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Abstract. The detector pixel size can be a severe limitation in x-ray imaging of fine details in the human body. We demonstrate a method of using spectral x-ray measurements to image the spatial distribution of the linear attenuation coefficient on a length scale smaller than one pixel, based on the fact that interfaces parallel to the x-ray beam have a unique spectral response, which distinguishes them from homogeneous materials. We evaluate the method in a simulation study by simulating projection imaging of the border of an iodine insert with 200 mg/ml I in a soft tissue phantom. The results show that the projected iodine profile can be recovered with an RMS resolution of 5% to 34% of the pixel size, using an ideal energy-resolving detector. We also validate this method in an experimental study by imaging an iodine insert in a polyethylene phantom using a photon-counting silicon-strip detector. The results show that abrupt and gradual transitions can be distinguished based on the transmitted x-ray spectrum, in good agreement with simulations. The demonstrated method may potentially be used for improving visualization of blood vessel boundaries, e.g., in acute stroke care. © 2018 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: 10.1117/1.JMI.5.1.013507]

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1 Introduction

In spectral x-ray imaging, information about the material composition of the imaged object is obtained from x-ray attenuation measurement at two or more energies, using energy-resolving detectors or multiple exposures with different x-ray tube voltages or filtration. Spectral imaging is used in both projection radiography^{1,2} and in CT (Ref. 3, pp. 585–610).

X-ray attenuation in a material is described by the linear attenuation coefficient μ . The energy dependence of μ can be approximated as the linear combination of a number of basis functions $\mu(E) = \sum_{i=1}^M a_i \mu_i(E)$, where two terms are commonly used for human tissue, whereas three terms are needed in the presence of a heavy-element contrast agent. By measuring the transmitted flux at multiple energy levels, at least as many as the number of basis functions, the above equation can be solved for the basis coefficients a_i in a procedure referred to as basis material decomposition.^{4,5}

However, as will be demonstrated in Sec. 2, the fact that x-ray attenuation is described by the exponential Beer–Lambert law means that the above-mentioned low-dimensionality is violated in areas, where the projection of the linear attenuation coefficient varies strongly with position. This means that sharp interfaces parallel to the beam have a unique spectral response that can be distinguished from all homogeneous materials for which the low-dimensional approximation applies.

The purpose of this work is to demonstrate theoretically and experimentally how this insight can be used to infer information

about the distribution of the linear attenuation coefficient on a subpixel scale from a spectral projection x-ray image. The proposed method produces images, where steep gradients are enhanced, similar to differential phase contrast imaging⁶ but is sensitive to absorption instead of phase contrast and does not use gratings. The outline of the study is as follows: the mathematical framework of the method is developed in Sec. 2. Section 3 describes how this framework was applied in a simulation study in order to investigate the noise properties and robustness of the method and shows that it can be used to reconstruct a profile of the linear attenuation coefficient on a subpixel scale. (A preliminary version of the latter investigation was presented in Ref. 7.) We then demonstrate experimentally that the method is able to identify abrupt transitions in the attenuation profile of a projection image of a phantom. The results of the simulation and experimental studies are presented in Sec. 4 and discussed in Sec. 5. We also discuss possible future clinical applications of the proposed method.

2 Theory

Before describing the general theory behind the proposed method, we will demonstrate the working principle behind it in a simple situation. Consider an x-ray beam of $N_0(E)$ photons impinging on a volume containing equal amounts of two materials with linear attenuation coefficients μ_1 and μ_2 . If the materials are separated by an interface orthogonal to the beam direction, or if they are homogeneously mixed, the transmitted number of photons is $N_0(E) \exp[-\mu_1(E)t/2 - \mu_2(E)t/2]$, where t is the total path length through the material. If they are separated by an interface parallel to the beam, however,

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the transmitted number of photons is instead $N(E) = N_0(E) \{ \frac{1}{2} \exp[-\mu_1(E)t] + \frac{1}{2} \exp[-\mu_2(E)t] \}$. Since the effective attenuation coefficient is then a nonlinear combination of μ_1 and μ_2 , this observation is referred to as the nonlinear partial volume (NLPV) effect.^{8,9} This expression can be written in the same form as the attenuation of a three-basis combination:

$$N(E) = N_0(E) \exp[-A_1\mu_1(E) - A_2\mu_2(E) - A_{\text{NLPV}}\mu_{\text{NLPV}}(E)], \quad (1)$$

with $A_1 = A_2 = t/2$ and $A_{\text{NLPV}} = 1$, by defining a third basis function, which can be interpreted as the energy dependence of an attenuation coefficient of a fictitious NLPV material:

$$\mu_{\text{NLPV}}(E) = -\ln \left[\frac{1}{2} e^{-\mu_1(E)t} + \frac{1}{2} e^{-\mu_2(E)t} \right] - \mu_1(E) \frac{t}{2} - \mu_2(E) \frac{t}{2}. \quad (2)$$

Note that A_{NLPV} and $\mu_{\text{NLPV}}(E)$ are dimensionless, unlike A_1 , A_2 , $\mu_1(E)$, and $\mu_2(E)$. Equation (1) shows that the effective linear attenuation coefficient of the volume can be expressed as a three-basis combination, where the third (NLPV) basis coefficient will be nonzero only if the attenuation is inhomogeneous across the x-ray beam cross-section. Therefore, basis material decomposition can be used to generate a map of the NLPV basis coefficient, where sharp interfaces parallel with the beam are highlighted and thereby distinguishable from gradual transitions.

We now turn to developing a mathematical description of this method that applies to arbitrary attenuation profiles. Consider a rectangular detector pixel irradiated orthogonally by a parallel x-ray beam, which is a good approximation if the x-ray source is small and located far from the detector (Fig. 1). Assume that the linear attenuation coefficient μ in the imaged volume can be expressed as a linear combination of two basis functions, $\mu(E, x, y, z) = a_1(x, y, z)f_1(E) + a_2(x, y, z)f_2(E)$, and define the basis projections $A_j(x, y) = \int a_j(x, y, z) dz$ for $j = 1, 2$.

If the detector is energy-resolving with M energy bins, and S_i denotes the sensitivity function giving the expected number of counts in energy bin i for every incident photon with energy E , the number of expected counts in energy bin i is as follows:

$$\lambda_i = \frac{1}{D} \iint_D \left\{ \int_0^{\text{kVp}} N_0(E) S_i(E) \times \exp \left[- \sum_{j=1}^2 A_j(x, y) f_j(E) \right] dE \right\} dx dy, \quad (3)$$

Fig. 1 Parallel x-rays impinging on a detector pixel.

where D denotes the detector pixel area and $N_0(E)$ is the total number of photons per differential energy, which would impinge on the detector in the absence of any object in the beam. Letting an overline denote average over the detector area: $\overline{g(x, y)} = \frac{1}{D} \iint_D g(x, y) dx dy$, this can be written as follows:

$$\lambda_i = \int_0^{\text{kVp}} N_0(E) S_i(E) \exp \left[- \overline{\sum_{j=1}^2 A_j(x, y) f_j(E)} \right] dE. \quad (4)$$

We would like to use this forward model to infer some information about the space-variant basis projections $A_j(x, y)$. Since it is a general principle in statistical estimation theory that estimation uncertainty increases with the number of estimated parameters, we want a small number of scalar parameters describing $A_j(x, y)$. Therefore, we select two functions $A_1^b(x, y)$ and $A_2^b(x, y)$ and construct a third basis function f_{NLPV} from these as follows:

$$f_{\text{NLPV}}(E) = -\ln \exp \left[- \sum_{j=1}^2 A_j^b(x, y) f_j(E) \right] - \overline{A_1^b} f_1(E) - \overline{A_2^b} f_2(E), \quad (5)$$

where $\overline{A_j^b}$ is the average of $A_j^b(x, y)$ over the detector pixel. Equation (4) then gives, with $A_j(x, y) = A_j^b(x, y)$ for $j = 1, 2$,

$$\lambda_i = \int_0^{\text{kVp}} N_0(E) S_i(E) \exp \left[- \sum_{j=1}^2 \overline{A_j^b} f_j(E) - f_{\text{NLPV}}(E) \right] dE. \quad (6)$$

This suggests replacing the forward model [Eq. (4)] by

$$\lambda_i = \int_0^{\text{kVp}} N_0(E) S_i(E) \times \exp \left[- \sum_{j=1}^2 A_j f_j(E) - A_{\text{NLPV}} f_{\text{NLPV}}(E) \right] dE, \quad (7)$$

where our change of notation from $\overline{A_j^b}$ to A_j indicates that these are now viewed as parameters to be estimated.

In this way, Eq. (4) has been replaced by a function of three scalar parameters: A_1 and A_2 , which capture the spatial average of each basis function, and A_{NLPV} , which captures the deviation from homogeneous distributions. Note that this expression has the same form as the forward model normally used in projection-based basis material decomposition. If $A_1(x, y)$ and $A_2(x, y)$ coincide with the functions $A_1^b(x, y)$ and $A_2^b(x, y)$, Eq. (7) describes the forward model exactly with $A_1 = \overline{A_1^b}$, $A_2 = \overline{A_2^b}$, and $A_{\text{NLPV}} = 1$, and the same holds with $A_{\text{NLPV}} = 0$ if $A_1(x, y)$ and $A_2(x, y)$ are both constant with respect to x and y . Otherwise, Eq. (7) is an approximation of Eq. (4). The method used in this study builds on the assumption that A_{NLPV} can nonetheless be used as an indicator of the deviation from homogeneity, at least if $A_1(x, y)$ and $A_2(x, y)$ are relatively similar to the functions $A_1^b(x, y)$ and $A_2^b(x, y)$ used to construct f_{NLPV} . The validity of this assumption will be investigated in Sec. 3.1.1.

Again, A_{NLPV} is defined to be dimensionless since it does not measure a physical thickness but instead it quantifies the deviation from homogeneity across the pixel. Here, we have chosen to define $f_{\text{NLPV}}(E)$ such that the magnitude of A_{NLPV} will typically assume values between 0 and 1, but if desired, A_{NLPV} could be made to assume another range of values by multiplying the definition of $f_{\text{NLPV}}(E)$ in Eq. (5) by a constant scale factor. This will not affect the results of basis material decomposition in any other way than by rescaling the A_{NLPV} values, but it could be useful to increase the convergence rates of some numerical algorithms.

Given measured counts $N_1, \dots, N_M$ each energy bin, the maximum likelihood method can be used to estimate the basis projections A_j , $j = 1, 2, 3$ with the maximum likelihood method by minimizing the negative log-likelihood function:¹⁰

$$l(A_1, A_2, A_{\text{NLPV}}) = \sum_{i=1}^M \lambda_i(A_1, A_2, A_{\text{NLPV}}) - N_i \ln \lambda_i(A_1, A_2, A_{\text{NLPV}}). \quad (8)$$

In the present study, we have solved this optimization problem using the Newton method with backward line search.¹¹

This results in estimated values of A_1 and A_2 , which are, as usual, interpreted as the average projected thickness of the two basis materials over the detector pixel area, and A_{NLPV} , which measures the deviation from homogeneity within the extent of the detector pixel. This means that a large A_{NLPV} value corresponds to sharp transition. This can be used to generate edge-enhanced images without applying a high-pass filter.

The reader should note that the NLPV basis function is constructed from a mathematical model of the imaging system for specific assumed spatial distributions of $A_1^b(x, y)$ and $A_2^b(x, y)$ across the pixel. Once the basis function is constructed in this way, it can be used to make basis material decomposition of measured data. We thus do not make any assumption that $A_1^b(x, y)$ and $A_2^b(x, y)$ or their average values $\bar{A}_1^b$ and $\bar{A}_2^b$ are known a priori, only that we are able to guess a profile shape that is similar enough to the measurement to allow the constructed NLPV basis function to capture the measured inhomogeneity.

In addition to enabling sharp and gradual transitions to be distinguished, the NLPV basis image allows the slope of the transition to be inferred, so that the attenuation profile can be approximately reproduced on a subpixel scale. To see this, consider the iodine profile depicted in Fig. 2. A conventional imaging system measures the average iodine thickness across the extent of each pixel and estimates the iodine thickness profile by interpolation between the pixel midpoints. If an NLPV basis image is available, however, the imaging system can use the fact that A_{NLPV} is large in the pixel at the transition to make a more informed guess about the true shape of the profile, i.e., interpolate the drop as a sharp edge. The conventional imaging system, on the other hand, does not have any means of distinguishing between sharp and gradual transitions and therefore cannot choose to interpolate a transition as a sharp drop without being wrong in other cases, where the transition is smooth. This means that the NLPV basis image can be used to decrease the width of the edge-spread function of the system to less than the pixel size, i.e., achieve super-resolution.

Fig. 2 Conceptual illustration of the principle for resolution improvement using the NLPV effect. The best guess of the image profile from ordinary x-ray measurements is done through linear interpolation through the measurement points (black solid curve), but this does not reproduce the ground truth (red dash-dot curve) accurately. In the proposed method, the NLPV effect is used to measure the slope in the center pixel, thereby yielding a higher-resolution image of the step (blue dashed curve).

3 Materials and Methods

3.1 Simulation Study

To study the theoretically achievable performance of the method, we simulated transmission through the edge of an iodinated contrast agent insert embedded in soft tissue. The geometry of the edge was assumed to be such that the projected thickness of an iodinated contrast agent is a piecewise linear profile in the x direction and constant along the y direction (both the x and y directions are transverse to the beam). The path length of soft tissue and iodine solution was kept constant at 120 mm. This situation resembles imaging of a carotid artery in the human neck, which has a typical diameter of around 6 mm.

The simulation geometry is shown in Fig. 3. The transmitted photons were measured with a single simulated pixel, measuring $0.5 \text{ mm} \times 0.5 \text{ mm}$ in the object plane (corresponding to $1 \times 1 \text{ mm}^2$ at the detector with a magnification factor of 2). The pixel is located between $x = 0 \text{ mm}$ and $x = d = 0.5 \text{ mm}$ in the used co-ordinate system. The detector pixel was modeled as an ideal energy-resolving detector, with unity detection efficiency, perfect energy resolution, 1 keV wide energy bins covering the range from 20 to 120 keV. An 120-kVp 7 deg W anode x-ray tube spectrum¹² with 7-mm Al filtering, discretized in steps of 0.1 keV, was simulated. Linear attenuation coefficients and tissue

Fig. 3 Piecewise linear iodine path length profile $A_2(x, y)$ within a single detector pixel of width d . Δx is the width of the transition and x_c is the center point. $A_2(x, y)$ is assumed to be constant with respect to the orthogonal position, y .

compositions were obtained from the National Institute of Standards and Technology¹³ and the International Commission on Radiation Units and Measurements.¹⁴ The space-variant transmitted spectrum was simulated by subdividing the pixel into 100 subpixels along the x direction. The piecewise linear iodine profile is parameterized by the width Δx of the linear transition region, the projected iodine concentration thickness in the background before the transition A_2^{bg} (equal to the height of the contrast agent thickness step since the thickness is 0 mm on the other side of the transition), and the position x_c of the center of the linear transition region relative to the pixel center (see Fig. 3).

3.1.1 NLPV component robustness

As we noted in Sec. 2, the addition of an NLPV basis component to the set of basis vectors does not describe transmission through an inhomogeneous pixel except in very special cases, and therefore, we investigated the robustness of the methods to variations in geometry. To this end, we generated an NLPV basis function for one fixed geometry and carried out three-material basis decomposition with two ordinary basis functions (soft tissue and 40 mg/ml iodinated contrast agent) and one NLPV basis function, for different piecewise-linear iodine profile shapes. This was accomplished by minimizing the negative log-likelihood [Eq. (8)]¹⁰ using the Newton method, with the sum taken over 1-keV wide energy bins from 20 to 120 keV.

To define the NLPV basis function, we used a centered sharp step transition ($\Delta x = 0$, $x_c = 0.25$ mm) from $A_2^{\text{bg}} = 5$ mm to 0 mm of 40-mg/ml iodinated contrast agent, embedded in 120-mm soft tissue. We then simulated the x-ray transmission through piecewise linear profiles for different choices of the parameters x_c (from 0 to 0.5 mm in steps of 0.0625 mm) and A_2^{bg} (from 0 to 10 mm in steps of 1 mm) for constant $\Delta x = 0$ mm. Poisson noise was simulated, and the basis projections in each of the three basis materials were estimated from the Poisson counts by minimizing Eq. (8). The number of prepatient photons per measurement was 2.04×10^8 , corresponding to ~ 100 mAs at 1000 mm source-to-detector distance for a commercial CT scanner (GE VCT) operated at 120 kVp with a medium bowtie filter.¹⁵ The results were averaged over 1000 noise realizations. To investigate the influence of the gradient steepness on the results, a similar simulation was also made for different Δx (0 mm to 1 mm in steps of 0.125 mm) at fixed $x_c = 0.25$ mm and $A_2^{\text{bg}} = 5$ mm. Furthermore, to investigate the robustness of the method to model errors, the latter investigation was repeated with the same transition geometry but with iodine concentrations of 20 and 100 mg/ml used when generating simulated projection data. Similarly, we investigated replacing the iodine contrast with bone or replacing the surrounding soft tissue with water or adipose tissue. For all these investigations, we used soft tissue and a 40 mg/ml iodinated contrast agent as basis materials together with the NLPV basis function constructed from the sharp transition between these materials as described above.

3.1.2 NLPV component noise

To investigate the achievable noise properties of an NLPV basis image, we simulated three-material basis decomposition with soft tissue, iodinated contrast agent, and NLPV as basis functions. In each case, the basis decomposition was evaluated for the same geometry as was used to generate the basis function, i.e., it

was assumed that there is no model error. The transmission was simulated for a parallel x-ray beam passing across a piecewise linear iodine contrast agent profile, Poisson distributed counts were simulated for the resulting measurements, and basis material decomposition was performed, in the same way as described in Sec. 3.1.1. The variance of the resulting A_{NLPV} was calculated from 1000 noise realizations. This simulation was repeated for different numbers of prepatient photons per detector pixel (10^6 , 10^7 , 10^8 , and 10^9), iodine concentrations (20, 40, 100, and 200 mgI/ml), transition widths Δx (0 to 1 mm in steps of 0.25 mm), step heights A_2^{bg} (1, 2.5, 5, and 10 mm), and center positions x_c (from 0.025 to 0.475 mm). For these simulations, a 120-kVp spectrum and an ideal spectral response were used.

The dependence on x-ray spectrum, scatter, and detector response was investigated by repeating these simulations for 80, 100, and 120 kVp with an ideal detector model, and for 120 kVp with scatter and nonideal detector models. These simulations were made with 40 mgI/ml, 10^6 , 10^7 , 10^8 , and 10^9 prepatient photons/detector pixel and a steep, centered transition ($A_2^{\text{bg}} = 5$ mm, $\Delta x = 0$ mm, and $x_c = 0.25$ mm). Scattering in the object was simulated by adding a constant number of background counts to the registered spectrum, corresponding to a scatter-to-primary ratio of 10% on the detector and with a spectrum similar to a spectrum transmitted through 120-mm soft tissue but convolved with a Gaussian of standard deviation 7 keV (with an upper cut-off at 120 keV) to simulate the spectral broadening due to energy loss in scattering events. Since scatter from the object is slowly varying in space, the number of scatter counts was taken to be constant across the pixel, i.e., independent of the amount of iodine contrast traversed by the x-ray beam. This is consistent with a CT detector with a one- or two-dimensional antiscatter grid, which gives scatter-to-primary ratios of 2% to 20% on the detector, with an energy distribution of scatter similar to the primary distribution.¹⁶

Furthermore, a simulation without scatter but with an imperfect energy response was done using the nonideal detection efficiency and energy response of the silicon-strip detector, as described in the Appendix. This energy response was used for one simulation with 1 keV wide energy bins from 5 keV to the maximum x-ray energy, and one simulation with 8 bins, where the lowest threshold is at 5 keV and seven higher thresholds are selected to give equally many counts in each bin. In addition, the silicon response function was combined with a simple model of pulse pileup, by assuming that a fraction of the photons is missed by the detector and that the deposited energy of each of these photons is summed together with the deposited energy of another photon, giving a detected number of counts $N = N_{\text{in}}/(1 + \beta)$, where N_{in} is the incident number of counts, and a registered spectral distribution $f(E) = \frac{2N - N_{\text{in}}}{N} f_{\text{in}}(E) + \frac{N_{\text{in}} - N}{N} f_{\text{in}}(E) * f_{\text{in}}(E)$, where $*$ denotes convolution and $f_{\text{in}}(E)$ is the distribution of photon energies in the absence of pileup, normalized to 1. We use $\beta = 0.25$, which means that the detector is operating at 25% of its saturation count rate, and we use this value for all photon fluences, i.e., we assume that the exposure time is varied while the photon fluence rate is kept fixed. This corresponds to the nonparalyzable model for pileup count statistics and a delta-pulse model for spectral distortion,¹⁷ although with higher-order pileup neglected. Note that our pileup model is also simplified in the sense that the counts at different energies are assumed to be Poisson distributed and independent.

3.1.3 Subpixel resolution imaging

We investigated the possibility of using the NLPV effect to improve spatial resolution by simulating projection imaging of a 5-mm thick iodine insert ($A_2^{\text{bg}} = 5$ mm) containing 200 mg/ml iodinated contrast agent. Although 200 mg/ml iodine is a very high concentration, it can occur in interventional procedures when the contrast agent is injected intravenously at the site of the imaging. The incident fluence was assumed to be 1.22×10^6 prepatient photons/detector pixel, corresponding to 0.6 mAs and 1 m source-to-detector distance in a commercial CT scanner.¹⁵ This is comparable to the dose in one single angular view in a CT image.

The basis materials used for basis decomposition were soft tissue, 200 mg/ml iodine solution, and the NLPV basis function. The NLPV basis function was constructed according to Eq. (5) for a beam half of which passes through 5 mm 200 mg/ml iodine solution and half of which passes through 0 mm iodine, with a sharp transition in the center of the pixel.

We will now describe how we investigated the possibility of using the NLPV component to reproduce piecewise linear iodine thickness profiles on a subpixel scale.

A look-up table of basis projections ($A_1, A_2, A_{\text{NLPV}}$) was generated by performing basis material decomposition for different piecewise linear edge profiles of $A_2^{\text{bg}} = 5$ mm thick 200 mg/ml iodine inserts in 120-mm soft tissue for different transition widths Δx (0 to 3 mm in steps of 0.0125 mm) and transition center points x_c (from -1.5 to 2 mm in steps of 0.0125 mm). A_1 , A_2 , and A_{NLPV} were obtained by minimizing Eq. (8) with N_i replaced by the expected number of counts, i.e., noise-free data were assumed.

In this way, a mapping from the space of $(\Delta x, x_c)$ -values to the set of basis projections ($A_1, A_2, A_{\text{NLPV}}$) is obtained. Of these three basis projection components, only A_2 (the iodine basis projection) and A_{NLPV} contain information about the iodine profile shape. By inverting the mapping $(A_2, A_{\text{NLPV}}) = f(\Delta x, x_c)$, Δx and x_c can be obtained from A_2 and A_{NLPV} . (The invertibility of f is demonstrated in Secs. 4.1.3 and 5.) The inversion of the mapping was accomplished by minimizing $\|(A_2, A_{\text{NLPV}}) - f(\Delta x, x_c)\|$ with respect to $(\Delta x, x_c)$ under the conditions that $\Delta x \geq 0$ and that at least some part of the transition region (or one of its endpoints) lies within in the studied pixel. Here, $\|\cdot\|$ denotes the two-norm of a vector.

To evaluate this method, transmission through piecewise linear iodine profiles was simulated for $A_2^{\text{bg}} = 5$ mm and for

different Δx (0 to 0.5 mm in steps of 0.0625 mm) and x_c (0.0625 to 0.4375 mm in steps of 0.025 mm). In contrast to the look-up table, which was generated without noise, Poisson noise was included in this simulation. Basis projections were estimated by minimizing Eq. (8), and $(\Delta x, x_c)$ was estimated from (A_2, A_{NLPV}) by the procedure described above. This was done with the `fmincon` function in MATLAB (The Mathworks, Inc., Natick, Massachusetts), whereby linear interpolation was used to obtain values of $f(\Delta x, x_c)$ between the simulated data points.

To determine the spatial resolution of the method, the true profile was convolved with a Gaussian point-spread function with the standard deviation as a free parameter. By iteratively searching for the Gaussian standard deviation that would give the best agreement between the convolved profile and the edge-spread function obtained by averaging 1000 simulations, an RMS resolution could be established.

3.2 Experimental Study

To demonstrate the method experimentally, we used an energy-resolving x-ray detector to acquire a projection image of a phantom resembling a carotid artery in the human neck (Fig. 4), made of a 120-mm diameter cylinder of polyethylene (PE) with a 6-mm diameter hole in the center filled with an iodinated contrast agent (200 mg/ml I). PE was chosen since its attenuation is similar to that of soft tissue. A computer-simulated image profile of the same phantom was also computed for comparison.

3.2.1 Experimental setup

The x-ray imaging was done in a table-top laboratory setup for projection imaging, consisting of an x-ray tube (at position $z = 0$ m), a 0.5-mm wide vertical precollimator slit at $z = 0.3$ m, the imaged phantom at $z = 0.5$ m, and a 1-mm wide vertical postcollimator slit at $z = 0.8$ m followed by an antiscatter grid consisting of 32-mm long vertical tungsten lamellae (0.1-mm thick with 1-mm spacing) and a detector at $z = 0.9$ m. Here, the z axis extends from its origin at the focal spot of the x-ray source in the direction toward the detector, i.e., along the x-ray beam direction. The detector used is a photon-counting silicon strip detector, which registers each incoming photon in one of eight energy bins by comparing its deposited energy to eight threshold levels. It has an active

Fig. 4 (a) The phantom imaged in the experiment. It consists of a 120-mm diameter PE cylinder with a 6-mm diameter hole in its center, filled with the iodinated contrast agent (200 mg/ml I). (b) Sketch of the imaging setup. A single detector module, comprising a vertical linear array of 50 detector pixels, is used. To obtain a two-dimensional projection image, the phantom is translated across the field-of-view in steps. The pre- and postcollimator slits and antiscatter grid are not shown in the figure.

absorption length of 30.4 mm and each detector pixel is subdivided into nine depth segments along the beam direction. This detector is described in Ref. 18 and a similar detector module, with a larger number of depth segments, has been characterized in detail previously.^{19,20} The detector was mounted with its edge toward the source (Fig. 4), forming a linear vertical array of 50 detector pixels, each 0.4 mm high and 0.5 mm wide. The lowest energy threshold was set to 16 to 20 keV, different in different depth segments (see Table 1), and the higher thresholds were set to, on average, 24, 36, 41, 50, 55, 63, and 70 keV. The x-ray tube (MXR-160HP/11 by Comet, Flamatt, Switzerland) was operated at 120 kVp and 6.5-mA tube current with a 0.4×0.4 mm² focal spot, and the beam was filtrated through 0.8-mm Be, 2-mm Al, and 7.5-mm glass. The measured count rate behind the phantom outside the iodine insert was 2×10^4 cps.

A two-dimensional projection image of the iodine insert was obtained by scanning the phantom across the x-ray beam in 99 steps with 0.125 mm in between, and at each position data was acquired during 22.5 s (Fig. 4). Since the detector module has 50 detector pixels in the vertical direction, such a scan yields a projection image with 50 rows and 99 columns, with a pixel pitch of 0.4 mm vertically and an effective pixel pitch of 0.125 mm horizontally. Note, however, that the horizontal pixel width (0.5 mm) is larger than the horizontal step size. This scanning procedure was repeated eight times to get more statistics. Inhomogeneities in the detector response across the width of the sensor can cause the measured signal to differ depending on whether the iodine is on the right or left side of the interface, as seen from the detector toward the source in Fig. 4. To average out this effect, four of the eight scans were made with the phantom rotated 180 deg around the vertical axis and the corresponding images were flipped digitally during postprocessing. As these images were averaged after the basis material decomposition (See Sec. 3.2.3), the result of this procedure is an image showing the average of the two possible detector orientations relative to the phantom. The total current–time product for the used image data was 2.8 As for each point in the imaged area. Note that this experiment has not been optimized for high dose efficiency and short acquisition time, and both could be improved for a clinical application.

3.2.2 Calibration

In conjunction with the imaging, we performed calibration measurements of homogeneous thicknesses of PE and the 200-mg/ml iodinated contrast agent. The transmission through each of the 32 thickness combinations of 0 to 140 mm PE in steps of 20 mm and 0 to 6 mm iodinated contrast agent in steps of 2 mm was measured, during 225 s each. The iodine solution thickness was varied by placing three glass cuvettes in the x-ray beam, and letting a variable number of them contain

Fig. 5 Simulation geometry for a parallel beam passing the edge of a cylindrical hole filled with the iodinated contrast agent.

iodine solution and letting the rest contain air, hereby giving a variable iodine thickness as well as the 7.5-mm glass prefiltration mentioned above. This was done once before and once after the acquisition of image data, and the correction factors used in the basis decomposition were interpolated between these two datasets. To compensate for fluctuations in the x-ray flux, we performed air scans for every tenth translation step during imaging and for each of the thickness combinations in the calibration measurement. These measurements were used to compensate for count rate fluctuations, by multiplying the measurements with a correction factor for each energy bin.

3.2.3 Data processing

Using a combination of a computer model of the detector and correction factors derived from the calibration measurements, a forward model mapping basis projections A_1 , A_2 , and A_{NLPV} to expected registered counts $\lambda_1, \dots, \lambda_8$ in each energy bin were developed. For details about how the forward model was constructed, see the Appendix. Three basis functions were used: the linear attenuation coefficients of PE, iodine contrast agent, and an NLPV basis function. The NLPV basis function was constructed to give $A_{NLPV} = 1$ for the case of a beam passing through the edge of a 6-mm diameter cylinder of 200 mg/ml iodine contrast agent (Fig. 5) positioned such that the cylinder covers 75% of the beam width, for a 0.3-mm wide beam (the detector pixel width of 0.5 mm downsampled by the geometric magnification factor 1.65). The PE basis projection used for this case was 120 mm minus the path length through the cylindrical hole.

From the measured number of counts in the eight energy bins, the basis projections $A_i = \int a_i dl$, i.e., the line integrals of the basis coefficients along the x-ray beam, were calculated with the maximum likelihood method [by minimizing Eq. (8)]. The projection images resulting from the eight consecutive scans were processed individually in this way, and subsequently averaged.

Table 1 Estimated energy thresholds in keV averaged over all detector pixels and groups of three depth segments. The standard deviation of the estimated threshold locations among the channels used for each average varies between 1.3 and 3.6 keV for the different entries in the table.

Threshold	1	2	3	4	5	6	7	8
Depth segment 1 to 3	16	24	36	42	51	56	64	71
Depth segment 4 to 6	21	24	36	41	51	55	63	70
Depth segment 7 to 9	18	24	35	41	50	55	63	70

To compare the NLPV image to a projection image, where the location of the iodine insert is visible, synthetic monoenergetic images^{5,21} were calculated from the basis images as $\int \mu(E)dl = A_1 f_1(E) + A_2 f_2(E) + A_{\text{NLPV}} f_{\text{NLPV}}(E)$, where $E = 60$ keV was selected here. For comparison, a

simulation of the same imaging situation was also calculated, with the same parameters but with a point x-ray source. The simulation that used the same forward model was used as the experimental image, including the correction factors.

Fig. 6 Mean estimated basis projection A_{NLPV} when the measurement geometry differs from the geometry used to define the NLPV basis function. The NLPV basis function was defined for a 40 mg/ml contrast agent, $A_2^{\text{bg}} = 5$ mm, $x_c = 0.25$ mm, and $\Delta x = 0$ mm. A 120 kVp spectrum and an ideal detector model were used. The plots show A_{NLPV} variation with (a) contrast thickness step height A_2^{bg} and (b) transition center position x_c .

Fig. 7 Mean estimated basis projection A_{NLPV} when the iodine profile steepness and the material composition differ from the situation used to define the NLPV basis function. The NLPV basis function was defined for the 40 mg/ml contrast agent, $A_2^{\text{bg}} = 5$ mm, $x_c = 0.25$ mm, and $\Delta x = 0$ mm. A 120-kVp spectrum and an ideal detector model were used. (a) A_{NLPV} variation with transition width Δx for different iodine concentrations. (b) A_{NLPV} variation with transition width Δx for different materials in the insert and in the surrounding phantom. The insert contains 40 mg/ml I in all cases except one where it contains bone.

4 Results

4.1 Simulation Study

4.1.1 NLPV component robustness

Figures 6 and 7 show the robustness of the average estimated A_{NLPV} in the presence of a model error. Figure 6 shows A_{NLPV} when the transition center position x_c and transition thickness deviate from the values used to construct the NLPV basis function. Figure 7 shows A_{NLPV} as a function of transition width Δx when the basis function was constructed for $\Delta x = 0$. It also shows the effect of model errors, with plots of A_{NLPV} when the projections were generated for different iodine concentrations and material combinations than the ones used for the NLPV basis construction and material decomposition.

4.1.2 NLPV component noise

The variance of the estimated NLPV basis projection, for a 120-kVp spectrum and an ideal detector, is shown in Fig. 8, for different incident photon fluxes, iodine concentrations, transition widths, iodine profile step heights, and transition center points. In each case, the NLPV basis function was generated for the same geometry that was used to evaluate the variance. Also shown in this figure is the approximate noise level $\sigma^2(A_{\text{NLPV}}) = 0.04$ mm below which the NLPV component can be detected by looking at a single detector pixel. This noise level corresponds to a signal-difference-to-noise ratio of 5, since $A_{\text{NLPV}} = 1$ by definition for the geometry used to define the basis function. Figure 9 shows plots of the estimated NLPV component for different kVp and nonideal detector models.

Fig. 8 Variance of the estimated basis projections A_{NLPV} resulting from basis material decomposition with a 120-kVp spectrum and an ideal detector. For each data point, the NLPV basis function was constructed for the same case as was used in the evaluation. The dashed line is the highest noise level that allows detection of the NLPV basis component in a single pixel. (a) Variance as a function of prepatient count rate for different iodine concentrations, for $A_2^{\text{bg}} = 5$ mm, $\Delta x = 0$ mm, and $x_c = 0.25$ mm. (b) Variance as a function of prepatient count rate for different transition widths Δx , for 40 mg/ml I, $A_2^{\text{bg}} = 5$ mm, and $x_c = 0.25$ mm. (c) Variance as a function of prepatient count rate for different transition step heights A_2^{bg} , for 40 mg/ml I, $\Delta x = 0$ mm, and $x_c = 0.25$ mm. (d) Variance as a function of the transition center point x_c for different transition prepatient count rates, for 40 mg/ml I, $A_2^{\text{bg}} = 5$ mm, and $\Delta x = 0$ mm.

Fig. 9 Variance of the estimated basis projections A_{NLPV} resulting from basis material decomposition, for different kVp and energy response functions. In each case, 40 mg/ml I was used and the NLPV basis function was constructed for the same case as was used in the evaluation. The dashed line is the highest noise level that allows detection of the NLPV basis component in a single pixel. (a) Variance as a function of prepatient count rate for different kVp, for $A_2^{\text{bg}} = 5$ mm, $\Delta x = 0$ mm, and $x_c = 0.25$ mm. (b) Variance as a function of prepatient count rate in the presence of scatter and imperfect spectral response, for $A_2^{\text{bg}} = 5$ mm, $\Delta x = 0$ mm, and $x_c = 0.25$ mm. Si response: response function modeling the silicon strip detector.

4.1.3 Subpixel resolution imaging

The contour plot in Fig. 10 illustrates the generated look-up table by showing all three basis projections as functions of the center position x_c and transition width Δx . Figure 11 shows five samples of the reconstructed iodine profiles for different noise realizations and for three different profile shapes. Figure 12 shows the average of the estimated profiles for 1000 noise realizations for nine different profile shapes. The RMS spatial resolution of the proposed method is plotted as a function of the profile shape parameters x_c and Δx in Fig. 13.

4.2 Experimental Study

The forward model of the imaging system is shown in Fig. 14, as the expected number of registered counts in each measurement

(lasting 22.5 s) for different combinations of 0 to 140 mm soft tissue and 0 to 6 mm iodinated contrast agent. Both the uncorrected mathematical model (dashed lines) and the model corrected by calibration measurements (solid lines) are plotted.

To verify that the used basis material decomposition method is accurate, the basis projections profiles A_1 (PE) and A_2 (iodine solution), measured across the iodine insert, are plotted in Fig. 15. In this figure, the nominal basis projections according to the phantom drawing are also shown, for comparison. As further verification of the ability of the used forward model to describe the imaging setup accurately, the measured count profile in each energy bin is shown in Fig. 16 together with the profiles of expected counts predicted by the forward model from the phantom drawing and from the basis projections fitted

Fig. 10 Basis projections ($A_1, \dots, A_{\text{NLPV}}$) resulting from basis material decomposition of noise-free data, when the beam passes through 120 mm soft tissue and a linear path-length gradient from 5 to 0 mm of 200 mg/ml iodine in water, with parameters x_c and Δx . A 120-kVp spectrum and an ideal detector model were used.

Fig. 11 Estimated iodine profiles A_2 within a single detector pixel, for five different noise realizations. The beam passes through 120-mm soft tissue and a linear path-length gradient, from 5 to 0 mm, of 200 mg/ml iodine in water. Also plotted is the ground truth profile. A 120-kVp spectrum and an ideal detector model were used. (a) Abrupt transition near left border. (b) 0.25 mm wide transition near pixel center. (c) 0.50 mm wide transition near right border.

Fig. 12 Average of iodine profiles A_2 within a single detector pixel. The beam passes through 120 mm soft tissue and a linear path-length gradient, from 5 to 0 mm, of 200 mg/ml iodine in water. Also plotted is the ground truth profile. (a) Transitions centered near left border. (b) Transitions centered near pixel center. (c) Transitions centered near right border.

to data through basis material decomposition, i.e., from both of the basis projection profiles, as shown in Fig. 15.

Figure 17 shows the NLPV basis image together with a synthetic monoenergetic image for comparison. Figure 17(a) shows the synthetic monoenergetic image at 60 keV, showing higher attenuation of the iodine-filled hole as a bright mass in the center of the image. A horizontal profile of this image, given by the columnwise average of Fig. 17(a), is shown in Fig. 17(b). The

NLPV basis image is shown in Fig. 17(c) and the corresponding profile is shown in Fig. 17(d). It exhibits two bright bands, coinciding with the edges of the iodine insert, as shown in the synthetic monoenergetic image [Figs. 17(a) and 17(b)]. Also shown in Figs. 17(b) and 17(d) are simulated image profiles, which are in agreement with the measured data, both for the synthetic monoenergetic image and for the NLPV basis image.

Fig. 13 RMS spatial resolution of the proposed method for as a function of transition center x_c and width Δx .

5 Discussion

As shown in Figs. 6 and 7(a), the estimated NLPV component varies smoothly with the shape parameters of the iodine transition. A_{NLPV} increases approximately quadratically with the step height A_2^{bg} [Fig. 6(a)], showing that the NLPV signal increases rapidly with increasing inhomogeneity across the pixel. Plotted as a function of x_c , A_{NLPV} reaches its maximum when slightly more than half the detector pixel is covered by iodine and falls off to zero at $x_c = 0$ mm and $x_c = 0.5$ mm, where there is no

Fig. 15 Experimentally measured basis projections (a) A_1 (PE) and (b) A_2 (iodine solution), averaged over all detector pixels. Also shown are the nominal profiles according to the phantom drawing.

NLPV signal since the measured radiation field is homogeneous across the pixel [Fig. 6(b)]. Also, as plotted in Fig. 7(a), A_{NLPV} falls off as a function of Δx , which is to be expected since a more gradual transition decreases the inhomogeneity of the transmitted radiation across the pixel.

Figure 7 also shows the impact of model errors, i.e., when the basis material used for NLPV basis function [Eq. (5)] is different from the materials in the actual phantom. Varying the iodine concentration in the phantom [Fig. 7(a)] gives the same qualitative behavior as the case without model error (the 40 mg/ml curve) but with an NLPV signal amplitude that increases with the iodine concentration. If the material in the insert or in the

Fig. 14 Forward model of the experimental imaging system, giving the expected counts in each energy bin and each measurement as a function of the ordinary basis materials A_1 and A_2 . Both the uncorrected, mathematical forward model, and the model corrected by the calibration measurements are shown. Each sub-figure shows one of the eight energy bins.

Fig. 16 Experimentally measured count profiles in each energy bin, averaged over all detector pixels and over repeated acquisitions. Also shown are two simulated count profiles, one calculated from the phantom drawing, and one calculated from the decomposed basis projections, i.e., fitted to the measured data.

surrounding phantom differs from the materials assumed in the basis material decomposition, on the other hand, a nonzero NLPV component can be obtained even in the absence of a sharp transition. Note that the NLPV component still decreases with increasing transition width Δx , so it can still be used to identify sharp transitions if the baseline A_{NLPV} is known from a simulation. The method is thus robust to variations in geometry and iodine concentration, i.e., such variations do not cause too large differences between the true forward model [Eq. (4)] and the approximate forward model [Eq. (7)], but it is sensitive to errors in the assumed material composition of the surrounding tissue, since such a model error can incorrectly lead to a signal in the NLPV basis function even in the absence of a steep interface.

The proposed method builds on detecting minute spectral differences, which is only possible if the quantum noise is low enough, i.e., if the photon flux is sufficiently high. The photon flux requirements for the method to work can be seen from Fig. 8, which shows how the basis image variance varies with the photon flux and with the parameters of the iodine profile. As shown in Fig. 8, detecting the difference between $A_{\text{NLPV}} = 0$ and $A_{\text{NLPV}} = 1$ without averaging over several detector pixels requires either a very high iodine concentration (100 to 200 mg I/ml) or a high dose (10^9 prepatient photons per measurement). The latter may be achieved with a dose similar to that

of a CT scan concentrated in a single projection image. Nonetheless, it is clear that there is a need for investigating potential methods for reducing the dose of this method, as discussed below.

Figures 8(b) and 8(c) show that the lowest noise level in the NLPV basis image is obtained for the steepest gradients and the largest step heights. This is consistent with the variation of the NLPV signal with the profile geometry parameters in Figs. 6 and 7(a). Figure 8(d) shows that the NLPV basis image variance is lowest for a transition positioned near the center and increases as the transition is moved toward the borders of the pixel. This can be understood by noting that the NLPV basis function becomes more and more similar to one of the two constituent materials as the pixel becomes more and more homogeneous, and this makes the problem of separating out the NLPV component from the other basis functions more ill-conditioned.

Figure 9(a) shows that the NLPV basis image noise is almost independent of the kVp of the x-ray beam. Note, however, that this applies if the photon fluence is kept constant, whereas keeping the tube current–time product fixed would give a higher fluence and lower noise at higher kVp.

Figure 9(b) shows that the image variance is degraded if scatter from the object or an imperfect detector response is included in the model. Adding 10% scatter counts, as is typical for CT,

Fig. 17 Measured projection images of the vertical 6-mm diameter iodine contrast the PE cylinder. (a) Synthetic monochromatic image of the projected attenuation coefficient $\int \mu dl$ at 60 keV, computed from the decomposed basis images. (b) Columnwise average of the measured image in (a) (solid blue line) and a simulated image (dashed red line). (c) NLPV basis image. Scale bar length 1 mm. (d) Columnwise average of the measured image in (c) (solid blue line) and a simulated image (dashed red line).

increases the basis image variance by a small amount due to measurement noise caused by the extra counts. Modeling the energy response of a silicon-strip detector causes a degradation of a factor of 4, caused by nonideal detection efficiency and imperfect energy resolution. If the transmitted spectrum is measured in 8 energy bins instead of a large number of 1-keV intervals, then the A_{NLPV} variance increases further by a factor of ~ 1.8 . If the silicon-strip detector is instead combined with a pileup model, a further variance increase of approximately a factor 1.5 is obtained compared to the case with only the silicon model. The models employed here should be seen as simple examples of nonideal detector models. For example, the spectral distortion in a cadmium telluride detector is dominated by fluorescence and charge sharing in contrast to silicon, where the main degrading effect is Compton scatter, but the effect on the spectrum is that some photons are registered with an incorrect, too low, energy in both cases. A more complete detector model could also take into account that cross-talk between detector pixels can give rise to interpixel correlations. Similarly, the pileup model employed in our simulations is simplified but nonetheless takes the most important degrading effects, count loss, and spectral distortion, into account. The scatter is modeled as a constant number of additional counts, independent of local tissue variations, which is not the case in reality but still a good approximation since scatter has a low-frequency character.¹⁶ Although more sophisticated detector models could also be investigated, these results are sufficient to draw the conclusion that good energy resolution is necessary for the proposed method to be effective.

Figure 10 shows that A_1 and A_2 exhibit relatively smooth transitions between their endpoint values at $x_c = 0$ and $x_c = 0.5$. These basis components change relatively little with Δx , as can be expected since the inhomogeneity should mainly be captured by the NLPV component. Figure 10(c) demonstrates that the signal in the NLPV image decreases with

increasing transition width Δx and attains a maximum close to $x_c = 0.4$ while going to 0 at $x_c = 0$ and $x_c = 0.5$. This is similar to Figs. 6 and 7(a), but evidently the A_{NLPV} as function of x_c is more asymmetric for the higher iodine concentration (200 mg I/ml) used here.

Figure 10 also shows that there is a one-to-one mapping between x_c and Δx on one hand and the basis projections A_2 and A_{NLPV} on the other. In particular, a given value of A_2 corresponds to one of the near-vertical contour lines in Fig. 10(b), and the additional knowledge of A_{NLPV} can be used to select a single point in $(x_c, \Delta x)$ space. This means that knowledge of A_2 and A_{NLPV} is sufficient to infer the iodine gradient location and steepness, thereby justifying the inversion of the mapping f in Sec. 3.1.3.

Figure 11 shows that the estimated profiles are able to approximate the true profile shape relatively well. In the case shown in the rightmost panel of this figure ($x_c = 0.44$ mm and $\Delta x = 0.50$ mm), outliers (such as the steepest line shown in the plot) can occur for slow transitions, where the weak NLPV component makes the shape of the slope harder to estimate. As can be seen in Fig. 12, the expected value of the estimated profiles resembles a slightly smoothed version of the true profile, demonstrating that imaging on a subpixel scale has been achieved.

The full-width half-maximum (FWHM) of the Gaussian blur kernel (that gives the best fit to the edge-spread function) varies from 0.023 to 0.17 mm (Fig. 13) for transition widths of 0 to 0.5 mm. This corresponds to 5% to 34% of the pixel width. Better resolution is obtained for sharper interfaces, since the large NLPV component makes estimating the curve shape easier in this case compared to less steep interfaces. The fact that the agreement between the theoretical and measured profiles is different for, e.g., $x_c = 0.06$ mm and $x_c = 0.44$ mm, as can be seen by comparing the upper and the lower rows of Fig. 12 and from Fig. 13, shows that the result is altered if iodine and soft tissue are exchanged within the transition region. This is explained by the asymmetry of the NLPV basis projection in Fig. 10(c). This asymmetry is related to the fact that iodine in such high concentration is much more highly attenuating than the surrounding tissue, so that the quantum noise level in the measurement is different depending on whether iodine covers more or less than half the pixel.

In a more realistic situation, the transition will not look exactly like a piecewise linear function. However, as long as the profile shape is monotonic within each pixel, the piecewise-linear model will be a reasonably good approximation, and we therefore expect that the used method can be used even when the ground truth is not piecewise linear. Although the NLPV basis function was constructed from a steep interface in the case studied here, a smoother and more realistic profile may be more suited for generating the basis function, to minimize the model error. Furthermore, the assumption that the background step height of the iodine concentration is known beforehand is not limiting the applicability of the method, since the diameter of a blood vessel can be estimated from the original projection image, by assuming that the blood vessel is circular, or measured in a CT image if available.

Figure 14 shows the forward models used for the decomposition, both the uncorrected, mathematical forward model used for the simulated profile in Fig. 17 and the corrected forward model used for the measured data. The plot shows that the general trend of the data is captured by the mathematical model, but

the correction factors derived from the calibration adjust the absolute level of the number of counts in each bin. The mathematical model therefore serves as an interpolation method, ensuring that the forward model varies in a realistic way between the acquired calibration data points.

The measured basis projection profiles in Fig. 15 agree with the nominal profiles with an error of less than 1 mm, showing that the calibration procedure and basis material decomposition method used here are accurate enough for measuring the phantom composition. The observed deviation from the nominal thickness may be a combination of calibration errors and differences between the drawing and the actual phantom. The forward model is also validated by Fig. 16, which shows that the experimentally measured energy bin counts are very close to those predicted by the forward model from the phantom drawing. Figure 16 also shows that the basis material decomposition is able to fit count profiles to the experimentally measured ones with excellent agreement.

As shown in Figs. 17(c)–17(d), the NLPV basis projection is close to zero for all parts of the image except near the boundary of the iodine insert, where it rises to around 1, in agreement with the simulations. The fact that the NLPV image exhibits a large nonzero value only at the locations of the interfaces and is close to zero in the regions where the attenuation varies slowly, as predicted by theory, demonstrates that the signal in the NLPV image can be used to distinguish between sharp and gradual transitions. Note that the basis material decomposition algorithm processes the different projection measurements independently, meaning that the peaks in the NLPV image are caused by the uneven distribution of the linear attenuation coefficient within the extent of the pixel, not by differences between neighboring pixels. These peaks therefore demonstrate that the proposed method is able to obtain subpixel spatial information from the spectral measurements.

The fact that the measured profile assumes slightly larger values than the simulated profile behind the interior of the iodine insert in Fig. 17(d) is probably caused by limited accuracy of the calibration. The larger variations around the baseline outside the insert for the measured profile compared to the simulated one in Fig. 17(d) may be caused by fluctuations in the x-ray tube output that partly remain after applying the air scan corrections. The faint horizontal streaks visible in the NLPV image [Fig. 17(c)] stem from detector pixel response variations that the decomposition algorithm has not been able to suppress completely.

Although an image showing the location of interfaces can easily be generated by high-pass filtering of an ordinary projection image, the NLPV basis image has some fundamental advantages. The method does not rely on comparing adjacent pixel values to each other but gives information about the structure within each pixel, which is not available in an ordinary image. Also, the additional information provided by the NLPV image can be combined with any information already available in the ordinary projection image, at no extra dose penalty. These two properties are what made it possible to reconstruct subpixel profiles in the simulation study.

In the present case, two ordinary basis functions are enough to describe the phantom attenuation away from interfaces, whereas in other cases, three may be needed, such as if both soft tissue and bone is present in the beam path. However, a larger number of basis functions means that there will be more noise in each basis image, so if possible, it is preferable

to keep the number of basis materials low, e.g., by approximating the bone attenuation coefficient to be a linear combination of those of water and iodine, as is commonly done in dual energy CT (Ref. 22, pp. 35–41).

Though the experiment was made for a projection image, the method can also be used to generate a CT image by generating an NLPV basis image for each projection angle and then applying filtered backprojection. Although the iodine concentration used here, 200 mg/ml, is higher than commonly used in CT applications, it could be achieved by injecting a contrast agent intra-arterially upstream from the imaging site.

An important requirement for being able to use this method clinically is that it is robust to patient motion. For the NLPV signal to be detectable in a moving object, the imaged interface must move less than one pixel width during the duration of the measurement. For a CT acquisition, this is the time during which one view angle is measured, typically a few hundred microseconds. A pixel width of 0.5 mm in isocenter and a 300 μ s view time give a maximum speed of 1.7 m/s, signifying a relatively high robustness to motion. On the other hand, Fig. 8 shows that commonly used iodine concentrations require $10^8 - 10^9$ pre-patient photons per measurement, corresponding to a projection image with a tube current of ~ 50 to 500 mAs. In this case, the imaged feature needs to be stationary during a time scale of hundreds of milliseconds.

Although further development is needed in order to translate the proposed method from a lab environment to a clinical setting, we will now discuss some clinical situations, where distinguishing between sharp and gradual transitions on a sub-pixel scale can be important. The examples shown here come from stroke care, where diagnosis and treatment planning require good visualization of vascular lesions, such as dissections, which is the most common cause of stroke in young adults,^{23–25} as well as ruptured plaques and aneurysms.^{26–32}

An example of a clinical situation, where improved visualization of the contrast versus noncontrast interface using the proposed method could be advantageous, is visualization of microdissections and recent ruptures in blood vessels, in both projection radiography and CT. These situations are illustrated in Fig. 18 with anonymized example patient images acquired at Karolinska University Hospital, Stockholm, Sweden, using imaging systems in current clinical use. The digital subtraction angiography (DSA) image in Fig. 18(b) does not exhibit any visible damage either in the acute [Fig. 18(b)] or the later phase, despite the presence of bleeding [Fig. 18(a)]. A dissection that is hard to delineate in the CT image [Fig. 18(c)] can be seen more clearly in the higher resolution three-dimensional DSA image [Fig. 18(d)]. An anterior choroidal artery [Figs. 18(e) and 18(f)] that has been iatrogenically perforated during intervention subsequently develops a pseudoaneurysm [Fig. 18(f)] despite normal appearance in the first follow-up angiography examination [Fig. 18(e)]. There is thus a need for detecting minute vascular wall injuries both in CT angiography and in DSA.

The proposed technique could be used to determine whether the vessel boundary is a sharp or diffuse transition, signifying a healthy or damaged vessel, respectively. Examples of such situations are diagnosing microdissections responsible for intracranial hemorrhage and for determining which aneurysm has ruptured in patients with multiple intracranial aneurysms. Improving such diagnosis would improve the treatment strategy and the clinical outcome. Another possible clinical application is assessing the vulnerability of atherosclerotic plaques by

Fig. 18 Clinical examples demonstrating the need for improved visualization of blood vessel walls. (a) Head CT showing a subarachnoid hemorrhage (SAH) in a patient with (b) normal digital subtraction angiography (DSA), i.e., there is acute vessel damage that is not detectable with standard DSA technique. (c) CT angiography of another patient with SAH, showing the presence of a dissection (arrow). (d) The dissection is better visualized with three-dimensional DSA (arrow) but it is not possible to decide which of the two irregularities that caused the bleeding. (e) False normal DSA 1 week after iatrogenic perforation of the anterior choroidal artery (arrow) causing SAH. Despite normal appearance, there must be a vessel damage since DSA (f) after a new spontaneous SAH, which the patient suffered 2 weeks after the perforation, demonstrates development of a pseudoaneurysm (arrow). The CT image in (a) was acquired with a GE Discovery CT750 HD scanner and the image in (c) with a GE Optima CT660, both with a detector slice width of 0.625 mm in isocenter. The DSA images (b, d–f) were acquired with a Philips Allura Xper FD20/15 Clarity system with $154 \times 154 \mu\text{m}$ pixels (in isocenter) for the frontal images (b,d) and $184 \times 184 \mu\text{m}$ pixels in the lateral images (e, f).

visualizing small irregularities in the lumen wall that would aid in determining the true unstable plaque in situations where multiple causes for a thromboembolic event are plausible. The method could also be used, e.g., for studying the surface location and shape of a bone or metal prosthesis with high resolution and may also be applicable to nonmedical applications, such as nondestructive testing.

In this work, we have demonstrated that spectral x-ray measurements can be used to infer information about the distribution of the linear attenuation coefficient within a single pixel. This is a form of super-resolution imaging, in the sense of imaging with higher resolution than the pixel width (rather than imaging below the diffraction limit for which the word is often used in optics).

There are other techniques for increasing resolution in x-ray projection or CT images, for example, by decreasing the pixel size, which gives a more narrow point-spread function, or by oversampling.^{33,34} The proposed method is not meant to replace those methods but rather to complement them. Decreasing the

pixel size as much as possible is the most effective way of improving spatial resolution, but typically the pixel sizes of x-ray imaging systems are limited by effects degrading the dose efficiency, such as the need for reflecting layers in scintillators or charge sharing or fluorescence in direct conversion semiconductor detectors.³⁵ In addition, decreasing the pixel size increases the data rate and power consumption, which is challenging from an engineering point of view and increases cost. The NLPV effect, on the other hand, is “free” in terms of data rate, power, and cost and can be used to improve the resolution beyond the minimum pixel size made possible by physics. Another way to increase resolution is by using oversampling, which does not change the pixel aperture and point-spread function but instead reduces aliasing, which may enable a sharper reconstruction kernel to be used. The ability of the NLPV imaging to reduce the blur caused by the pixel aperture size means that it can be used to complement oversampling. Finally, differential phase contrast imaging⁶ can be used to obtain high-resolution image information by enhancing edges, similar to the proposed method, but requires mounting gratings in the beam path.

We want to emphasize that the results presented here constitute a proof-of-principle for the new method, rather than an algorithm ready for use in the clinic. The most important limiting factor of the proposed method is the large dose or high iodine concentration that is needed to separate the NLPV component from the iodine and soft tissue. Both of these are very high compared to clinical levels in the experimental demonstration since the experiment was not optimized for dose efficiency, and therefore, the variance simulations in Fig. 8 are more useful as an indication of the dose requirements. Note that the simulated detector is an ideal energy-resolving detector, and the results should be interpreted as giving an upper limit of what can be achieved with a real detector. Since Fig. 8 shows that either a very high iodine concentration or a dose level comparable to a CT scan is needed, it will be important to develop data processing algorithms that can reduce the dose by aggregating the information in several different projection lines or by introducing additional prior information.

To outline how dose could be reduced by assuming prior information, note that the method in its present form builds on estimating three basis components, but only two of these are actually used for estimating the iodine profile. A way to avoid estimating three components is to assume that the total phantom thickness is constant across the studied transition so that the sum of the soft tissue and iodine basis projections is constant. By exploiting this fact, only two basis components need to be estimated, which can be done with less photon statistics than what is needed for three basis components. This would also make it possible to use the method with a dual-energy imaging system, which measures at only two energy levels.

6 Conclusions

We have demonstrated theoretically and experimentally how subpixel spatial information can be retrieved by measuring the energy dependence of the x-ray transmission and that this information can be utilized to distinguish between sharp and gradual transitions, e.g., for differentiating between healthy and damaged blood vessel walls. We have also showed in a simulation study that the proposed method can be used to recover attenuation profiles on a subpixel scale. Future studies will be

needed to identify clinical situations, where the proposed method can be useful and to develop algorithms for making optimal use of the subpixel information.

Appendix: Implementation Details

This section describes the forward model of the x-ray source and the photon counting silicon strip detector that was used in the experimental study (Sec. 3.2). A detailed study of a similar model for the same detector has been published previously.¹⁸

The x-ray spectrum incident on the detector:

$$N_0(E) \exp[-A_1 f_1(E) - A_2 f_2(E) - A_{\text{NLPV}} f_{\text{NLPV}}(E)], \quad (9)$$

which was calculated with an energy discretization step of 0.1 keV and with $N_0(E)$ taken to be an 120-kVp tungsten anode spectrum with 11 deg anode angle filtered by 0.8-mm Be, 2-mm Al, and 7.5-mm glass, i.e., as in the measurement. A tabulated x-ray tube spectrum,¹² PE composition from Ref. 36, and linear attenuation coefficients from Berger et al.¹³ were used. The number of photons in the x-ray spectrum of the forward model was tuned to make the uncorrected forward model agree with the total measured count rate for the air scan. Since each detector pixel is subdivided into nine depth segments, the bin sensitivity function $S_i(E)$ in Eq. (7) was modeled as follows:

$$S_i(E) = \sum_{k=1}^9 D_k(E) \int_{E'=0}^{\text{kVp}} B_{ik}(E') R_{ik}(E, E') dE', \quad (10)$$

where $D_k(E)$ is the fraction of all incident photons at energy E that interact in depth segment k and $R_{ik}(E, E')$ is the probability density that a photon with energy E that interacts in depth segment k will deposit an energy E' taking Compton scatter in the detector and charge sharing into account. $B_{ik}(E')$ is a bin sensitivity function. In the absence of electronic noise, it would be equal to one for E' in energy bin i in depth segment k and zero otherwise. To take electronic noise into account, however, this function was convolved with a Gaussian function with standard deviation $\sigma = 1.6$, as measured in the low-flux limit at 60 keV.²⁰

Equation (7) can then be rewritten as follows:

$$\lambda_i = \sum_{k=1}^9 \int_0^{\text{kVp}} B_{ik}(E') \int_0^{\text{kVp}} N_0(E) D_k(E) R_{ik}(E, E') \cdot \exp[-A_1 f_1(E) - A_2 f_2(E) - A_{\text{NLPV}} f_{\text{NLPV}}(E)] dE dE'. \quad (11)$$

At each energy, $D_k(E)$ was calculated using the linear attenuation coefficient of silicon and the known length of each depth segment (1.26, 1.45, 1.69, 1.99, 2.41, 3.01, 3.94, 5.56, and 9.09 mm, respectively), taking into account that the beam is attenuated by 0.6 mm inactive silicon before reaching the first depth segment.

The energy response function $R_{ik}(E, E')$ was precalculated by a Monte Carlo simulation of the photon transport inside the silicon wafer, using a model described in detail in Ref. 37. For each incident energy in steps of 1 keV, 10^5 simulated photons were sent into a detector pixel, and the photon transport in the silicon was simulated taking photoelectric, Compton and Rayleigh interactions into account. Charge sharing was modeled

Fig. 19 (a) Unattenuated spectrum incident on each detector pixel of the silicon-strip detector according to the simulation model. (b) Deposited spectrum in the first (1) and last (9) depth segment. The peak toward 0 keV in the deposited spectra is dominated by Compton interactions.

by an energy-dependent initial charge cloud size and broadening by charge diffusion was modeled. Pulse pileup was not included in the model. In this way, $R_{ik}(E, E')$ was obtained as a probability distribution of the deposited energies E' for each incident photon energy E .

The resulting incident and deposited spectra are shown in Fig. 19.

The bin thresholds for each individual detector channel (i.e., for each depth segment of each detector pixel) were estimated by fitting a cumulative spectrum of deposited energies calculated in the way described above to the measured threshold scans of air spectra with 0.8-mm Be and 4-mm Al prefiltration. A detailed study of this calibration method has been published previously.³⁷ Table 1 lists the resulting thresholds, averaged over depth segments in groups of three and over detector pixels. Even though this method only gives approximate threshold locations, the estimated thresholds can be used in an approximate forward model, which is subsequently corrected using calibration measurements.

In the above, we have described a mathematical forward model g mapping basis projections ($A_1, A_2, A_{\text{NLPV}}$) to expected counts $g_{ij}(A_1, A_2, A_{\text{NLPV}})$ in each detector pixel i and energy bin j . To improve the accuracy of the forward model, correction factors $c_{ij}(A_1, A_2)$ were calculated for each detector channel and energy bin and for each of the 36 thickness combinations used in the calibration measurement. The correction factors were obtained as ratios between the measured number of counts and the number of counts calculated from the mathematical forward model:

$$c_{ij}(A_1, A_2) = \lambda_{ij}^{\text{measured}}(A_1, A_2) / \lambda_{ij}^{\text{calculated}}(A_1, A_2). \quad (12)$$

The correction factors were then used to create a corrected forward model:

$$g_{ij}^{\text{corr}}(A_1, A_2, A_{\text{NLPV}}) = c_{ij}(A_1, A_2) (k_{ij} A_{\text{NLPV}} + 1) g_{ij}(A_1, A_2, A_{\text{NLPV}}), \quad (13)$$

where k_{ij} is a constant chosen such that the forward model gives correct output for the case of a beam through an iodine cylinder embedded in 120 mm PE, similar to the case that was used to design the NLPV basis function. To interpolate the calibration factors, we fitted a polynomial of degree 7 in the PE thickness variable and degree 3 in the iodine thickness to the measured data points.

Disclosures

The following authors declare competing financial interests. M.P., S.K. and H.B.: stockholders and consultancy, Prismatic Sensors AB. M.D.: Stockholder and CEO, Prismatic Sensors AB.

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