consideration must be made for the material's comparatively high L-edge. This property produces high levels of contrast enhancement at low tube potentials which can lead to diminished visualization in a subtracted dual-energy image.

## METHODS

Simulated radiographic images were recorded using Monte Carlo technique with the EGSnrc software package. Imaging geometry consisted of a 15 cm thick tissue phantom (ICRU 4-component). A cylindrical volume of contrast media (either gold or iodine in water at a concentration of 10% w/v) was located horizontally within the central region of the phantom. At the base, circular rings of contrasting tissue types (soft tissue, lung, cortical bone, and muscle) were included to for comparison and later subtraction (figure 1).

Exposures were simulated for a parallel beam of incident X-ray photons at 4 different energy settings: 80 kVp, 120 kVp, 120 kVp with 0.18 mm added Au filtration, and 160 kVp with 0.98 mm added Cu filtration. The first two exposures were recorded with iodinated contrast media, while the latter two correspond to gold-based contrast media. For the sake of efficiency, energy spectra were collected in a separate simulation of a standard X-ray tube with tungsten anode at a 20° angle. Energy spectra were found to be in close accordance to data from the IPEM-78 report [10].

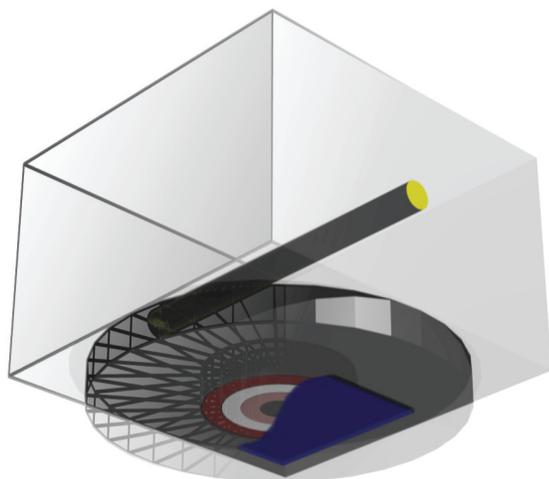


Figure 1: Geometry of tissue phantom used in imaging. Images scored as pixel dose values in a 0.8 mm layer of cesium-iodide.

Images were recorded as a set of dose values per pixel within a 0.8 mm thick layer of Cesium Iodide. Each pixel had dimensions of 1 mm x 1 mm and the overall image was recorded over an area of 100 cm<sup>2</sup>. Each simulation was run for 100 million photon histories incident upon the surface of the image receptor (between 1 and 2 billion histories from the source, depending on tube potential). Iodine and gold image sets were normalized and subtracted. Subtracted images were evaluated for contrast-to-noise ratio over rectangular regions of interest with dimensions of 11 x 100 pixels. Two adjacent regions on either side were selected as background and analyzed for mean pixel dose and image noise (standard deviation). A third region was selected within the margins of the contrast media sample. Contrast was determined as the difference in mean pixel dose between the central region and the surrounding background ROIs.

## RESULTS

Filter thickness and material were determined on the basis of known attenuation coefficients and previous experimentation [6]. Gold filter thickness was chosen to be 0.18 mm. This dimension removes 95.4% of incident photons at 80.7 keV. The removal of this energy range limits the appearance of gold in a radiographic image, at high tube potentials. The element copper shows similar attenuation properties to gold between the energies of 12 and 80 keV, albeit requiring 5.4 times greater material thickness [11].

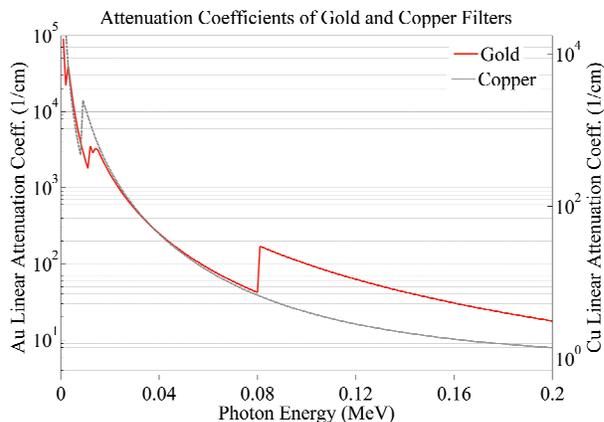


Figure 2: Linear attenuation coefficients for gold and copper.

Using these dimensions, energy spectrum measurements showed good separation at the K-edge of gold. This can be seen in figure 3. Spectra have been normalized to overlap below 80.7 keV. With the addition of copper filtration, the 160 kVp spectrum shows close similarity at low energies to the spectrum at 120 kVp with gold filtration; the primary exception being the K<sub>α</sub> and K<sub>β</sub> characteristic peaks from the tungsten anode. The subtracted energy spectrum, which represents the energy range responsible for variations in attenuation between the high and low kVp images, has also been plotted. In the subtracted spectrum, 89.3% of the total photon count is above 80.7 keV, the K-edge of gold.

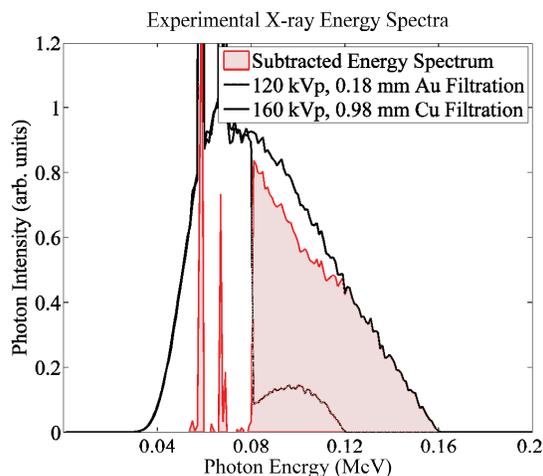


Figure 3: Filtered energy spectra at tube potentials of 120 and 160 kVp. Subtracted spectrum shown as area graph.

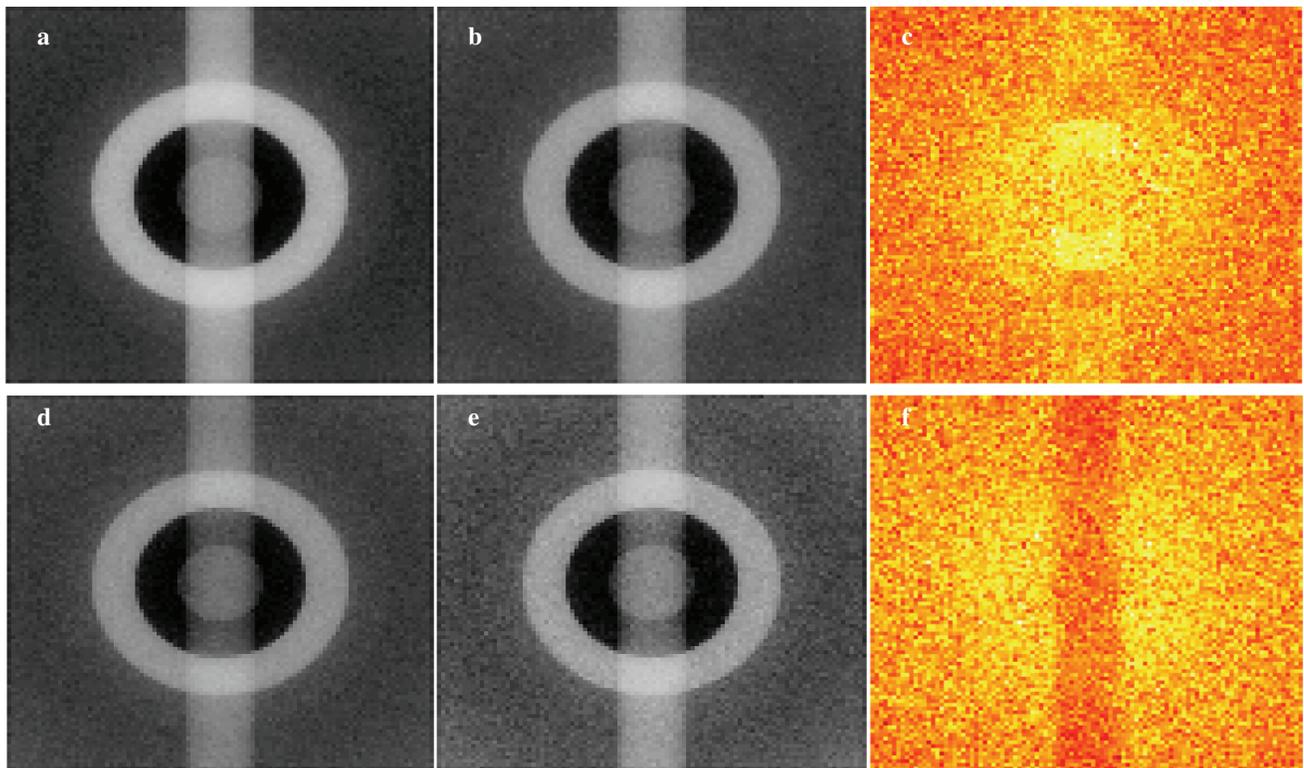


Figure 4: **a** iodinated contrast media at 80 kVp; **b** iodinated CM at 120 kVp; **c** subtracted image of both iodine simulations; **d** gold CM at 120 kVp with 0.18 mm Au filtration; **e** gold CM at 160 kVp with 0.98 mm Cu filtration; **f** subtracted image of both gold simulations.

## DISCUSSION

Monte Carlo simulation of images recorded the appearance of both gold and iodine solutions as expected (figures 4a-f). CM samples are oriented vertically in the images. Rings of contrasting tissue types can be clearly seen in the raw (unsubtracted) images. Areas of lung and bone are distinctly visualized as circles of black and white, respectively. These structures have been subtracted from the compound images (figures 4c & 4f). In the case of the gold sample, a clear subtraction of unwanted anatomical features is seen. In the subtracted iodine image, some persistent rings remain, particularly in the area of lung that overlays the CM.

Images show significant noise and, as a result, CNR values are expectedly low. In the subtracted sets, the contrast-to-noise ratios for gold and iodine are 1.23 and 0.68, respectively. In this instance, gold shows 80.1% greater enhancement using the filtered subtraction protocol, than a conventional dual-energy subtraction technique with iodinated CM.

This experiment was aimed at determining a protocol for maximizing visualization of a gold-based contrast medium using standard radiographic equipment. An ideal beam of coherent, mono-energetic X-rays could be supplied by a synchrotron. Due to cost, size, and limited availability, however, such a technique is not practical for widespread clinical use. In such an idealized scenario, two scans could be performed at 80.6 and 80.7 keV, where there would be a significant change in the attenuation of gold atoms with only a marginal shift in the appearance of any other anatomical structures. A direct subtraction of those images would identify the presence of gold almost exclusively. This experiment has aimed to provide the nearest possible replication of that scenario with a standard x-ray tube.

This work represents a unique approach toward radiographic detection of gold Nanoparticles. Special consideration has been given to the energy-dependent attenuation of gold as an element. Iodine has a high probability of attenuation at high energies, relative to normal tissue. Gold, however displays similar enhancement in both low and high-energy image sets due to its 11.9 keV L-edge. These Monte Carlo simulations indicate that we can significantly suppress the appearance of gold in a low-

energy image through the use of a thin filter manufactured out of gold. At 120 kVp, the energy spectrum is shifted heavily into the range of 40 to 80 keV, where it is abruptly cut off by photo-electric absorption in the filter. By filtering the high-kV image with copper, confounding contrast from other anatomical structures is reduced, thus improving the appearance of gold in the normalized and subtracted image set.

Although these simulations are recorded using projection-type geometry, the principles of image-formation are analogous to those in computed tomography. A similar algorithm to those in place for separation of iodinated contrast media in CT could be determined through measurement and calibration. There are some limitations in the present study. Although both iodine and gold are clearly visualized, contrast-to-noise ratios are relatively low due to the statistical uncertainty inherent in Monte Carlo simulations. Comparison of radiographic exposure protocols have been made against an older set of exposure parameters, rather than newer tin filtered and high kVp settings. Lastly, though the thicknesses of filters chosen provide good spectral separation between images, they also attenuate the intensity of the incident beam significantly. At 160 kVp with Cu filtration, the beam fluence decreases by nearly 50%, while the Au-filtered 120 kVp exposure drops to just 9.6% of its initial intensity. Longer exposure times would be required to compensate without increasing image noise.

## CONCLUSION

This study presents a new technique for measuring the presence of gold against other anatomical features in radiography. We have compared our protocol using filtered X-ray beams to a conventional method for detecting iodine. Results show superior enhancement with good removal of undesirable structures. With continued research in the design and fabrication gold Nanoparticles (particularly those with cell or cancer-specificity), a non-invasive technique for the detection of trace amounts of gold within the body will be increasingly important. The radiographic technique proposed is both simple and cost-effective. Current dual-source CT scanners could support such an examination with only minor modification. Through this work we hope to encourage further research in diagnostic applications of gold Nanoparticles, particularly through directed delivery and localization.

## REFERENCES

[1] T. Flohr, C. McCollough, H. Bruder, et al., "First performance evaluation of a dual-source CT (DSCT) system," *Eur. Radiol.*, 16, 256-268, 2006.  
 [2] M. Petersilka, H. Bruder, B. Krauss, et al., "Technical principles of dual source CT," *Eur. Radiol.*, 68, 362-368, 2008.

[3] J. Hainfeld, D. Slatkin, T. Focella and H. Slimowitz, "Gold Nanoparticles: a new X-ray contrast agent," *Br. J. Radiol.*, 79, 248-253, 2006.  
 [4] D. Kim, S. Park, J. Lee, et al., "Antibiofouling polymer-coated gold Nanoparticles as a contrast agent for in vivo X-ray computed tomography imaging," *J. Am. Chem. Soc.*, 129, 7661-7665, 2007.  
 [5] Q. Cai, P. Kim, K. Choi, et al., "Colloidal gold nanoparticles as a blood-pool contrast agent for X-ray computed tomography in mice," *Invest. Radiol.*, 42, 797-806, 2007.  
 [6] P. Jackson, W. Rahman, C. Wong, et al., "Potential dependent superiority of gold Nanoparticles in comparison to iodinated contrast agents," *Eur. J. Radiol.*, doi: 10.1016/j.ejrad.2009.03.057  
 [7] C. Loo, A. Lowery, N. Halas, et al., "Immunotargeted nanoshells for integrated cancer imaging and therapy," *Nano Lett.*, 5, 709-711, 2005.  
 [8] J. Copland, M. Eghtedary, V. Popov, et al., "Bioconjugated gold Nanoparticles as a molecular based contrast agent: implications for imaging of deep tumors using optoacoustic tomography," *Molec Imaging & Biol.*, 6, 341-349, 2004.  
 [9] I. El-Sayed, X. Huang and M. El-Sayed. "Selective laser photo-thermal therapy of epithelial carcinoma using anti-EGFR antibody conjugated gold nanoparticles," *Cancer Lett.*, 239, 129-135, 2005.  
 [10] K. Cranleg, B. Gilmore, G. Fogarty and L. Desponds, "IPEM Report 78: catalogue of diagnostic X-ray spectra and other data (CD-Rom edition 1997)," Electronic version prepared by D. Sutton, The Institute of Physics and Engineering in Medicine (IPEM), 1997.  
 [11] M. Berger and United States National Bureau of Standards, "XCOM, photon cross sections on a personal computer [microform] Prepared for U.S. Department of Commerce, National Bureau of Standards, Office of Standard Reference Data [and] Department of Energy, Office of Health and Environmental Research, " The Bureau ; Order from National Technical Information Service, Gaithersburg, MD : Springfield, VA, 1987.