DETECTION AND QUANTIFICATION OF CORONARY CALCIUM FROM
DUAL ENERGY CHEST X-RAYS: PHANTOM FEASIBILITY STUDY

by

BO ZHOU

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CASE WESTERN RESERVE UNIVERSITY
SCHOOL OF GRADUATE STUDIES

We hereby approve the thesis of

Bo Zhou

Candidate for the degree of Master of Science

Committee Chair

Dr. David L. Wilson, Chair

Committee Member

Dr. Anant Madabhushi

Committee Member

Dr. Robert C. Gilkeson

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Thank you!
LIST OF ABBREVIATIONS

CAC: Coronary artery calcification

DECCI: dual energy coronary calcium image

DE: Dual energy

PA: Pulmonary artery

CT: Computer tomography

3D: three dimension

FOV: Field of view

SID: Source to image receptor distance

SOD: Source to object distance

GEHC: General electric healthcare

BF: Bucky factor

PT: Primary transmission

ADC: Analogue-Digital converter

PSF: Point spread function
BH: Beam hardening

SC: Scatter correction

woS: Without scatter

wS: With scatter

CACS: Coronary artery calcium scoring

MESA: Multi-Ethnic Study of Atherosclerosis

CHD: Coronary heart disease
Detection and Quantification of Coronary Calcium from Dual Energy Chest X-Rays: 

Phantom Feasibility Study

Abstract

by

BO ZHOU

We have demonstrated the ability to identify coronary calcium using non-gated, 2-shot, dual energy (DE) chest x-ray imaging. Here we used digital simulations to characterize DE calcium signals and the role of potential confounds such as beam hardening, scatter estimation, cardiac motion, and pulmonary artery pulsation. For the DE calcium signal, we will consider quantification, as compared to CT calcium score. We created digital 3D phantoms including heart, lung, coronary calcium, spine, ribs, pulmonary artery, and adipose. We simulated x-ray acquisitions with x-ray spectra, energy dependent attenuation, scatter, ideal detector, and automatic exposure control (AEC). Phantoms allowed us to independently vary adipose thickness, cardiac motion, etc. to study the potential confounds. We used specialized dual energy coronary calcium (DECC) processing that includes corrections for scatter and beam hardening. Simulations indicate that proper DECC processing can faithfully recover coronary calcium signals. Potential confounds above are all manageable. Simulations are valuable as we continue to optimize DE coronary calcium image processing and quantitative analysis.
Chapter 1 INTRODUCTION

1.1 Overview

Coronary artery calcification (CAC) is a risk factor for adverse outcomes in the general population and in patients with coronary artery disease (Fig 1.1). CAC, as assessed via CT, is a lead biomarker for coronary artery disease. Recent large studies show that adding CT coronary calcium score as a risk factor significantly improves the ability to predict a cardiac event in a population of persons with no known cardiac disease.$^{1,2}$ Coronary calcium is much better than lipids, C-reactive protein, and carotid intima media thickness as measured from ultrasound or MRI as a predictor of cardiovascular risk.$^{1,2}$ Calcium score reclassifies about 50% of intermediate-risk individuals to high or low risk, where there are established treatment strategies.$^3$ Currently the American Heart Association and the combined European Society of Cardiac Radiology and North American Society for Cardiovascular Imaging Guidelines have recognized the value of adding coronary artery calcium to the Framingham score.$^4$ Coronary calcium is an excellent biomarker of cardiovascular disease and could be used to trigger aggressive drug therapy, lifestyle changes, and perhaps additional testing, e.g., CT calcium score. Imaging can have unexpected impact, as simply showing patients their CT coronary calcium images and discussing calcium scores improved adherence to statin drug therapy to 90%.$^5$ Some are arguing that CT coronary calcium can be used to determine next steps in therapy. The ACCF/AHA published a consensus document which includes the role of coronary calcium in the management of patients presenting with symptoms.$^6$
For predicting obstructive angiographic CAD, accuracy of coronary calcium was significantly higher (80%) than alternatives: treadmill testing (71%) and technetium-stress (74%). In the UK, CT coronary calcium score is currently being used in the NICE practice guidelines as a gatekeeper in the CAD diagnostic pathway (coronary angiography). Others have discussed the use of CT calcium score as a gateway exam to SPECT. Some are suggesting that coronary calcium is a good indicator for aggressive statin therapy. Not only is there a need for risk stratification in general population, there are needs with specific, large patient classes. One class consists of those persons at high risk of coronary artery disease due to a condition such as diabetes, rheumatoid arthritis, HIV, or psoriasis. The second class consists of patients undergoing interventions such as cancer chemotherapy or radiation therapy, treatments that increase the risk of cardiovascular disease or any surgery because surgery increases risk and because one might not advise “elective” surgery to a person with high cardiovascular risk.

CT as compared with chest radiography has a much higher radiation dose and higher cost. These exams require much lower dose, cost and time. The standard position for a patient is the posterior-anterior x-ray exposure with wall stand detector (Fig 1.2).
Figure 1.1. Illustration of coronary artery and coronary artery calcification

Figure 1.2. Illustration of posterior anterior exposure with chest x-ray system
Figure 1.3. Dual energy imaging of coronary calcium. The clinical “bone” image (a) with motion artifacts and DECC image (b) contain a coronary calcification (red arrow). DECC processing greatly reduces motion artifacts and improves calcification contrast.

The invention of dual energy (DE) decomposition technique makes it possible to separate the chest x-ray image into two images with different types of materials\textsuperscript{12,13}, typically soft tissue and bone (Fig 1.3) with the different energy dependent attenuation properties. Two types of dual energy systems are commonly used in the hospital. First, the two shots dual energy system acquires both low and high kVp x-ray images with a very short time delay. Second, dual layer detector systems\textsuperscript{14,15} require only one high energy x-ray. The first layer tends to detect low energy x-rays and the second layer preferentially detects higher energy x-rays which went through the first layer. The two shots system gives better energy separation and better image quality and better signal to noise ratio. Radiologists use DE decomposition images to enhance calcification,
nodule and plaque reading in the lung and heart regions\textsuperscript{16,17} since the appearance of digital detector and evaluate the quantification of them.\textsuperscript{18,19} The DE technique also possess the ability to be used in radiotherapy using commercial on-board imaging system.\textsuperscript{20}

CAC is high density, hard material in the coronary artery vessel wall. Earlier studies have shown that CAC can be detected in dual energy bone images.\textsuperscript{17,21} However, results were quite variable due to scattering, noise, obscuring tissues, motion, and low contrast.\textsuperscript{22} With our image processing algorithm, we can create a dual energy coronary calcium (DECC) image that is similar to the dual energy bone image, but enhances visualization of CAC in the heart region using our CorCalDx technique.\textsuperscript{23} With the dual energy x-ray technique, we can tremendously decrease the radiation dose required as compared to CT and give a higher temporal resolution with down to 50ms for each shot than in CT with up to 250ms.\textsuperscript{24}
However, there are issues that could affect the CAC contrast and its identification, such as the patient thorax size variation creating beam hardening\textsuperscript{25}, scattering due to patient\textsuperscript{26} and pulmonary artery overlap in the heart region.\textsuperscript{27} Furthermore, with the ability to detect the CAC in dual energy radiography; we can investigate if we can use this as a CAC scoring tool as compared to the current gold standard CAC scoring.\textsuperscript{28,29}

\textbf{Figure 1.4.} Illustration of two-shot dual energy chest radiography with 60kVp and 120kVp x-ray exposures
1.2 Motivation

We have determined that one can visualize coronary artery calcium in 2-shot, non-gate dual energy chest x-rays\textsuperscript{30,31} and that specialized dual energy coronary calcification (DECC) processing, can greatly improve visualization.\textsuperscript{23} Briefly, we create a DECC image that is similar to the dual energy bone image, but enhances visualization of coronary artery calcification (CAC) in the heart region. This is important as it could enable physicians to detect and quantify coronary calcium from low-cost, low radiation, dual energy (DE) chest x-ray. The chest x-ray is the most common medical imaging procedure, with \textasciitilde450M exams per year worldwide\textsuperscript{32}, \* creating an opportunity to perform population screening at little or no extra cost or radiation.\textsuperscript{33} Although DE is currently a small percentage of studies, it is not particularly technically challenging with modern flat panel x-ray detectors.

Although processing can enable visualization of coronary calcification in clinical DECC images, we are concerned about many potential confounding factors including beam hardening, scatter estimation errors, cardiac motion, overlaying tissues, etc. To investigate, we have created digital 3D phantoms including heart, lung, coronary calcium, spine, ribs, pulmonary artery, adipose, and a scatter model validated with physical measurements. We will realistically simulate high and low kVp images, process

\* There are over 150-M chest x-ray exams per year in the US. To estimate the number of procedures in the world, we used a conservative times 3 factor, giving 450 M exams per year.
with DECC, and evaluate calcium signal as a function of these potential confounding variables. In addition, we will assess the ability to recover a coronary calcium score from DECC image as compared to CT calcium score. \textsuperscript{17,34}
Chapter 2 PHYSICS-BASED DIGITAL PHANTOM AND DUAL ENERGY X-RAY SIMULATION

2.1 Digital phantoms

To study different effects like beam hardening, scattering, potential artifacts etc. in the high kVp, low kVp, standard, bone and soft tissue radiographies, phantom study is the best way to look into these effects, which provide a way to alter organ parameters, CAC parameters and x-ray spectrums/geometry at will. We can make quantitative measurements based on the digital phantom simulations. For instance, we can change the patient size causing different beam hardening to test the effect of CAC signal and test the solution performance (section 3.1). We can test how the scattering will affect the different CAC signal and test the potential solution performance (section 3.2). We can test if other structure overlap in the heart region will cause confounds to the CAC signal (section 3.3). Finally, we can also investigate the ability that dual energy radiography can be used as a coronary calcium scoring tool as compared to the current gold standard tools by putting different CAC into the phantom (section 3.4).

2.1.1 Stylized phantom

Stylized phantom is a digital voxel based phantom consisted of different organs with simple geometric shape representations like elliptic cylinders and flat cubes, so that the
tested effects can be better and simpler to visualized and measured. The stylized phantom is a 512 x 512 x 621 size volume with voxel size equal to 0.78125mm x 0.78125mm x 0.644mm, which have similar size as compared to a real human chest anatomy. Visualization of the stylized phantom is shown in Fig 2.1. Different organs are included in this phantom with appropriate size; heart (red), ribcage (grey), adipose (orange), muscle (yellow), pulmonary artery overlap with heart (blue), lung (purple) and CAC (green).

![Image of stylized phantom with heart (red), ribcage (grey), adipose (orange), muscle (yellow), pulmonary artery overlapping heart (blue), lung (purple), and calcification (green).]

**Figure 2.1.** 3D visualization of stylized phantom with heart (red), ribcage (grey), adipose (orange), muscle (yellow), pulmonary artery overlapping heart (blue), lung (purple), and calcification (green).

The voxel values in the phantom volume are indexes that represent what material they are (Air:0 Adipose:1 Bone:2 Blood:3 Coronary artery:4 Pulmonary artery:5 Muscle:6 CAC:7 Lung:8) and it will have corresponding photon energy – attenuation coefficient table (section 2.2.1) which will retrieve the corresponding attenuation coefficient by knowing what energy photon comes to interact.
2.1.2 Anatomical phantom

Anatomical phantom is also a digital voxel based phantom consisted of different organs, but with more complex geometric shape representations, so that the tested effects will be much realistic. The contours of different organ and tissues were marked and built based on real human CT scan data volumes. Some slices of the anatomical phantom are shown in Fig2.2. Different color areas represent different organs/materials in the anatomical phantom (Adipose: purple Muscle: green Bone: red Lung: azure Blood: yellow Pulmonary artery: orange Coronary artery: blue).

![Figure 2.2](image)

**Figure 2.2.** Transverse views of the anatomical phantom in the heart region. blood (yellow), coronary artery (blue), bone (red), adipose (purple), muscle (green), lung (azure), pulmonary artery (orange).

The anatomic phantom is a 512 x 512 x 621 size volume with voxel size equal to 0.78125mm x 0.78125mm x 0.644mm, which have approximately identical size as
compared to a real human chest anatomy. Different organs with appropriate size can be constructed by using the contours we marked. The visualization of the anatomical phantom is shown in Fig 2.3, which the outmost layer is the adipose and muscle, the red tube on the heart is coronary artery where we will put CAC in it and the black materials around the heart is the pulmonary arteries.

Figure 2.3. 3D visualization of Anatomical phantom with different views. Adipose and muscle (brown), the vessel on the heart is coronary artery (red) where we put CAC in it and the pulmonary arteries (black) are around the heart.

The voxel values in the phantom volume are also indexes that represent what material they are (Air:0  Adipose:1  Bone:2  Blood:3  Coronary artery:4  Pulmonary artery:5 Muscle:6  CAC:7  Lung:8) and it will have corresponding photon energy – attenuation coefficient table (section 2.2.1) which will retrieve the corresponding attenuation coefficient by knowing what energy photon comes to interact.
2.2 X-ray exposure, anti-scatter grid and detector

To acquire a radiography image from the chest x-ray system, the system need to have several essential parts including x-ray source, collimator, anti-scatter grid and x-ray digital detector. The configuration of these parts is illustrated in Fig 2.4.

![Diagram of X-ray source to X-ray detection configurations](image)

**Figure 2.4.** Illustration of the chest x-ray source to x-ray detection configurations

The process of getting radiography is: First, the x-ray beams will be shot from the x-ray tube and collimated by the collimator so there will be a specific field of view. Second, the x-ray beams will penetrate the object/patient with photoelectric absorption, Compton scattering and Rayleigh scattering. Finally, the penetrated primary x-ray beams and scattering x-ray will be detected by the digital detector and most of the scattering will be rejected by anti-scatter grid.
In radiotherapy, the Monte Carlo method is commonly used to plan the radiation field and model the x-ray scatter\textsuperscript{35}, but very time consuming. In our simulation, we model the x-ray scatter based on beam stopping technique measured scatter fraction, which is much more efficient. And we also build up a virtual scintillator based x-ray detector.

\textbf{2.2.1 X-Ray exposures and geometry}

To simulate the radiography by modeling the chest x-ray system, we need to simulate the x-ray spectrum generated from x-ray tube which contains the information about the characteristic of the x-ray beam. We used commercialized x-ray spectrum simulation software – SpekCalc\textsuperscript{36,37} to generate the x-ray spectrums. After the x-ray shot out, it will pass a pre-filtration configuration to reduce the number of low energy photon, so there will be less radiation dose to the patient. In the following simulations, we used 2mm aluminum pre-filtration for all x-ray spectrums.

To simulate the dual energy radiography, we need two x-ray exposures including high kVp (120kVp) exposure and low kVp (60kVp) exposure with 150ms time delay in between. The x-ray spectrums for these two exposures with 2mm aluminum pre-filtration are shown in Fig 2.5.
Figure 2.5. X-ray spectrums used in two-shot dual energy system after 2mm aluminum pre-filtering. (a) Raw spectrums with same mAs. (b) Low and high kVp spectrums used in two-shot system.

The y-axis unit in the x-ray spectrum is (Photon number) / (cm$^2$ mAs). The final exposure spectrums are also determined by the x-ray field of view, tube current and exposure time. For optimal dual energy subtraction (section 2.3), the high and low x-ray spectrums should have similar radiation dose to give better signal in final subtracted image. For the final simulated x-ray spectrums (Fig 2.5 (b)), mAs comparable to clinic system are used (High-kVp: $\approx 0.9$mAs Low-kVp: $\approx 8$mAs). In clinic chest x-ray system, this process is controlled by AEC (Automatic Exposure Control).

The chest x-ray beam is cone beam geometry, but it will be blocked by the x-ray collimator to only expose a rectangle field of view (FOV) which typically is a 40cm by 40 cm FOV (Fig 2.6). The posterior-anterior (PA) view chest x-ray protocol is set with source to image receptor (SID) equal to 180cm and source to object (SOD) approximately equal
to 130cm, which the patient will hold the bar behind the wall stand detector to keep the acquisition process stable.

![Diagram of chest x-ray exposures geometry](image)

**Figure 2.6.** Illustration of chest x-ray exposures geometry

Before the x-ray arrive each scintillator element before the image receptor/detector, each primary x-ray line will penetrate the digital phantom/object as a straight line. The x-ray attenuation is modeled by the Beer-Lambert law (equation 2.1).

$$E_{dep, primary} = \int E \times Spectrum(E) \times e^{-\int \frac{\mu(x,y,z,E)}{\rho} d\rho} ds \, dE$$  \hspace{1cm} (2.1)

The attenuation coefficient $\mu$ is determined by the material type in location $(x, y, z)$ and the photon energy that the current photon shooting in. The distance that photons travel through for each phantom voxel is calculated by the distance of two intersection points (equation 2.2) when the x-ray intersect with the voxel cube (Fig 2.7).
Distance \(= \sqrt{(x_1 - x_2)^2 + (y_1 - y_2)^2 + (z_1 - z_2)^2}\) \hspace{1cm} (2.2)

\[\text{Figure 2.7. Illustration of photon travel distance calculated with intersection points between x-ray and the voxel cube.}\]

For each voxel inside the digital phantoms, there is a material index value for them. And we use both the material index and the incoming photon energy to retrieve the corresponding attenuation coefficient from different materials’ attenuation coefficient curves (Fig 2.8) for this phantom voxel, including adipose, muscle, bone, blood, lung and CAC. The attenuation coefficient tables were taken from NIST.\(^{38}\)
Figure 2.8. Attenuation coefficient curves for different materials in human anatomy. (a) Dry air. (b) Adipose tissue. (c) Muscle. (d) Bone. (e) Blood. (f) Lung tissue. (g) CAC.

After all the steps above, we can simulate the primary x-ray beam energy after x-ray penetrating the digital phantom as correspond to each scintillator on the image receptor side.

2.2.2 Anti-scatter grid

Besides from the primary beam penetrate the object, Compton scattering and Rayleigh scattering are also generated when x-ray pass the object (Fig 2.9). In this case, we will
need to use the anti-scatter grid to reduce the scattering that arrive the image receptor (Fig 2.9).

![Figure 2.9](image.png)

**Figure 2.9.** Illustration of focused anti-scatter grid effect on primary x-ray beam and x-ray scattering.

In General Electric Healthcare (GEHC) chest x-ray radiography system, the anti-scatter grid protocol for 180cm wall stand exposure is 13:1 ratio with 70 lines / cm focused grid which is used in Posterior-Anterior view x-ray acquisition. To determine what the scatter fraction is when the x-ray finally arrive the image receptor, we can either use a Monte Carlo simulation\(^\text{35}\) to model the scatter or use the beam stopping technique\(^\text{39}\) to measure them and then simulate based on that. The scatter fraction measurement is shown in table 2.1 and table 2.2 which are with anti-scatter grid and without anti-scatter grid. Since the Monte Carlo simulation is computational intense, we will use the
beam stopping technique to do measurement based on real x-ray system (Fig 2.10) and simulate the scattering.

Figure 2.10. X-ray chest image of a real geometric phantom with beam stopping technique to calculate the scatter fractions in different regions in the thorax.

With the primary beam, the scatter fraction before passing the grid and focused grid parameters, we can calculate the primary beam intensity and scatter intensity after passing the anti-scatter grid. The grid parameters we used to estimate the left out scatter after the grid are Bucky factor (equation 2.3) and Primary transmission (equation 2.4). The Bucky factor for the grid is 3.5 and Primary transmission is ~60%. The left out scatter after the anti-scatter grid can be calculated by using equation 2.5. The scatter fraction after x-ray pass the grid is shown in table 2.2.
\[ BF = \frac{\text{Incident Radiation transmiss Radiation}}{\text{Primary before grid + Scatter before grid}} = \frac{\text{Primary before grid + Scatter before grid}}{\text{Primary after grid + Scatter after grid}} \quad (2.3) \]

\[ PT = \frac{\text{Primary after grid}}{\text{Primary before grid}} \quad (2.4) \]

\[ \text{Scatter}_{after\ grid} = E_{\text{dep scatter}} = \frac{(1 - BF \times PT) \times \text{Primary before grid + Scatter before grid}}{BF} \quad (2.5) \]

<table>
<thead>
<tr>
<th>Scatter Fraction (without grid)</th>
<th>Mediastinum</th>
<th>Rib</th>
<th>Lung</th>
<th>Heart</th>
<th>Heart/Spine</th>
</tr>
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<tbody>
<tr>
<td>60kVp</td>
<td>0.89</td>
<td>0.78</td>
<td>0.69</td>
<td>0.84</td>
<td>0.94</td>
</tr>
<tr>
<td>120kVp</td>
<td>0.91</td>
<td>0.81</td>
<td>0.76</td>
<td>0.87</td>
<td>0.96</td>
</tr>
</tbody>
</table>

**Table 2.1.** Different regions’ scatter fractions under 60kVp and 120kVp x-ray exposures when no anti-scatter grid was used.

<table>
<thead>
<tr>
<th>Scatter Fraction (with grid)</th>
<th>Mediastinum</th>
<th>Rib</th>
<th>Lung</th>
<th>Heart</th>
<th>Heart/Spine</th>
</tr>
</thead>
<tbody>
<tr>
<td>60kVp</td>
<td>0.54</td>
<td>0.32</td>
<td>0.26</td>
<td>0.46</td>
<td>0.57</td>
</tr>
<tr>
<td>120kVp</td>
<td>0.55</td>
<td>0.34</td>
<td>0.27</td>
<td>0.44</td>
<td>0.56</td>
</tr>
</tbody>
</table>

**Table 2.2.** Different regions’ scatter fractions under 60kVp and 120kVp x-ray exposures when anti-scatter grid was used.
In the simulated scatter image, different regions in the radiography will have different scatter intensity and it will be distributed uniformly and smoothly. So after the absolute scatter image calculated from the primary beam image, we interpolated the region between the measured points and use a Gaussian low pass filter to smooth the image to better simulate the scattering distribution.

2.2.3 Digital detector

After the x-ray pass the anti-scatter grid, the x-ray photons will arrive the image receptor on the opposite side of x-ray source. The scintillator will first detect the x-ray photons, which convert the x-ray photons into optical photons. Then the detector will finally detect the optical photons and convert it to the displayed image through Analogue-Digital Converter (ADC)\textsuperscript{40}.

We can calculate the energy deposition that arrive the scintillator with known x-ray source after penetrating the digital phantom (section 2.1). It can be represented by equation 2.6.

\[
E_{\text{dep}} = E_{\text{dep, primary}} + E_{\text{dep, scatter}}
\]  \hspace{1cm} (2.6)

The conversion rate of x-ray photons to optical photons is based on the scintillator materials’ luminosity. The number of optical photon \((n)\) released from the scintillator can be calculated with Equation 2.7.
\[ n = l \times \frac{E_{\text{dep}}}{1\text{MeV}} \]  

(2.7)

Where \( l \) is the scintillator’s luminosity. The typical scintillator material used in the x-ray detector is BaBr\(_2\): Eu, which has luminosity equal to 58000 photons per MeV.

To better describe the image receptor behavior, we included the point spread function (PSF) to represent the result of many physical phenomena that happen inside it, including scintillator and optical photon detector. The PSF model considers three different phenomena: the optical photon scattering in scintillator, the Compton scattering and electron scattering inside the optical photon detector.

For the scintillator, the PSF (Fig 2.11) is modeled based on the scattering of optical photons inside the scintillator material and the scatter are normally distributed with a certain variance when arrive the detector surface. The variance is a function of depth at which the interaction happen range from 0 to \( \sigma_0 \) (Equation 2.8).

\[ \sigma_S^2(L - z) \approx \sigma_0^2 \frac{L-z}{L} \]  

(2.8)

Where \( z \) is the depth that x-ray photons travel. At the output surface of scintillator/input surface of detector, the scintillator PSF can be represented as Equation 2.9.

\[ n_S(x, y, L) = n \frac{e^{-\frac{(x-x_0)^2+(y-y_0)^2}{2\sigma_S^2(L-x_0)}}}{2\pi\sigma_S^2(L-z)}} \]  

(2.9)
When optical photons enter the detector, they also create a PSF for electron collections.

The detector PSF (Fig 2.11) is modeled as a random walk of the electrons that scatter inside the detector as well. The detector PSF variance and PSF model can be represented as (equation 2.10, 2.11)

\[
\sigma_d^2 (L - z) \approx \sigma_{d0}^2 \frac{L-z}{L} \tag{2.10}
\]

\[
n_d(x, y) = n_e \frac{e^{-(x-x_0)^2 + (y-y_0)^2}}{2\pi \sigma_d^2 (L-z)} \tag{2.11}
\]

**Figure 2.11.** Illustration of the detector PSF function. (a) 3d view of the PSF function. (b) Intensity distribution of the PSF function.
The total PSF of the image receptor is the convolution of the scintillator PSF and the optical detector PSF. And it is actually a Gaussian function with a variance equal to (Equation 2.12)

$$\sigma_t^2 \approx \sigma_s^2(z, L) + \sigma_d^2(z, L)$$

(2.12)

The total PSF in the image receptor is mostly contributed by the scintillator, the contribution of the optical detector is negligible. The distributed electrons in detector pixels can be calculated by convolving the total PSF to the incoming x-ray photons distribution.

The final step is to convert the electrons to gray scale numbers, which is the processing in ADC. After the optical detector collect the electrons into pixel wells, the simulator passes the data to ADC for generating the gray levels. The ADC has two parameters; one is the number of bits per pixel (b), which in chest radiography, it is 16 bits; another is the sensitivity (r) of gaining electrons. And the converted gray level is an integer value determined by the ratio of the number of electrons collected ($n_p$) and the well depth ($W_d$) per pixel (Equation 2.13).

$$g = \text{int} \left( \left[ 2^{16} - 1 \right] \left[ \frac{\sum n_p}{W_d} \right] r \right)$$

(2.13)

Where ‘int’ means the integer conversion of the quantities inside brackets and the sum means the total number of electrons collected inside a pixel after the application of total PSF. The resulting gray scale value should be in the range of 0 to $2^{16}$-1. If the saturation
occurs which the value is beyond this range. The values beyond will be set at the
maximal value of the range (Equation 2.14).

\[
G = \begin{cases} 
g, & \text{if } g < 2^b - 1 \\
2^b - 1, & \text{otherwise}
\end{cases}
\tag{2.14}
\]

2.3 Dual energy subtraction

We use the dual energy material decomposition technique to create bone (calcium) and
soft tissue images. For each of the high and low kVp images, we can write the detected
intensity as a function of bone (b) and soft tissue (s) attenuation and thickness as given
below.

\[
I = I_0 e^{-\left(\mu_s t_s + \mu_b t_b\right)} + S
\tag{2.15}
\]

Since scatter (S) will degrade the image and violate dual energy decomposition, it is
important to subtract it.\textsuperscript{41} Writing Equation (2.16 and 2.17) for high and low kVp images
and taking logarithms, we obtain.

\[
\log(I_{\text{low}} - S_{\text{low}}) = \log(I_{0\text{low}}) - (\mu_{s\text{low}} t_s + \mu_{b\text{low}} t_b) \tag{2.16}
\]

\[
\log(I_{\text{high}} - S_{\text{high}}) = \log(I_{0\text{high}}) - (\mu_{s\text{high}} t_s + \mu_{b\text{high}} t_b) \tag{2.17}
\]
We solve this set of equations for the effective bone and material thicknesses, $t_b$ and $t_s$, respectively, in Equation 2.18. The Equation 2.19 for the bone image is shown below, where $w_b$ is a function of attenuation coefficient. In practice, we adjusted $w_b$ between 1.32 and 1.35 experimentally.

\[
\begin{bmatrix}
    t_s \\
    t_b
\end{bmatrix} = \left[ \begin{array}{cc}
    -\mu_{s,\text{low}} & -\mu_{b,\text{low}} \\
    -\mu_{s,\text{high}} & -\mu_{b,\text{high}}
\end{array} \right]^{-1} \begin{bmatrix}
    \log(l_{\text{low}} - S_{\text{low}}) \\
    \log(l_{\text{high}} - S_{\text{high}})
\end{bmatrix}
\]  

(2.18)

\[
l_B = \log(l_{\text{low}} - S_{\text{low}}) - w_b \log(l_{\text{high}} - S_{\text{high}})
\]  

(2.19)

\[
l_{\text{Bdis}} = \exp(\log(l_{\text{low}} - S_{\text{low}}) - w_b \log(l_{\text{high}} - S_{\text{high}}))
\]  

(2.20)

\[
w_b = \frac{\mu_{s,\text{high}}}{\mu_{s,\text{low}}} 
\]  

(2.21)

Because we use spectral, rather than mono-energetic x-ray beams, there will be beam hardening. To reduce this effect, we use a quadratic dual energy subtraction algorithm (Equation 2.22) as described by Veronique et al.\textsuperscript{42}

\[
l_{DECC} = \log(l_{\text{low}} - S_{\text{low}}) - w_1 \log(l_{\text{high}} - S_{\text{high}}) + \\
    w_2[\log(l_{\text{high}} - S_{\text{high}})]^2 + w_3 \log(l_{\text{high}} - S_{\text{high}}) \times \log(l_{\text{high}} - S_{\text{high}}) + \\
    w_4[\log(l_{\text{low}} - S_{\text{low}})]^2
\]  

(2.22)
\[
I_{DECCdis} = \exp[\log(l_{low} - S_{low}) - w_1 \log(l_{high} - S_{high}) + \\
\quad w_2 [\log(l_{high} - S_{high})]^2 + w_3 \log(l_{high} - S_{high}) \times \log(l_{high} - S_{high}) + \\
\quad w_4 [\log(l_{low} - S_{low})]^2] \quad (2.23)
\]

In this instance, we have replaced a single constant \( w_b \) with 4 weighting constants. Weights were estimated from a clinical image data set and fixed for our experiments. To calculate the scatter term \( S \) for the above equations, an exponential shape kernel was convolved with kVp images to estimate the x-ray scatter distribution profile. This was scaled using the intensity values behind the collimator plates. Without considering the scatter scale estimation error, the scatter estimation errors in single kVp images are less than 10\%. The optimized values for these terms are: \( w_1 = 0.686564, w_2 = 0.794393, w_3 = -0.122075, w_4 = 0.252449, w_5 = -0.154831 \).

### 2.4 Summary

The first section in this chapter covers the modeling process, including the structures of the digital stylized and anatomical phantoms. The second section describes the whole process of how to simulate the radiography of the digital phantoms with chest x-ray system in details, including the x-ray source generation, x-ray geometry, pre-filtration settings, x-ray penetrating the objects/phantoms, x-ray scattering, anti-scatter grid and x-ray detector. In the last section, the dual energy decomposition algorithms, including
the traditional subtraction algorithm (linear) and innovative subtraction algorithm (quadric) is presented. From all the steps above, we can generate simulated radiographs based on the parameters we set. Some simulated stylized phantom and anatomical phantom radiography examples with and without scattering are shown in Fig 2.12 and Fig 2.13.
Figure 2.12. Simulated radiographies of the stylized phantom with 1mm CAC in the heart region. (a) 60kVp radiography with scattering after anti-scatter grid (b) 120kVp radiography with scattering after anti-scatter grid (c) 60kVp radiography without scattering after anti-scatter grid (d) 120kVp radiography without scattering after anti-scatter grid (e) Stylized phantom without scatter. (f) Stylized phantom with scatter.
Figure 2.13. Simulated radiographies of the anatomical phantom with 1mm CAC in the heart region. (a) 60kVp radiography with scattering after anti-scatter grid (b) 120kVp radiography with scattering after anti-scatter grid (c) 60kVp radiography without scattering after anti-scatter grid (d) 120kVp radiography without scattering after anti-scatter grid (e) Anatomical phantom without scatter. (f) Anatomical phantom with scatter. In the left column, the anti-scatter grid
was included in the simulation. In the right column, the anti-scatter grid was not included in the simulation.

With this simulation software, we can generate the radiographies of different phantoms with different anatomies or chest x-ray systems with different configurations like different SID/SOD. Most important, we can investigate and study different effects on CAC signal from different human anatomy, x-ray, etc. So we can optimize and better guide the image processing in the future.
Chapter 3 STUDYS OF CORONARY ARTERY CACIFICATION IN DUAL ENERGY RADIOGRAPHY

Coronary artery calcification is a very small and hard material on the coronary vessel wall. CAC observed with single energy radiography is not easy since it mixes with soft tissue signals, so we use the dual energy technique to suppress the soft tissue signal to enhance the conspicuity of CAC. But we are concerned about the potential side effects can affect the CAC signal and conspicuity on the DECC. Confounding factors including, the scattering from both kVp exposures after anti-scatter grid, the scatter correction errors in single kVp images\(^{44,45}\), the beam hardening caused by different patient size\(^{25}\) and the confound signal from other organs overlapped in the heart region\(^{27}\). In this chapter, we look into how these side effects will affect the CAC signal in the DECC image. With the ability to visualize CAC in the DECC image, it is possible to do coronary calcium scoring by using the DECC image. Similar quantification of dual energy CAC has been analyzed in other papers\(^{21,34,46}\). And similar quantification information for tumor thickness in soft tissue images were also analyzed.\(^{47}\) So we will show the ability to compute a DE calcium score using two DE calcium scoring algorithm and compare it to three gold standard CT calcium scores\(^{28,29}\) from the anatomical phantom simulations.

\[
\Delta I_{CAC} = \text{Contrast}_{CAC} = \left| \text{mean}(I_{CAC}) - \text{mean}(I_{Background}) \right| \quad (3.1)
\]
We calculated the CAC contrast, $\Delta I_{CAC}$, as given in Equation 3.1. The CAC contrast is calculated by measuring the delta-gray between CAC mean pixel values (20 pixels by 20 pixels’ square region) and mean pixel values around the CAC (30 pixels by 30 pixels’ square region except CAC square region).

3.1 Exp1: Beam Hardening

Beam hardening is one of the issues in the poly-energetic X-ray system which the lower energy photons are easier to be absorbed and causes the absolute pixel value in the radiography instable. To analyze the effect of beam hardening on the coronary artery calcium (CAC) signal, we varied the adipose layer thickness in the stylized phantom with AEC exposures and calculated the CAC absolute contrast, $\Delta I_{CAC}$, as given in Equation 3.1

Here CAC and background (BG) intensity values were obtained in manually identified regions of interest (ROIs). In simulation experiments, we measured $\Delta I_{CAC}$ in low and high kVp images assuming perfect x-ray scatter removal, as well as processed DECC images. We varied adipose thickness from (0 cm to 30 cm) to cover a very large range of chest habitus.
In Figure 3.1, we show the effect of adipose layer thickness on the calcium signal. At 30 cm as compared to 0 cm adipose, the calcium signal absolute contrast ($\Delta I_{\text{CAC}}$) is degraded in high and low kVp images by about 8% and 4%, respectively. The greater effect on the high kVp image is obtained because the shift to a higher energy spectrum results in less difference between calcium and soft tissue. With DECC processing, degradation is less than 12% and is further reduced to only 3% with quadric beam hardening correction. As compared to high and low kVp curves, DECC curves tend to flatten at larger adipose thicknesses. As a result, values at 20 cm are similar to those at 30 cm.

### 3.2 Exp2: Scattering

When x-ray penetrates the patient, x-ray will be absorbed by photoelectric effect and scattered by Compton and Rayleigh effects. For the x-ray arrive on the image receptor, they are either belong to primary x-ray beam which is useful radiation signal or scatter x-ray which is useless radiation signal. The distribution of x-ray scattering is uniform and smooth. But the x-ray scattering before anti-scatter grid distribute more uniform than
the scattering after anti-scatter grid because the grid only allow certain angles of x-ray’s penetration. The scattering behavior was discussed in earlier sections (section 2.2.2). Different kVp x-ray exposures have different scattering behavior. The DECC image is subtracted from high kVp and low kVp exposures which include different levels of scattering.

We varied the amount of scatter correction to determine the effect of scatter correction error (SCE) on CAC absolute contrast, $\Delta I_{CAC}$, in DECC image. We simulated high and low kVp stylized phantom data with anti-scatter grid. We simulated ideal scatter correction and errors in scatter correction of up to $\pm 50\%$ in both high and low kVp images (Equation 2.22). In addition, we varied the calcium thickness to determine the interplay of scatter and scatter correction error on DECC calcium signal.
Figure 3.2. Effect of scatter correction error (SCE) on CAC percent change in contrast in DECC images. (a) Percent change in CAC contrast (change in $\Delta I_{CAC}$ with scatter divided by $\Delta I_{CAC}$ without scatter) is displayed in color as a function of SCE, which is varied $\pm 20\%$ in each of the high and low kVp images. Positive (negative) correction in both single kVp images increases (decreases) the contrast percent change by $<3\%$ over this range. (b) CAC contrast percent change (yellow region) is plotted over a wide range of absolute SCE in each of the high and low kVp images. For each absolute SCE value, there are minimum and maximum percent changes and all values between. Note that just as there is a curve for zero percent change in the figure on the left, the percent change in this figure can also be zero.
Figure 3.3. Effect of scatter correction error (SCE) and calcification thickness on $\Delta I_{CAC}$ in DECC image. $\Delta I_{CAC}$ with zero scatter (perfect scatter correction, red curve) is degraded with scatter following anti-scatter grid (black curve). DECC image after scatter correction with 10% SCE lead $\Delta I_{CAC}$ deviating close to perfect scatter correction $\Delta I_{CAC}$ (yellow area).

Perfect scatter correction in DECC processing will eliminate degradation due to scatter (Figure 2.12 and Figure 2.13), but given the difficulty in estimating scatter; we investigated the role of imperfect correction. Effects of scatter correction errors on DECC $\Delta I_{CAC}$ are shown in Figures 3.2 and 3.3. In Figure 3.2a, both positive and negative changes of DECC $\Delta I_{CAC}$ are shown as a function of scatter correction error in each of high and low kVp images. Iso-curves show that over a very large region, error is less than...
±3%. Following the curve for zero error, one can see that a positive scatter correction error at 120 kVp can be compensated by a negative one at 60 kVp. Even when scatter correction error is increased up to 50% in kVp images, the maximal variation of $\Delta I_{CAC}$ is less than ±9% (Figure 3.2b). In Figure 3.3, we show the effect of scatter and its correction on recovery of the magnitude of the calcification signal. We first observe that DECC $\Delta I_{CAC}$ is much degraded by scatter present with the grid (black curve) as compared to that with scatter removed (red curve) and that the curve with scatter is decidedly non-linear. When scatter is corrected within ±20%, results are close to that for perfect correction.

### 3.3 Exp3: CAC Misregistration

To test the effect of misregistration, we use the stylized phantom and modeled calcification displacement between high and low kVp images, with and without a change in “heart filling”. The calcification was 6mm x 4mm x 1mm (length x width x thickness) with 3 g/mm$^3$. Without change in heart filling, we modeled variable displacement from zero to no overlap (0 - 4 mm) of the calcification between the high and low kVp image acquisitions. This was repeated with a change in heart filling by increasing the heart “thickness” from 0 cm to 3.5 cm between the high and low kVp images. We analyzed the CAC signal in DECC images which had characteristic dark, gray, and light regions when there was misregistration. We extracted an image patch containing the CAC signal,
subtracted the average background, and segmented the dark and medium gray regions, hereafter called black. We compared two signal analysis methods: (i) black region integration and (ii) full region integration where we integrated over the entire patch. A mathematical analysis of this is shown in Appendix B.

![Figure 3.4. DECC images of stylized phantom in the presence of misregistration between high and low kVp images. Images are: (a) no misregistration, (b) small misregistration, and (c) large misregistration. In (d), regions of interest include background (BG), bright, gray, and dark.](image)
(a) Integral CAC vs. CAC Misreg Distance (mm)

(b) Integral CAC vs. Δthickness_{heart} (%)
Figure 3.5. Integrated DECC CAC signals with misregistration and changes in heart filling. (Left) Absolute “dark” (gray & dark) and “all” (entire image patch following background subtraction) region integrations are plotted as a function of displacement where 0 and 4 mm give full overlap and no overlap of the 4 mm calcification. (Right) Large region integrations are plotted as a function of the change in heart filling thickness and amount of misregistration (no, moderate, severe). The nominal heart thickness is 15 cm in the low kVp image and fills up to an decrease of 25% (11.25 cm) in the high kVp image. The small deviation from the red curve (no misregistration) is due to a secondary effect of beam hardening.

The effects of misregistration and heart filling on integrated calcium signals are determined in Figure 3.4 and 3.5. With misregistration, DECC images show characteristic very-dark, gray, and light regions as well as background (Figure 3.4d). Curves in Figure 3.5a shows that “all” region $\Delta I_{\text{CAC}}$ integration is nearly independent of percent overlap, while “dark” region $\Delta I_{\text{CAC}}$ (gray + very dark) integration changes by nearly 50%. Figure 3.5b shows changes in $\Delta I_{\text{CAC}}$ integral within “all” regions when heart filling and CAC mistregstration are simulated. When the heart thickness difference changed up to 25%, it gave rise to a change of 17% in $\Delta I_{\text{CAC}}$ integration.

3.4 Exp 4: Pulmonary Artery Artifact

In the posterior-anterior x-ray system, the pulmonary artery (PA) will overlap with the heart region according to the human anatomy. According to the dual energy bone material subtraction model, the pulmonary artery as soft tissue component should be
eliminated. However, dark pulmonary arteries are sometimes seen within the heart boundary in dual energy “bone” images, leading to a potential confound in detection of coronary calcium. This is confusing as pulmonary arteries are filled with blood and should not show up in bone images. In the stylized phantom, between high and low kVp acquisitions, we simulated motion of a “blood filled” pulmonary artery (10 mm diameter) from no overlap to mostly overlap. In addition, we simulated filling of the artery due to pressure pulsations, reported to be as much as 20% change in diameter depending on the phase of the cardiac cycle.\(^\text{27}\) In the stylized phantom, we changed pulmonary artery diameter from 10 mm to 12 mm, a 20% increase and decrease, between low and high kVp images, respectively, simulating the change in systole and diastole.

**Figure 3.6.** Illustration of pulmonary pulsation artifact in clinic case. Red arrow indicates the corresponding location of pulmonary artery. Green arrow indicated the corresponding location of coronary artery calcification (CAC).
Figure 3.7. Pulmonary artery artifacts due to pulsations in arterial filling are seen in DECC images. 
(a) DECC image of stylized phantom without pulmonary artery pulsation. (b) DECC image with 
pulmonary artery filling during cardiac systole. (c) DECC image with pulmonary artery filling 
during cardiac diastole. (d) Intensity profiles of DECC image with pulmonary artery filling during 
cardiac systole. (e) Intensity profiles of DECC image with pulmonary artery filling during cardiac 
diastole.

We investigated why dark, non-calcified pulmonary arteries are sometimes seen in DECC 
images. Clinical examples are shown in Figure 3.6. Simulations of pulmonary artery 
pulsation filling under cardiac systole and diastole between high and low kVp images 
shows artifacts in DECC images with signal levels similar to CAC (Figure 3.7). Without 
pulsation filling, no pulmonary artery is visible (Figure 3.7a), but when there is a change 
in filling, a residue is evident (Figure 3.7b, c). White pulmonary artifact is much less 
detectable than dark artifact. Plots of a row of pixels show that the signal level of the 
artifact is similar to a CAC (Figure 3.7d, e). In the case of pulmonary artery with 10mm
diameter and pulsation overlapping the heart region, it gives about 50% delta gray compared to 1mm thickness CAC (3 g/mm³).

3.5 Exp5: Calcium Scoring with Dual Energy Radiography

As it is possible to detect the CAC in the DECC image, DECC image has the potential to be used as a calcium scoring tool as compared to CT calcium scoring. To test this idea, various coronary artery calcifications were used in the phantom simulations to test the correlation between the existing CT calcium scoring algorithms and the proposed DE calcium scoring algorithms. We compared 2D DE calcium scores to CT calcium scores using the anatomical phantom. The DECC score was obtained by summation of $\Delta I_{CAC}$ over the area of the simulated calcification, a method similar to that used previously by us on standard DE bone clinical images. We created a rectangular solid calcification with variable width (4 mm – 8mm), thickness (0.1mm – 3 mm) and density (1.92 g/cm³ – 3 g/cm³). We varied adipose thickness (0cm-30cm). In DECC images; we subtracted the average background surrounding the calcification. We calculated CT Agatston score, mass score, volume score and compared to the proposed DECC score.
Figure 3.8. Relationship between CT calcium scores and DECC score. Scatter plots of CT calcium scores (volume, Agatston, and mass) as a function of DECC scores were obtained by simulating a wide range of independent variables in the anatomical phantom. Coefficients of determination, R² are 0.9992, 0.9990 and 0.9999 for volume, Agatston, and mass, respectively.

We determined the relationships between CT calcium scores and DECC score (the full region score described in earlier this section): DECC Scoring (Figure 3.8). Independent variables in simulations include CAC density, CAC size, background location (rib/non-rib), and thorax adipose thickness in the anatomical phantom, and results are mixed together. Plots for CT calcium scores (volume, Agatston, and mass) are each reasonably described by a linear equation. Since DECC scoring cannot distinguish between a thin
high density and a thick low density calcification, the spread with CT volume data is much more pronounced. Due to its non-linear mapping of HU to “weighting factor,” Agatston has a non-zero intercept and slight evidence of a non-linear relationship with DECC score. There is a clear one-to-one relationship between DECC score and CT mass score.

3.6 Discussion

Simulation experiments have shown the feasibility of obtaining a viable coronary artery calcification signal in dual energy (DE) chest x-rays. Effects of beam hardening, improper scatter estimation, misregistration, and pulmonary artifacts can all degrade coronary artery calcium signals. However, the sizes of the effects are all manageable.

Beam hardening is much less of an issue that we initially presumed. CAC signal with linear subtraction degrades less than 10% when 20 cm adipose thickness is used. Quadric beam hardening correction reduces error to less than 3% even in the presence of 30 cm of adipose.

Errors in scatter correction might be the most important limitation for accurate determination of a DE CAC signal. If we use an anti-scatter grid and estimate the remaining scatter within ±10% or ±50% error, then the error in calcium signal is ±2% or ±9%, respectively. In DECC processing, we currently correct for scatter using an
exponential convolution kernel, a method advocated by multiple investigators.\textsuperscript{48,49} Using such a method, scatter can be estimated within ±10% over a chest image if the proper overall “scaling” factor is used.\textsuperscript{43} There are a variety of methods for estimating scatter from x-ray images.\textsuperscript{44-50} We are investigating methods for estimating the scatter scaling factor including beam stops and scatter behind the collimator.\textsuperscript{51,52} Simulations suggest that our design goal should be estimation of scatter within ±50%, over a limited region containing the coronary arteries.

Simulations indicate that misregistration between high and low kVp images is manageable. Calcification displacements can be compensated by rigid body image registration techniques. Any residual misregistration of a calcification in DECC images can be compensated by integrating the background subtracted signal over the full region containing dark and bright areas as described in Methods. Using this method, DECC score is affected less than 2% by misregistration. Changes in heart filling were a more important effect.

Through simulations, we surprisingly discovered that pulsatile filling and motion of pulmonary arteries can create a calcification-like artifact in DECC images that are designed to suppress soft tissue and blood. This type of artifact is of concern only when a major pulmonary artery overlaps the coronary artery region during diastole or systole when the largest changes in pulmonary artery diameter occur over a short time interval. The chance of observing a confounding pulmonary artifact is low. We found only 3 out of 108 clinical images. Moreover, with experience, a radiologist should be able to
discriminate these artifacts which typically have a more vertical orientation as compared to the LAD, the typical site for calcification.

In simulations, DECC score compared most favorably to CT calcium mass score. The relationship to Agatston score was good and might be improved with more consideration to intensity values. The promising result with mass score suggests to us that DECC imaging can be used to derive a reasonably accurate quantitative calcification score. We will investigate these in future clinical studies with corroborative CT images.

In conclusion, simulation experiments suggest that it is quite feasible to image coronary calcifications using DE chest x-rays. Degradations and artifacts due to beam hardening scatter estimation, motion and pulmonary artifacts all appear quite manageable. Moreover, with appropriate processing it might be possible to obtain quantitative estimates of calcifications akin to the CT calcium score. Not only are the simulations important for showing feasibility, they suggest processing and acquisition schemes to improve results, e.g., methods to improve scatter estimation. We are greatly encouraged to continue our pursuit of improved computational methods for visualization and quantification of coronary calcium in clinical dual energy images.
Chapter 4 FUTURE WORK

In this paper, we developed realistic digital phantoms and build a non-gated, two shot chest x-ray imaging simulation software validated with physical measurements (Appendix A). We studied the potential adverse effects like beam hardening, scatter, misregistration, pulmonary artery artifacts on the calcium signal in DECC images and studied the DECC score’s correlation to CT CAC scores.

With the simulated images with known exposure parameters and target object information, we can efficiently evaluate image processing, analysis, optimize parameters, and demonstrate sensitivities for imaging calcium with dual energy x-ray.

The x-ray scatter used in the simulation software is based on the assumption that the digital phantom is a medium size patient. In reality, scatter property can vary from patient to patient. Larger patient will generate more x-ray scatter than the smaller size patient which is not fully consider in this simulation, but scatter only varied within about 20% from small patient to large patient. In the future, we should investigate how the scatter from different patient size will affect the CAC signal on the DECC image and evaluate the scatter correction error on different size’s patient data.

More complex misregistration motion of CAC can be simulated with the digital phantoms besides from the rigid translation in this paper. Investigation of what kind of complex motion should be simulated in the misregisrination experiment and if the integral scoring method will immune to the complex motion are needed in the future.
The chest radiography rib-suppression algorithm can be evaluated with the simulated images with known target images (simulated images without posterior ribs in digital phantom). The effect of rib-suppression on CAC signal overlapping rib and DECC score will be evaluated in the future.

Finally, the run time of the simulation software is relative long because of the poly-energetic x-ray spectrums contain different KeV photon and trigger different attenuation properties for different materials. VTK with C++ CUDA acceleration should be able to decrease the run time tremendously and speed up the future experiments when involve varying multiple variables of the digital phantom, like CAC location, size and patient size.
Appendix A: Physical phantom measurements

Simulation software was validated with physical measurements on an acrylic physical phantom (Model L-769 Acrylic Modular X-ray phantom) with an added “calcification” and compared to simulations on an identical digital phantom. We imaged a 25 cm x 25 cm x 7.6 cm acrylic phantom with 1.5 mm, 2 mm, and 2.5 mm thick calcium objects in the air gap of the phantom. We optionally added an array of lead beam stops (Figure A1b) on the x-ray entrance side of the acrylic phantom x-ray scatter. We took dual energy exposures similar to clinical imaging (120 kVp, 6.4 mAs and 60 kVp, 25 mAs) with AEC and grid. In simulation, we constructed an identical digital phantom and used the same dual energy exposures. In the analysis, we determined intensity values under beam stops (scatter), in flat region (primary + scatter) and their ratio (scatter fraction) for both physical measurement and simulation. We determined primary (P) intensity values with varied acrylic thickness for both physical measurement and simulation. We compared calcium contrasts in 60 kVp, 120 kVp, and DECC images. In physical measurements, the DECC image without scatter can be determined by subtracting the intensity value under beam stops.

Simulation results are compared to experiments in Table A1 and Figure A1. Values for S, S+P, P, and SF agree between simulations and experiments within 3%. In simulations, a single scaling factor between intensity values from total energy arrived detector to gray scale was adjusted. SF values were obtained from the literature for chest and used without adjustment. The validation result of calcium contrast in 60kVp, 120kVp images
and DECC images are shown in Figure A1e and f; less than 10% mean error is observed between calcium contrast in DECC images between physical measurement and simulation when calcium density, $\rho$, used in simulation was property adjusted. As in the main text, DECC images are rendered for display following an exponential conversion of the “linear,” processed results in Equation 12 with quadric beam hardening correction. For all numerical results, we report the result prior to taking the exponential. i.e., results from Equation 10 or 13.

**Table A1.** Comparison of physical phantom and simulation. Scatter (S) was estimated under the beam stop; P+S were estimated in the background; and P and scatter fraction (SF) were computed.

<table>
<thead>
<tr>
<th></th>
<th>P+S</th>
<th>S</th>
<th>P</th>
<th>SF</th>
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</thead>
<tbody>
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<td>185</td>
<td>695</td>
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<td>36</td>
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<td>186</td>
<td>686</td>
<td>0.213</td>
</tr>
<tr>
<td>Simulated 60kVp</td>
<td>289</td>
<td>38</td>
<td>251</td>
<td>0.129</td>
</tr>
</tbody>
</table>
Figure A1. Phantom construction and measured and simulated calcium signals. The acrylic phantom (a) was imaged with the beam stop array (b) to get the 60 kVp image (c). Primary (P) is plotted for low and high kVp images as function of the Acrylic thickness (d). Calcium contrasts ($\Delta I_{CAC}/I_{BG}$) are plotted for low and high kVp images as a function of the CAC thickness (e). Contrasts in DECC images are plotted (f) with and without scatter, as reported in Table A1.
Appendix B: Misregistration analysis

The mathematic analyze of CAC contrast ($ΔICAC$) integral within in all CAC regions is shown as follows.

\[ S_{\text{light}} = \sum_{[x,y] \in R_{\text{light}}} \{ V_{\text{ICAC}} - V_{\text{BG}} \} \]

\[ = \sum_{[x,y] \in R_{\text{light}}} \{ [\text{wlog}(I_{\text{H}}_{\text{CAC}}) - \log(I_{\text{L}}_{\text{BG}})] - [\text{wlog}(I_{\text{H}}_{\text{BG}}) - \log(I_{\text{L}}_{\text{BG}})] \} \]  \hspace{1cm} (1)

\[ S_{\text{vdark}} = \sum_{[x,y] \in R_{\text{vdark}}} \{ V_{\text{vdCAC}} - V_{\text{BG}} \} \]

\[ = \sum_{[x,y] \in R_{\text{vdark}}} \{ [\text{wlog}(I_{\text{H}}_{\text{BG}}) - \log(I_{\text{L}}_{\text{CAC}})] - [\text{wlog}(I_{\text{H}}_{\text{BG}}) - \log(I_{\text{L}}_{\text{BG}})] \} \]  \hspace{1cm} (2)

\[ S_{\text{CAC}} = \sum_{[x,y] \in R_{\text{CAC}}} \{ V_{\text{CAC}} - V_{\text{BG}} \} \]

\[ = \sum_{[x,y] \in R_{\text{CAC}}} \{ [\text{wlog}(I_{\text{H}}_{\text{CAC}}) - \log(I_{\text{L}}_{\text{CAC}})] - [\text{wlog}(I_{\text{H}}_{\text{BG}}) - \log(I_{\text{L}}_{\text{BG}})] \} \]  \hspace{1cm} (3)

In CAC mis-registration, we have $R_{\text{CAC}} = R_{\text{light}} = R_{\text{very-dark}}$. After simplification of $S_{\text{light}} + S_{\text{very-dark}}$, we will have:

\[ S_{\text{light}} + S_{\text{vdark}} \]

\[ = \sum_{[x,y] \in R_{\text{CAC}}} \{ [\text{wlog}(I_{\text{H}}_{\text{CAC}}) - \log(I_{\text{L}}_{\text{CAC}})] - [\text{wlog}(I_{\text{H}}_{\text{BG}}) - \log(I_{\text{L}}_{\text{BG}})] \} \]  \hspace{1cm} (4)

So

\[ S_{\text{bright}} + S_{\text{dark}} = S_{\text{CAC}} \]  \hspace{1cm} (5)
In Equation 1 and Equation 2, Sdark and Slight are the integral of misregistration $\Delta I_{CAC}$ in CAC very dark and light regions, respectively, as illustrated in figure 7 (d). In equation 3, SCAC is the integral of $\Delta I_{CAC}$ when no misregistration interferes. After simplifying the sum of Sdark and Sbright, we can write the simplified addition of them as Equation 4, which is identical to the result when no CAC mis-registration interferes, as given in Equation 3. This analyze is valid when the motion severity is not extremely high without heart filling.
Appendix C: Simulation Software Manual

Dual Energy X-ray Coronary Calcium (DEXCC) simulation software mainly consists of 3 parts written in MATLAB, including:

2. X-ray trajectory computation with specific beam geometry (Cone beam with SID: 180cm) and digital phantom.
3. High and low kVp X-ray exposure with
   a) Specific kVp spectrums, mAs.
   b) Specific Adipose thickness.
   c) Specific CAC location, size and thickness.

MATLAB Code can be found in google drive: ‘https://drive.google.com/open?id=0B_xDcuiE9Tq9QkxlcFpaRWdQUXM’.

MATLAB Code Running Guide:

To generate simulation images:

Step1: Run ‘CalculatePhantomIndVoxel.m’ to generate ray tracing volume with cone beam geometry x-ray. It will generate two matrixes, including:

1. Material_ind_mat.m (1000x1000x621): Material index along the ray.
2. Distance_mat.m (1000x1000x621): Voxel intersection distance of the ray.

Step2: Run ‘PhantomProjection.m’ to generate the final 14 bits simulated x-ray images, you can specify:
1. X-ray mAs for low and high kVp images, respectively.
2. Simulate images with or without poison noise.
3. CAC location, width, height and thickness.
4. Phantom’s adipose thickness.
5. You can alter the detector property in ‘Dector_Sim.m’ function
6. You can alter the anti-scatter grid’s property in ‘Scatter_Grid_Sim.m’ function

‘Material_Parameters’ folder contains:

1. The attenuation curves and densities (NIST) of different materials.
2. The x-ray spectrum with pre-filtration generated from ‘Spekcal’ software.

‘Phantom_Stylized’ and ‘Phantom_Anatomic’ folder contain:

1. 3D material index volume of stylized phantom.
2. 3D material index volume of anatomic phantom.
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