Experimental feasibility of xenon-enhanced dual-energy radiography for imaging of lung function

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Abstract
Chronic obstructive pulmonary disease (COPD) is a leading cause of death worldwide. We experimentally investigated the feasibility of two-dimensional xenon-enhanced dual-energy (XeDE) radiography for imaging of lung function. We optimized image quality under quantum-noise-limited conditions using a chest phantom consisting of a rectangular chamber representing the thoracic volume and PMMA slabs simulating x-ray attenuation by soft tissue. A sealed, air-filled cavity with thin PMMA walls was positioned inside the chamber to simulate a 2 cm thick ventilation defect. The chamber was ventilated with xenon and dual-energy imaging was performed using a diagnostic x-ray tube and a flat-panel detector. The contrast-to-noise ratio of ventilation defects normalized by patient x-ray exposure maximized at a kV-pair of approximately 60/140-kV and when approximately one third of the total exposure was allocated to the HE image. We used the optimized technique to image a second phantom that contained lung-parenchyma-mimicking PMMA clutter, rib-mimicking aluminum slats and an insert that simulated ventilation defects with thicknesses ranging from 0.5 cm to 2 cm and diameters ranging from 1 cm to 2 cm. From the resulting images we computed the area under the receiver operating characteristic curve (AUC) of the non-prewhitening model observer with an eye filter and internal noise. For a xenon concentration of 75%, good AUCs (i.e. 0.8–0.9) to excellent AUCs (i.e. >0.9) were obtained when the defect diameter is greater than 1.3 cm and defect thickness is 1 cm. When the xenon concentration was reduced to 50%, the AUC was ~0.9 for defects 1.2 cm in diameter and ~1.5 cm in thickness. Two-dimensional XeDE radiography may therefore enable detection of functional abnormalities associated with early-stage COPD, for which xenon ventilation defects can occupy up to 20% of the lung volume, and should be further developed as a low-cost alternative to MRI-based approaches and a low-dose alternative to CT-based approaches.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of adult morbidity and mortality worldwide (Lozano et al 2012). COPD is characterized by airflow obstruction due to emphysema and small airways disease (Hogg et al 2004, McDonough et al 2011). COPD patients can suffer respiratory exacerbations that require hospitalization; these hospitalizations are the greatest burden of COPD on health-care systems (Global Initiative for Chronic Obstructive Lung Disease 2019). Detecting COPD in its earliest stages and predicting exacerbations is important for disease management. Spirometry is the clinical standard for diagnosis and staging of COPD (Johns et al 2014, Regan et al 2015, Global Initiative for Chronic Obstructive Lung Disease 2019), but is insensitive to early disease and cannot distinguish different COPD phenotypes (Hogg et al 1994, Hogg 2004, Regan et al 2015, Woodruff et al 2016, Labaki and Han 2018). Medical imaging techniques have been developed to probe the structural and functional changes associated with COPD (Taplin et al 1977, Garg et al 1983, Fain et al 2006, Kirby et al 2017).
Structural imaging of COPD includes the conventional chest x-ray, computed tomography (CT), digital tomosynthesis (DTS) and x-ray dark field imaging. Chest x-ray is an accessible, inexpensive and low-dose technique to detect emphysema and lung hyper-inflation due to gas trapping (Miniati et al. 2008). However, chest x-ray has shown poor sensitivity for detection of early emphysema (Washko 2010). CT can provide high diagnostic accuracy for detection of mild to moderate emphysema but at a much greater radiation dose compared to the chest x-ray (Sanders et al. 1988, Huda 2007). DTS enables detection of early emphysema with high sensitivity and has the potential to be used as a low-dose alternative to CT (Yamada et al. 2013). An emerging technique for structural imaging of COPD is dark-field imaging, which produces contrast based on local phase differences in the x-rays that pass through a patient due to refraction at the boundaries between different materials (e.g. healthy lung versus emphysematous lung) (Pfeiffer et al. 2006, 2008). Willer et al. showed that dark-field imaging has diagnostic accuracy similar to CT while using radiation doses similar to those of the conventional chest x-ray (Willer et al. 2021). A fundamental limitation of structural imaging of COPD is that functional small airways disease proceeds emphysema-related structural changes (McDonough et al. 2011, Bhatt et al. 2016).

Functional lung imaging has been shown to be sensitive to early disease-related changes (Taplin et al. 1977, Garg et al. 1983), and includes hyper-polarized (HP) noble gas magnetic resonance imaging (MRI) (Kirby et al. 2010, 2012), xenon-enhanced dual-energy (XeDE) computed tomography (CT) (Chae et al. 2008, Park et al. 2010, Honda et al. 2012, Kong et al. 2014, Lee et al. 2017) and ventilation/perfusion (V/P) single photon emission computed tomography (SPECT) (Jögi et al. 2010, Bajc et al. 2017), each of which use inhaled contrast agents to provide maps of lung ventilation. Hyper-polarized noble-gas MRI (Parraga et al. 2007, Kirby et al. 2012, 2015) is sensitive to early disease-related changes and can predict respiratory exacerbations (Kirby et al. 2013, 2014), but is primarily used as a research tool because of the associated cost and limited accessibility. Ventilation/perfusion SPECT is sensitive to early COPD and can classify the severity of functional abnormalities, but requires administration of a radioactive contrast agent and high radiation doses (Suga et al. 2006, Jögi et al. 2010, Bajc et al. 2017). XeDE CT is more economical and available than MRI-based techniques, but the associated radiation dose (Huda 2007) potentially precludes its use for widespread longitudinal monitoring of COPD patients.

We recently proposed two-dimensional XeDE radiography for imaging of lung function (Basharat et al. 2020). Using mathematical models of ventilation defects, anatomic noise, and the signal and noise properties of dual-energy (DE) imaging, we showed that XeDE radiography may enable detection of functional abnormalities associated with mild, moderate and severe COPD at typical radiographic exposures, (Basharat et al. 2020) which are two orders of magnitude lower than those used in XeDE CT (Honda et al. 2012). While the results of this theoretical work are encouraging, there has been no experimental demonstration of XeDE radiography in phantom or clinical studies. Furthermore, our previous models were simplistic in their treatment of x-ray scatter, and relied on a small-signal approximation to model the contrast of ventilation defects, image noise and the weighting factor used in the DE subtraction. Furthermore, in our previous work we assumed that the dual-energy subtraction completely suppresses lung parenchyma, which, if not properly suppressed would appear as an absence of Xe and constitute a source of anatomic noise. In light of these limitations of our models, and the potential clinical utility of XeDE radiography, an experimental demonstration and optimization of the image quality of XeDE radiography is warranted.

The purpose of this paper is to investigate the feasibility of 2D XeDE radiography in an experimental phantom study in terms of image quality. We experimentally optimize image quality under quantum-noise-limited conditions, and then, using the optimal parameters, quantify the effects of anatomic noise due to lung parenchyma and overlying ribs on the detectability of ventilation defects.

2. Methods and materials

2.1. Experimental DE imaging system

Figure 1 is a photograph of the bench-top x-ray imaging system used in our experiments. It consists of a Rad-92 x-ray tube from Varex Imaging (Salt Lake City, UT), a Varex Optica 40 collimator and an energy-integrating cesium iodide (CsI)/CMOS flat-panel detector from Teledyne Dalsa (Waterloo, Canada), all housed within a 2 × 2 × 1-m³ lead-lined cabinet. The detector model is the XINEOS-3030HS which has a pixel pitch of 151.8 μm and an active area of 296 × 296 mm². The x-ray tube is powered by an x-ray generator from EMD Technologies (Saint-Eustache, Canada).

2.2. Chest phantom

2.2.1. Phantom for the optimization study

A photograph and a schematic of our custom-built chest phantom are shown in figure 2. The phantom consists of a rectangular chamber and a solid PMMA slab. The length of the chamber along the beam path is 16 cm,
which is the depth of a female lung (Kramer et al. 2012), and its walls are 2.54 cm thick PMMA. An air-filled cylinder with an inner diameter of 2 cm and a length of 2 cm located inside the chamber simulates a ventilation defect. The walls of this air-filled cylinder are 1-mm-thick PMMA and the cylinder is supported by a 2 mm thick PMMA slab that was attached to the wall of the chamber. The thickness of this supporting slab was chosen to match the total thickness of the two faces of the cylindrical defect. A 5.64 cm thick PMMA slab was placed in front of the chamber along the x-ray path to account for scatter and x-ray attenuation through soft tissue. The total thickness of PMMA along the beam path was \( \sim 10.92 \) cm which matches approximately the x-ray attenuation due to soft tissue and lung tissue in adult females (Segars et al. 2010). A needle valve and a pressure gauge were used to control the partial pressure of Xe inside the chamber to achieve the desired fractional molar concentration, as described in section 2.2.4.

2.2.2. Clutter phantom

We modified our phantom to simulate anatomic noise due to lung parenchyma and rib structures as shown in figures 3(a) and (b). Our clutter phantom was inspired by (Gang et al. 2010), who used randomly-packed, solid PMMA spheres of varying diameter to simulate anatomic noise in chest radiography. The (Gang et al. 2010) phantom however was not designed for ventilation studies and does not contain air spaces that can be ventilated with Xe. We therefore replaced the solid PMMA spheres with hollow PMMA cylinders. The inner and outer diameters of the cylinders were chosen to yield an effective area density that approximated that of the lung which ranges from \( \sim 0.15 \) to \( \sim 0.30 \) g cm\(^{-2}\) depending on the breath cycle. As another constraint, to try to approximately match the spatial correlations of Gang et al.’s phantom, we limited the diameter of the hollow cylindrical tubes to the maximum diameter of Gang et al.’s spheres, which was \( \sim 16 \) mm. We therefore chose cylinders with an outer diameter of 15.875 mm and a wall thickness of 1.5875 mm. We used five different
cylinder lengths of 15.9, 12.7, 9.5, 6.4 and 3.2 mm; the relative number of each was 1, 1.25, 1.67, 2.50 and 5.00, respectively, which approximately matched the volume of space occupied by each set of cylinders of the same length. Measurement of the effective density (by weighing the phantom before and after filling it with the cylinders) yielded an effective density of 0.27 g cm$^{-3}$. To simulate rib structures, we placed Al slats on the front and back surfaces of the vacuum chamber to yield a criss-cross pattern, similar to what would be observed in a 2D chest radiograph. The thickness of each Al slat was 16 mm and the width of each slat was 13 mm.

2.2.3. Ventilation-defect stepwedge

To qualitatively demonstrate the ability to visualize defects of varying diameter and depth, we used the defect stepwedge shown in figure 3. The stepwedge consists of a PMMA casing with simulated defects with diameters of 1, 1.5 and 2 cm and depths of 0.5 cm, 1 cm and 2 cm.

2.2.4. Xenon density and fractional molar concentration

The effective density of Xe inside the lung is determined by the fractional molar concentration of Xe in a Xe/air mixture, in addition to the effective density of lung parenchyma (or parenchyma-simulating PMMA clutter). Here, we describe how to map the fractional molar concentration of Xe used in our experiments to those that would be required to provide the same contrast in a human lung.

In a human lung, the contrast of a ventilation defect is approximately proportional to the effective Xe density, which is given by (Basharat et al 2020)

$$[\rho_{\text{Xe}}]_{\text{Lung}} = \epsilon_{\text{Lung}} \rho_{\text{Xe}} \left(1 - \frac{\rho_{\text{Lung}}}{\rho_{\text{Soft-tissue}}} \right),$$

where $\epsilon_{\text{Lung}}$ represents the fractional molar concentration of Xe, $\rho_{\text{Xe}} = 5.887 \times 10^{-3}$ g cm$^{-3}$ represents density of Xe at standard temperature and pressure, $\rho_{\text{Lung}} \approx 0.16$ g cm$^{-3}$ represents the lung density at expiration, and $\rho_{\text{Soft-tissue}} \approx 1.00$ g cm$^{-3}$ represents the density of soft-tissue, which is assumed to have the same mass-attenuation as lung tissue.
In our experiments, we did not have lung tissue but instead have either a Xe/air mixture or hollow PMMA cylinders in addition to the Xe/air mixture. The effective Xe density inside the chamber is

\[ \rho'_{Xe} = \epsilon_{\text{Chamber}} \rho_{Xe} \left(1 - \frac{\rho_{\text{Clutter}}}{\rho_{\text{PMMA}}} \right) \]

where \( \rho_{\text{Clutter}} = 0.27 \text{ g cm}^{-3} \) represents the effective density of the cylinder-filled chamber and \( \rho_{\text{PMMA}} = 1.18 \text{ g cm}^{-3} \) represents the density of PMMA. Equations (1) and (2) provide a means of mapping the effective Xe density in our experimental set-up to those that would produce the same contrast (while holding all other variables fixed) in a human lung. More specifically, the fractional molar concentration in the human lung required to match the contrast of a ventilation defect inside a lung to that in our experiments is given by

\[ \epsilon_{\text{Lung}} = \epsilon_{\text{Chamber}} \frac{\rho_{\text{Soft-tissue}}}{\rho_{\text{PMMA}}} \frac{\rho_{\text{PMMA}} - \rho_{\text{Clutter}}}{\rho_{\text{Soft-tissue}} - \rho_{\text{Lung}}} \]

For the optimization study, for which \( \rho_{\text{Clutter}} = 0 \), \( \epsilon_{\text{Chamber}} \) ranged from 0.25 to 0.75, which corresponds to \( \epsilon_{\text{Lung}} \in [0.30 \ 0.89] \) which is consistent with the Xe concentrations used in clinical Xe-enhanced x-ray imaging studies (Lam et al 1990, Park et al 2010, Honda et al 2012, Kong et al 2014). For the anatomic clutter phantom, \( \epsilon_{\text{Clutter}} \) ranged from 0.55 to 0.83 which corresponds to \( \epsilon_{\text{Lung}} \in [0.50 \ 0.75] \). The area densities of Xe inside the chamber with and without the anatomic clutter ranged from 0.022 g cm\(^{-2}\) to 0.066 g cm\(^{-2}\) and from 0.036 g cm\(^{-2}\) to 0.073 g cm\(^{-2}\), respectively.

2.3. XeDE image formation

XeDE images of the chest phantom were formed by subtracting low-energy (LE) and high-energy (HE) images acquired after ventilating the phantom with Xe (Lehmann et al 1981)

\[ \text{DE} = - \log H + w_r \log L \]

where \( H \) and \( L \) represent HE and LE x-ray images with Xe, respectively, and \( w_r \) represents a weighting factor to either suppress bone or soft-tissue or cancel the contrast between soft-tissue and Xe (Lehmann et al 1981). We refer to these as bone-suppression, soft-tissue suppression and soft-tissue/Xe look-alike \( w_r \) values, respectively. We previously showed that reduced lung density due to emphysematous destruction has contrast opposite to that of ventilation defects in bone-suppressed XeDE images (Basharat et al 2020). Also, in soft-tissue-suppressed XeDE imaging, lung parenchyma may appear as an absence of Xe and thus constitute a source of anatomic noise. Therefore, we only considered a XeDE approach that suppresses the contrast between Xe and soft tissue (e.g. lung parenchyma). We refer to such images as soft-tissue/Xe-look-alike images. LE and HE images were acquired after filling the chamber with Xe to the desired partial pressures.

2.3.1. Acquisition parameters

For the optimization study, we imaged the optimization phantom using LE tube voltages ranging from 50 kV to 90 kV with 1.2 mm of Al filtration. We considered HE tube voltages ranging from 130 to 140 kV with 1.2 mm of Al filtration and 1.1 mm of Cu filtration. The source to detector distance (SDD) was fixed at 155 cm. Because our system does not have an anti-scatter grid, we controlled the amount of scatter reaching the detector by varying the air gap between the object and detector, which was chosen to yield scatter levels similar to those reported in a clinical setting (Ullman et al 2005, 2006). The methodology used to measure the scatter-to-primary ratio (SPR) is described in section 2.4.4.

The x-ray exposure [mR] incident upon the phantom, which we refer to as the entrance exposure, was measured using a Radcal 10X6-6 general purpose ion chamber. For each tube voltage combination, the total entrance exposure (i.e. \( X_{\text{ent}} = X_H + X_L \)) was 60 ± 3 mR. The exposure allocation factor (\( f \)), which we defined as the ratio of the HE entrance exposure to the LE entrance exposure (\( X_H/X_L \)), was varied from ~0.25 to 2. The imaging parameters are summarized in table 1.

2.3.2. Image pre-processing and DE subtraction

All images were gain and offset corrected. Offset correction was performed using 'dark' images which we acquired using a signal generator without exposing the detector to x-rays. The gain map with dark-field correction was obtained from the average of 40 dark-field-corrected flat-field images. For the optimization study, LE and HE gain-and-offset-corrected images were combined to produce a DE image via equation (4). The value of the tissue suppression parameter was varied from 0.5 to 2 in increments of 0.001. For each \( w_r \) value we calculated the contrast of the PMMA walls of the air-filled cavity relative to the Xe-ventilated background region. To this end, we sampled four 14 × 14-pixel ROIs within the PMMA wall and one large 100 × 100-pixel ROIs within the Xe ventilated region. The value of \( w_r \) used for all analyzes was that which provided the minimum PMMA contrast relative to the Xe-ventilated region.
where CNR represents the contrast-to-noise ratio: 

\[ \text{CNR} = \frac{C}{\sqrt{\sigma_d^2 + \sigma_b^2}}, \quad (9) \]

2.4. Optimization of quantum noise properties

2.4.1. Figure of merit

To motivate a figure-of-merit (FOM) for the quantum-noise optimization, we consider the Non-Pre Whitening observer with an Eye filter and Internal noise (NPWEi): (Burgess 1999, Richard and Siewerdsen 2008)

\[ \text{SNR}_{\text{NPWEi}} = \frac{\iiint_{\mathbb{R}^2} E^2(u) C^2 \Delta S^2(u) T^2(u) d^2u}{\left( \iiint_{\mathbb{R}^2} (E^4(u) \text{NPS}_b(u) + N_{\text{int}}) C^2 \Delta S^2(u) T^2(u) d^2u \right)^{1/2}}, \quad (5) \]

where \( u \) [mm\(^{-1}\)] is a 2D vector in spatial-frequency space, \( \iiint_{\mathbb{R}^2} d^2u \) [mm\(^{-2}\)] represents a 2D integral over the Nyquist region, \( C \) represents the contrast of a ventilation defect relative to the Xe-ventilated background, \( \Delta S(u) \) [mm\(^2\)] represents the Fourier transform of the 2D defect profile, the latter of which ranges from 0 to 1, \( T(u) \) represents the 2D modulation transfer function (MTF) of the imaging system, \( E(u) \) represents the frequency response of the human eye (i.e. the eye filter), \( \text{NPS}_b(u) \) [mm\(^2\)] represents the 2D NPS in the Xe-ventilated background region and \( N_{\text{int}} \) [mm\(^2\)] represents the internal noise of the observer. In general, the NPS in equation (5) includes both quantum noise and anatomic noise. In section 2.5 we described measurement of the anatomic NPS and quantum NPS for the clutter phantom described section 2.2. For the quantum-noise optimization, the anatomic NPS is ignored. The eye filter is given by

\[ E(u) = \alpha |u| e^{-c|u|}, \quad (6) \]

where \( |u| = \sqrt{u_x^2 + u_y^2} \) and \( \alpha \) [mm] is an arbitrary constant used to make the eye filter unitless. The variable \( c \) is such that the eye filter maximizes at 4 cycles per degree of angular vision, which corresponds to \( c = 2.2 \) mm at a viewing distance of 50 cm (Burgess 1994, Burgess et al. 1997, Gang et al. 2011). Internal noise was assumed to be uncorrelated white noise and given by (Burgess 1999):

\[ N_{\text{int}} = \eta \text{NPS}_{b,Q}(0), \quad (7) \]

where \( \text{NPS}_{b,Q}(0) \) represents zero-frequency quantum NPS in the background and \( \eta = 0.02 \) is a constant of proportionality calibrated by (Burgess 1999) to observer performance. The NPWEi SNR has been investigated extensively by (Burgess 1999) and more recently by (Richard and Siewerdsen 2008) It predicts observer performance in idealized tasks, for example the two-alternative forced choice detection task, more accurately than prewhitening observers and non-prewhitening observers that do not employ an eye filter nor suffer from internal noise.

For the defect profile, we assume defects with areas that are large relative to the point spread function of the imaging system. In this case, \( \Delta S(u)T(u) \approx \Delta S(u) \). Given that thoracic radiography systems typically have sub-millimeter spatial resolution, this assumption is likely satisfied for defects as small as 1 cm. Xenon ventilation defect percentages of early-stage COPD patients are ~20% of total lung volume (Kirby et al. 2012, Capaldi et al. 2016), which corresponds to a total defect volume ~450 cm\(^3\), so this is a reasonable approximation. With this assumption, as shown in appendix B, equation (5) becomes

\[ \text{SNR}_{\text{NPWEi}} \approx \zeta \gamma \text{CNR}, \quad (8) \]

where CNR represents the contrast-to-noise ratio:

\[ \text{CNR} = \frac{C}{\sqrt{\sigma_d^2 + \sigma_b^2}}, \quad (9) \]

| Parameter                     | Range/Value |
|-------------------------------|-------------|
| Low tube voltage (kV)         | 50–90 kV    |
| Low-energy filter             | 1.2 mm Al   |
| High tube voltage (kV)        | 130–140 kV  |
| High-energy filter            | 1.2 mm Al + 1.1 mm Cu |
| Relative concentration of xenon \((\varepsilon)(\text{Lam et al. 1990, Kong et al. 2014})\) | 0.25–0.75 |
| Xenon area density \((\text{g cm}^{-2})\) | 0.022–0.066 |
| Source to detector distance \((\text{SDD})\) (cm) | 155 |
| Scatter-to-primary ratio \((\text{SPR})\) | ~0.5 |
| Entrance exposure \((\text{mR})\) | 60 |
| Exposure allocation factor, \(f\) | 0.25–2 |

Table 1. List of XeDE imaging parameters for the optimization study.
where $C$ represents the contrast between defect and background ROIs in a XeDE image, and $\sigma_d^2$ and $\sigma_b^2$ represent the pixel variances in defect and background ROIs, respectively. The parameters $\gamma$ and $\zeta$ are given by

$$
\gamma = \frac{\sqrt{2} \sigma_b \int_{N_y} \Delta S^2(u) d^2u}{\left( \int_{N_y} (E^2(u)NPS_b(u) + N_{int}) \Delta S^2(u) d^2u \right)^{1/2}},
$$

and

$$
\zeta = \frac{\int_{N_y} E^2(u) \Delta S^2(u) d^2u}{\int_{N_y} \Delta S^2(u) d^2u},
$$

respectively. Equation (8) shows that, for defects that are much broader than the PSF of the imaging system, the SNR of the NPWii observer is proportional to the CNR through the parameters $\zeta$ and $\gamma$.

We performed a quantum noise optimization under the condition of complete suppression of anatomic noise due to lung parenchyma and ignore bone structures; the effect of bone structures on detectability are addressed in section 2.5. We also assume an x-ray detector with negligible electronic noise, such as that used in this work. Under these conditions, quantum noise is the only noise source and $NPS_b/\sigma_b^2$ (and therefore $\gamma$) is approximately independent of the LE and HE tube voltages and the exposure allocation between LE and HE images, as shown in figure 4. In addition, with the internal noise model given by equation (7), the factor of $N_{int}/\sigma_b^2$ in the denominator of $\gamma$ is independent of $\sigma_b^2$. Therefore, the parameter $\gamma$ is independent of optimization parameters, as is the parameter $\zeta$. We therefore used CNR normalized by patient entrance exposure as a FOM for optimization of the quantum noise properties:

$$
FOM = \frac{CNR}{\sqrt{X_{tot}}},
$$

where $X_{tot}$ [mR] represents the total entrance exposure. Experimental measurement of contrast and noise are described below.

2.4.2. Image contrast

**Experimental method.** Contrast was measured as

$$
C = DE_d - DE_b,
$$

where $DE_d$ and $DE_b$ represent the mean pixel values in defect and background ROIs, respectively. To calculate $DE_d$, four 30 $\times$ 30-pixel ROIs were selected within the defect region; $DE_d$ was calculated as the average of the four ROIs. Similarly, the average of four 30 $\times$ 30-pixel ROIs in the background was used to calculate $DE_b$. The background ROIs were within the PMMA structure supporting the simulated defect. As a result, the amount of PMMA traversed by the beam paths passing through the defect equaled that traversed by beam paths passing through the background.
Theoretical model. Assuming a small signal, $C$ is given by (Basharat et al. 2020)

$$C = \frac{1}{1 + SPR_H} \left( w'_L \mu_{Xe,L} - \mu_{Xe,H} \right) d\lambda,$$

(14)

where $SPR_H$ represents the SPR in the HE image, $w'_L$ represents the tissue-suppression parameter in the absence of patient scatter, and $d\lambda$ represents the thickness of the defect along the x-ray path, and $\mu_{Xe,L}$ and $\mu_{Xe,H}$ [cm$^{-1}$] represent the linear attenuation coefficient of Xe averaged over the LE and HE spectra (Tanguay et al. 2012):

$$\mu_{Xe,L} = \frac{\int_{0}^{\infty} \mu_{Xe}(E)G(E)q_t(E)T_E(E)\,dE}{\int_{0}^{\infty} G(E)q_t(E)T_E(E)\,dE},$$

(15)

where $q_t(E)$ [mm$^{-2}$ keV$^{-1}$] represents photon fluence per unit energy for the LE spectrum, $G(E)$ [quanta/mm$^2$] represents the large-area gain of the x-ray detector for energy $E$ [keV]; $\mu_{Xe,H}$ is given similarly. We assumed a cesium iodide (CsI) flat-panel detector with a 500 $\mu$m thick converter and 151.8 $\times$ 151.8 $\mu$m$^2$ elements and used the complex atom model described by (Hajdok et al. 2006) to calculate $G(E)$. The details on the theoretical calculation of $G(E)$ are described in our previous work (Basharat et al. 2020). In equation (15), $T_E(E) = e^{-\mu_{\text{ideal}}(E)\text{mass}}$ represents the x-ray transmission fraction in the background region of the images. X-ray spectra were computed using an in-house MATLAB script that implements the Tucker et al. algorithm (Tucker et al. 1991).

Assuming a low-contrast defect, as shown in appendix A, $w_L$ is given by

$$w_L = w'_L \frac{1 + SPR_L}{1 + SPR_H},$$

(16)

where $w'_L$ is the tissue-suppression parameter in the absence of scatter and $SPR_L$ represents the SPR for the LE image. The numeric value of the tissue-suppression parameter determines which type of tissue is suppressed from the DE images. In theory, for Al suppression, $w'_L = \mu_{\text{Al,H}}/\mu_{\text{Al,L}}$; for soft-tissue or PMMA suppression, $w'_L = \mu_{\text{PMMA,H}}/\mu_{\text{PMMA,L}}$ and for soft-tissue/Xe look alike XeDE image, $w'_L = (\mu_{\text{PMMA,H}} - \mu_{\text{Xe,H}})/(\mu_{\text{PMMA,L}} - \mu_{\text{Xe,L}})$. As described above, in this work we considered soft-tissue/Xe look-alike images, but we also show soft-tissue suppression images as an example. The bone-suppression weighting factor is presented for completeness. We used the empirical SPRs to compute the theoretical $w_L$ values.

2.4.3 Image noise

Experimental method. The pixel variances in the defect and background ($\sigma_{d}^2$ and $\sigma_{b}^2$) were calculated by averaging the variances of the ROIs that were also used to compute the respective mean pixel values.

Theoretical model. We only considered quantum noise and calculated the quantum noise power spectrum (NPS) [quanta/mm$^2$] for LE and HE images using the models described by (Hajdok et al. 2006) and (Yun et al. 2013). Our implementation and validation of these models is described in our previous work (Basharat et al. 2020). The DE NPS in the background was calculated as (Richard et al. 2005, Richard and Siewerdsen 2007)

$$\text{NPS}_b(u) = \frac{\text{NPS}_{H,L}(u)}{(1 + SPR_H)^2} + w_L^2 \frac{\text{NPS}_{L,H}(u)}{(1 + SPR_L)^2},$$

(17)

where $\text{NPS}_{H,L}(u)$ and $\text{NPS}_{L,H}(u)$ [mm$^2$] represent the LE and HE quantum noise power spectra, respectively, and $\bar{I}_L$ and $\bar{I}_H$ are the average pixel values in the LE and HE images, respectively.

The pixel variance was calculated by integrating the NPS over the Nyquist region in the 2D Fourier domain:

$$\sigma_{b}^2 = \int_{N_y} \text{NPS}_b(u)\,d^2u.$$  

(18)

The pixel variance in the defect ROI was calculated similarly.

2.4.4 Scatter to primary ratio

As noted above, the air gap between the object and detector was chosen to yield an SPR of $\sim$0.5, which is approximately that measured by (Ullman et al. 2005, 2006) for thoracic radiography. The SPR for each tube voltage was measured using the air-gap technique. To this end, the detector was fixed 153 cm from the x-ray source and the chest phantom was placed between the source and the detector. The amount of scatter reaching the detector was controlled by varying the air gap and the FOV of the x-ray beam. We assumed that when the phantom was $\sim$100 cm from the detector and the FOV was $2 \times 2$ cm$^2$ at the detector, that there was approximately no scatter reaching the detector. We therefore calculated the SPR for a given FOV and air gap as

$$\text{SPR} = \frac{I_{S+P} - I_P}{I_P},$$

(19)
where \( F \) represents the average pixel value in a 1 × 1 cm\(^2\) ROI of the image acquired with an air gap of 100 cm and a FOV of 2 × 2 cm\(^2\), and \( F_{1,2} \) represents the average pixel value in the same ROI of an image acquired using realistic air gaps and FOVs. The average pixel values in equation (19) were calculated from the average of 10 images. We fixed the FOV at 16 × 16 cm\(^2\) at the detector and varied the air gap to yield an SPR of approximately 0.5.

2.5. Defect detectability in anatomic noise

Dual-energy images of the clutter phantom were acquired at the parameters that optimized quantum noise properties. We used equation (B.4) to quantify detectability in the presence of anatomic noise due to any residual parenchyma-simulating PMMA cylinders not suppressed by the DE subtraction in addition to the bone-simulating Al slats. This required estimating the NPS and defining a mathematical form for the task function \( \Delta S(u) \).

2.5.1. NPS estimation

While the NPWEi SNR only requires an estimate of the total NPS, we independently measured the quantum NPS, anatomic NPS and total NPS so that we could compare the anatomic NPS of our clutter phantom with the literature. For the quantum NPS, we acquired 50 LE and 50 HE images of the clutter phantom using the exposure parameters that optimized the quantum noise properties and a total exposure of 60 mR. Each set of LE and HE images was used to produce a XeDE image. Each XeDE image was subtracted from another XeDE image to produce 25 difference images. This produced 25 ‘noise-only’ images that did not contain structured background. The background region of each difference image, i.e. that region not containing the defect step-wedge, was divided into ten partially overlapping 256 × 256 element ROIs, yielding a total of 250 ROIs. The 2D NPS was extracted from each ROI. The ensemble quantum NPS was then calculated as the average over all 250 NPS estimates.

For the total NPS, i.e. that containing quantum and anatomic noise, each of the 50 XeDE images was divided into ten partially overlapping 256 × 256 element ROIs, yielding a total of 500 ROIs. The NPS was extracted from each ROI and the ensemble total NPS calculated by averaging over all 500 total NPS estimates.

For the anatomic NPS, i.e. that associated with the Al slats and any residual PMMA clutter, instead of producing 50 XeDE images, we summed the 50 LE images to produce one high-exposure LE image; the same calculation was performed for the HE images. The high-exposure LE and HE images were used to produce a XeDE image with negligible quantum noise. The resulting image was then divided into 256 × 256 element ROIs from which the 2D anatomic NPS was calculated. To compare the anatomic NPS with that reported in the literature for bone-only DE thoracic imaging, we fit an inverse power-law model of the following form to the normalized anatomic NPS:

\[
\frac{\text{NPS}_{\text{an}}(u)}{\text{DE}_b} = \frac{\kappa}{\delta + |u|^\beta},
\]

where \( \kappa \) is typically referred to as the magnitude of anatomic noise and \( \beta \) is the power-law exponent. The parameter \( \delta \) was used to ensure that the anatomic NPS was finite at zero spatial frequency as opposed to the unrealistic situation of infinite NPS at zero frequency and therefore infinite pixel variance. Curve fitting was performed using non-linear least squares in MATLAB. Given that quantum noise was essentially zero in these images, the fit was performed from 0 cm\(^{-1}\) to 25 cm\(^{-1}\). We compared the fit values for \( \kappa \) and \( \beta \) with (Richard and Siewerdsen 2007) who reported \( \kappa \approx 1.5 \times 10^{-5} \) cm\(^{\beta-2}\) and \( \beta \approx 2.2 \) for bone-only DE thoracic radiography.

2.5.2. Task function

For the defect profile, to provide a quantitative complement to the XeDE images with clutter, we modeled cylindrical defects with diameters ranging from 1 cm to 2 cm and thicknesses up to 2 cm. The Fourier transform of the defect profile was then proportional to \( J_1(2\pi R |u|) / (2\pi R |u|) \) where \( J_1 \) is the first-order Bessel function of the first kind and \( R \) is the defect radius (Burgess et al 2001). For the contrast in equation (B.4), we measured the contrast from images acquired without the Al slats, which were treated as noise sources. Assuming contrast was linear in the defect thickness, we scaled the contrast of the 2-cm-thick defect to the desired thickness. We calculated SNR\(_{\text{NPWEi}} \) for defect thicknesses ranging from 0 to 2 cm and then converted SNR\(_{\text{NPWEi}} \) to area under the receiver operating characteristic curve (AUC) assuming Gaussian-distributed data. For both task functions, \( E \) (the eye filter) and \( \Delta S \) were sampled from the negative Nyquist frequency to the positive Nyquist frequency in increments of 0.0257 cm\(^{-1}\), which is one tenth of the sampling interval for the experimental noise power spectra. The NPS was interpolated onto the same grid. This fine grid sampling was used to ensure that the low-frequency content of the eye filter and the signal profile were properly sampled.
3. Results

3.1. Scatter-to-primary ratios

The SPR measurements described in section 2.4.4 resulted in an SPR of approximately 0.5 when the air gap was 8.5 cm. Table 2 lists the resulting SPRs for Xe-enhanced images for Xe concentrations ($c_{\text{Chamber}}$) of 0.25, 0.5 and 0.75 and tube voltage range considered in this study. For all three Xe concentrations, the SPR is approximately independent of tube voltage, and is relatively consistent with the SPRs reported by Ullman et al (Ullman et al 2005, 2006). The values in Table 2 were used in the theoretical calculations of contrast, noise and $X_{\text{CNR tot}}$. All images presented below were acquired using an 8.5-cm air gap.

3.2. XeDE images without clutter

Figure 5 shows XeDE images for three different $w_s$ values for $c_{\text{Chamber}} = 0.75$ and a 60/140 kV pair. The experimental $w_s$ value that produces bone-suppressed, soft-tissue-suppressed and soft-tissue/Xe look-alike XeDE images are 0.43, 0.80 and 0.89. In the bone-suppressed image, the defect contrast is not discernible from the contrast due to PMMA wall. In the soft-tissue suppression, the defect supporting slab is not visible. The defect and PMMA wall appear as an absence of Xe. In the soft-tissue/Xe look-alike, the defect supporting slab is not visible. The PMMA wall enclosing the defect is suppressed.

3.3. Image contrast

Figure 6 shows modeled and measured ventilation defect contrast as a function of LE tube voltage for a HE tube voltage of 140 kV. Results are shown for XeDE for $c_{\text{Chamber}} = 0.25, 0.5$ and 0.75, for $f = 0.5$. Fair agreement is

Table 2. SPR values for Xe-enhanced images.

| Tube voltage [kV] | $c_{\text{Chamber}} = 0.25$ | $c_{\text{Chamber}} = 0.5$ | $c_{\text{Chamber}} = 0.75$ |
|-------------------|-----------------|-----------------|-----------------|
| 50                | 0.50            | 0.52            | 0.56            |
| 55                | 0.49            | 0.51            | 0.54            |
| 60                | 0.48            | 0.49            | 0.52            |
| 65                | 0.47            | 0.48            | 0.50            |
| 70                | 0.47            | 0.48            | 0.49            |
| 75                | 0.47            | 0.47            | 0.49            |
| 80                | 0.47            | 0.47            | 0.49            |
| 85                | 0.47            | 0.47            | 0.48            |
| 90                | 0.47            | 0.47            | 0.48            |
| 130               | 0.47            | 0.47            | 0.46            |
| 135               | 0.48            | 0.48            | 0.47            |
| 140               | 0.48            | 0.48            | 0.46            |
observed between theory and experiment. Contrast is maximized for a LE tube voltage of 55 kV for all three Xe concentrations and (although not shown) for all three HE tube voltages. Although not shown here, contrast is approximately independent of the HE tube voltage. Figure 7 shows ventilation defect contrast as a function Xe concentration. Results are shown for a 55/140 kV pair and \( f = 0.5 \). The experimental contrast increases linearly with Xe concentration, indicating that the linear approximation in equation (14) is accurate for the defect thickness and range of Xe concentrations considered in this work.

### 3.4. Quantum noise

Figure 6 shows modeled and measured values of \( \sqrt{\sigma_b^2 + \sigma_d^2} \) multiplied by \( \sqrt{X_{tot}} \) for soft-tissue/Xe look-alike XeDE for an exposure allocation of 0.5. Noise is plotted as a function of LE tube voltage for a HE tube voltage of 140 kV. For both model and experiment, noise decreases monotonically with increasing LE tube voltage, although the model underestimates image noise at lower tube voltages. Noise increases with Xe concentration due to an associated increase in attenuation. This effect is most pronounced for the lowest LE tube voltage, for which x-ray attenuation is the greatest.

### 3.5. CNR

#### 3.5.1. Optimal tube voltage combination

Figure 6 shows CNR/\( \sqrt{X_{tot}} \) as a function of LE tube voltage for three different Xe concentrations and a HE tube voltage of 140 kV. The experimental CNR/\( \sqrt{X_{tot}} \) is maximized at \( \sim 65 \) kV for \( \epsilon_{\text{Chamber}} = 0.75 \), but optimizes at 55 kV for the other two (lower) concentrations. A similar trend is observed for the theoretical CNR/\( \sqrt{X_{tot}} \), although the theoretical CNR/\( \sqrt{X_{tot}} \) for \( \epsilon_{\text{Chamber}} = 0.75 \) appears to maximize at \( \sim 60 \) kV. Although not shown here, CNR/\( \sqrt{X_{tot}} \) has a weak dependence on the HE tube voltage, and the optimal LE tube voltage was independent of both HE tube voltage and exposure allocation.
3.5.2. Optimal exposure allocation

Figure 8 shows the theoretical and experimental optimizations of the exposure allocation factor. For all tube-voltage combinations and Xe concentrations, for both theory and experiment, $X_{\text{CNR \, tot}}$ is maximized for an exposure allocation of $\sim 0.5$ indicating that $\sim 1/3$ of the total exposure should be allocated to the HE image. While there is some disagreement between the theoretical and experimental $X_{\text{CNR \, tot}}$, the theoretical optimal exposure allocation agrees with that observed experimentally.

3.6. Effect of anatomic noise on detectability

Figure 9 shows LE and HE images of the clutter phantom. As expected, in the LE and HE images, the defects are not visible due to the presence of the PMMA clutter and the Al slats, which simulate lung parenchyma and ribs, respectively. Xenon-enhanced DE images of the clutter phantom acquired at the parameters that optimized quantum-noise properties are shown in figure 10. Both images were acquired using a total exposure of 60 mR. The PMMA clutter has been mostly suppressed, although there is some residual PMMA clutter. Incomplete PMMA clutter suppression is likely because the variations in PMMA thickness traversed by different beam paths exceeds that which can be suppressed using a simple linear subtraction of HE and LE images. Also, as expected, the Al slats are present in the XeDE images and obscure the simulated defects.

Example ROIs used for calculation of the anatomic, quantum and total NPS are shown in figure 11. Also shown are the measure noise power spectra. Note that the sum of the quantum and anatomic NPS is
approximately equal to the total NPS, as it should. Also shown is the power-law fit to the anatomic NPS. The power law fit yielded $\kappa = 1.3 \times 10^{-4} \text{ cm}^2 \beta$, $\beta = 2.70$, $\delta = 0.012 \text{ cm}^2 \beta$ and an $R^2$ value of 1.00.

Figure 12 shows the AUC of the NPWEi observer calculated using equation (B.4). The black lines represent contours at the indicated levels. For $\epsilon_{\text{Lung}} = 0.75$, good AUCs (i.e. 0.8 to 0.9) to excellent AUCs (i.e. $>0.9$) are observed when the defect diameter is greater than 1.3 cm and thickness is 1 cm. When $\epsilon_{\text{Lung}}$ is reduced to 0.5, the defects need to be larger in area and thicker for the NPWEi observer to achieve a good AUC. For example, a defect that is 1.2 cm in diameter and approximately 1.5 cm in thickness corresponds to an AUC of $\sim 0.9$. These trends are qualitatively consistent with the images shown in figure 10.

4. Discussion

This is the first study to experimentally investigate 2D XeDE radiography for imaging of lung function. We optimized image quality under quantum-noise-limited imaging conditions and then, using the optimized technique, estimated defect detectability in the presence of anatomic noise due to lung parenchyma and ribs, which were simulated using a PMMA clutter and Al slats.
Our results show that defect CNR will be maximized when the LE tube voltage is in the range of 55 kV to 65 kV, independent of the HE tube voltage; CNR was approximately independent of HE tube voltage. The optimal kV-pair found here is relatively consistent that reported by (Shkumat et al 2008) for conventional (un-enhanced) DE imaging. Shkumat et al. showed that optimality occurred at 60/130 kV. However, Shkumat et al showed that in soft-tissue-suppressed DE images allocating equal dose to the LE and HE image was optimal. The lower allocation to the HE image found here is likely due to the presence of Xe, which increases attenuation of the LE beam to a greater extent than that of the HE beam; allocating more dose to the LE image compensates for this increased attenuation. The optimal imaging parameters determined experimentally were approximately consistent with those determined using our theoretical models, which means the models can be used for the purpose of optimization under quantum-noise-limited conditions. However, the models tended to underestimate noise (and overestimate CNR) for LE tube voltages less than 70 kV. There could a number of reasons for this discrepancy, including the simplistic incorporation of SPR into our models and that no effort was made to calibrate our models of the gain and NPS to the detector used in our experiments. In addition, while our models may be suitable for optimization of quantum noise properties, they were not used to optimize detectability in the presence of anatomic noise.

Images of the clutter phantom and the corresponding SNRNPWEi calculation illustrated qualitatively and quantitatively, respectively, the effect of anatomic noise on defect detectability. The anatomic NPS followed a power law model with with $\kappa \sim 10^{-4} \text{cm}^2/\beta$ and $\beta \approx 2.7$. Richard et al reported power-law parameters of $\kappa \sim 10^{-5} \text{cm}^2/\beta$ and $\beta \approx 2.2$ for soft-tissue-suppressed DE images (Richard et al 2005). The resulting anatomic noise of the clutter phantom used here is therefore greater than that of Richard et al over the frequency range.
used in this work. As such, relative to the phantom used by Richard et al, results derived from our phantom may overestimate the detrimental effects of anatomic noise on defect detectability. In addition, our parenchyma-simulating PMMA clutter has higher effective density than the lung at expiration. As such, our phantom likely over-represents the magnitude anatomic noise due to lung parenchyma. This is likely one reason why the PMMA clutter was not completely suppressed by the DE subtraction. Again, this would have the effect of overestimating the detrimental effects of anatomic noise on defect detectability.

Despite this shortcoming of our phantom, for a Xe concentration of 75%, our analysis suggests that individual defects as small as approximately 1.3 cm in diameter and 1 cm in thickness correspond to AUCs greater than 0.9, which indicates they would likely be detectable in a two-alternative forced-choice detection task. While reducing the concentration to 50% reduced the AUCs, good AUCs were still observed when the defect diameter and thickness were both greater than 1 cm. This is roughly consistent with our previous model-based analysis which relied on published empirical values of the anatomic NPS for soft-tissue-suppressed DE imaging (Basharat at al 2020). While these SNRs are those for the highly idealized tasks used in observer performance studies, they suggest that XeDE imaging of lung function may enable detecting early-stage COPD, for which 20% of the lung volume appears as a ventilation defect in hyper-polarized xenon MRI (Kirby et al 2012, Capaldi et al 2016). This finding is consistent with previous studies on 2D Xe-enhanced temporal subtraction imaging of lung function that showed sufficient CNR for defect visualization (Bjork and Bjorkholm 1982, Lam et al 1990). In addition, further improvements in defect detectability may be possible by incorporating anatomic noise into the experimental optimization framework. However, even with further optimization, the ribs will continue to obscure the visibility of ventilation defects. Future work will focus on XeDE tomosynthesis for suppression of anatomic noise due to the ribs.

It should also be noted that the Xe concentrations used in this work were higher than those used in XeDE CT, which are ~30% (Park et al 2010, Kong et al 2014), but within the range used by (Lam et al 1990) and (Bjork and Bjorkholm 1982) in their Xe-enhanced 2D radiography studies. It is unlikely that 2D XeDE radiography will enable detecting single defects on the order of one to a few centimeters in diameter at the Xe concentrations used in XeDE CT.

5. Conclusions

We experimentally investigated XeDE radiography for functional imaging of COPD. Our main findings are:

(i) Two-dimensional XeDE chest imaging enables simultaneously suppressing soft tissues from chest images and providing contrast between ventilated and unventilated regions of the lung.

(ii) Numerical models of the contrast-to-noise ratio of ventilation defects yielded approximately the same set of optimal parameters as the experimental study and can therefore be used to optimize 2D XeDE radiography under quantum-noise-limited conditions.

(iii) Under quantum-noise-limited conditions, the contrast-to-noise ratio of ventilation defects is maximized for a tube-voltage combination of approximately 60/140 kV and when approximately one third of the total exposure is allocated to the high-energy image.

(iv) In the presence of anatomic clutter due to lung parenchyma and ribs, two-dimensional XeDE radiography may enable detecting individual ventilation defects as small as 1.5 cm in thickness and 1.5 cm in diameter at Xe concentrations of 50% which may enable detecting early-stage COPD, for which Xe ventilation defects comprise up to 20% of the lung volume.

We conclude that two-dimensional XeDE radiography may enable detection of functional abnormalities associated with early-stage COPD and should be further developed as a low-cost alternative to MRI-based approaches and a low-dose alternative to CT-based approaches.

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Appendix A. Theoretical tissue-suppression parameter

We derive analytic expressions for the DE tissue-suppression parameter and contrast in the presence of x-ray scatter. We consider the two beam paths in figure 13. The contrast between these two beam paths in the DE image is given by

\[ C = - \log \frac{H_d}{H_b} + w_s \log \frac{L_d}{L_b}, \]  

(A.1)

where the subscripts identify the defect and background regions. We assume that the amount of scatter in the background ROI is equal to that in the defect ROI and that the signal difference between defect and background is small such that a first-order Taylor expansion of the logarithms is appropriate. In this case

\[ \log \frac{H_d}{H_b} \approx \frac{H_d^p(1 - \Delta t_{ST}\mu_{H,ST} + (t_d + \Delta t_{ST})\mu_{H,\text{Xe}}) + H_b^s}{H_b^p + H_b^s} - 1, \]  

(A.2)

where the superscripts ‘p’ and ‘s’ indicate primary and scatter, respectively, and we have used

\[ H_d^p \approx H_b^p(1 - \Delta t_{ST}\mu_{H,ST} - t_d\mu_{H,\text{Xe}}) \]  

where \( \Delta t_{ST} \) represents the deviation of the thickness of the soft-tissue relative to the background, \( t_d \) represents the thickness of the defect, and \( \mu_{X,Y} \) represents the linear attenuation coefficient of material Y averaged over spectrum X. The preceding equation can be simplified to

\[ \log \frac{H_d}{H_b} \approx \frac{\Delta t_{ST}\mu_{H,ST} - (t_d + \Delta t_{ST})\mu_{H,\text{Xe}}}{1 + \text{SPR}_H}. \]  

(A.3)

Applying this approximation to the LE logarithm and applying the DE subtraction yields

\[ C \approx \frac{\Delta t_{ST}\mu_{H,ST} - (t_d + \Delta t_{ST})\mu_{H,\text{Xe}}}{1 + \text{SPR}_H} = w_s \frac{\Delta t_{ST}\mu_{L,ST} - (t_d + \Delta t_{ST})\mu_{L,\text{Xe}}}{1 + \text{SPR}_L}. \]  

(A.4)

The \( w_s \) value that suppresses the contrast due to the presence of the soft-tissue deviation is obtained from the solution to the following equation:

\[ \frac{\Delta t_{ST}\mu_{H,ST} - \Delta t_{ST}\mu_{H,\text{Xe}}}{1 + \text{SPR}_H} = w_s \frac{\Delta t_{ST}\mu_{L,ST} - \Delta t_{ST}\mu_{L,\text{Xe}}}{1 + \text{SPR}_L} = 0 \]  

(A.5)

which yields

\[ w_s = \frac{\mu_{L,\text{Xe}}}{\mu_{L,ST} - \mu_{L,\text{Xe}}} \frac{1 + \text{SPR}_L}{1 + \text{SPR}_H}. \]  

(A.6)

Substituting (A.6) into (A.4) yields equation (14).

Appendix B. Model-observer SNR for large defects

The numerator of equation (5) is given by

\[ \text{Signal} = \iint_{\text{Ny}} C^2E^2(u)\Delta^2S^2(u)T^2(u)\,d^2u, \]  

(B.1)

where \( \Delta S [\text{mm}^2] \) is the Fourier transform of the signal profile. We assume \( \Delta S(u)T(u) \approx \Delta S(u) \) and express the signal as
\[
\text{Signal} = \left( \iint_{\Omega_Y} \Delta S^2(u) d^2u \right) \zeta C^2, \tag{B.2}
\]

where \( \zeta \) is given by equation (11) and \( \iint_{\Omega_Y} \Delta S^2(u) d^2u \) is the total power of the defect profile. Applying the same approximation to the denominator of equation (2) yields

\[
\text{Noise} = \left[ \iint_{\Omega_Y} (E^2(u)\text{NPS}_B(u) + N_{int}) C^2 \Delta S^2(u) d^2u \right]^{1/2}. \tag{B.3}
\]

Taking the ratio of the signal to the noise yields

\[
\text{SNR}_{\text{NPWEi}} = \frac{\left( \iint_{\Omega_Y} \Delta S^2(u) d^2u \right) \zeta C}{\left( \iint_{\Omega_Y} (E^2(u)\text{NPS}_B(u) + N_{int}) \Delta S^2(u) d^2u \right)^{1/2}}. \tag{B.4}
\]

Multiplying and dividing the immediately preceding equation by the standard deviation of pixel values in a background ROI and utilizing the approximation \( \sigma_d^2 + \sigma_N^2 \approx 2\sigma_d^2 \) yields equation (8).

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