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A model-based iterative reconstruction algorithm DIRA using patient-specific tissue classification via DECT for improved quantitative CT in dose planning

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Purpose: To develop and evaluate—in a proof-of-concept configuration—a novel iterative reconstruction algorithm (DIRA) for quantitative determination of elemental composition of patient tissues for application to brachytherapy with low energy (< 50 keV) photons and proton therapy.

Methods: DIRA was designed as a model-based iterative reconstruction algorithm, which uses filtered backprojection, automatic segmentation and multimaterial tissue decomposition. The evaluation was done for a phantom derived from the voxelized ICRP 110 male phantom. Soft tissues were decomposed to the lipid, protein and water triplet, bones were decomposed to the compact bone and bone marrow doublet. Projections were derived using the Drasim simulation code for an axial scanning configuration resembling a typical DECT (dual-energy CT) scanner with 80kV and Sn140kV x-ray spectra. The iterative loop produced mono-energetic images at 50 and 88 keV without beam hardening artifacts. Different noise levels were considered: no noise, a typical noise level in diagnostic imaging and reduced noise level corresponding to tenfold higher doses. An uncertainty analysis of the results was performed using type A and B evaluations. The two approaches were compared.

Results: Linear attenuation coefficients averaged over a region were obtained with relative errors less than 0.5% for all evaluated regions. Errors in average mass fractions of the three-material decomposition were less than 0.04 for no noise and reduced noise levels and less than 0.11 for the typical noise level. Mass fractions of individual pixels were strongly affected by noise, which slightly increased after the first iteration but subsequently stabilized. Estimates of uncertainties in mass fractions provided by the type B evaluation differed from the type A estimates by less than 1.5% for most cases. The algorithm was fast, the results converged after 5 iterations. The algorithmic complexity of forward polyenergetic projection calculation was much reduced by using material doublets and triplets.

Conclusions: The simulations indicated that DIRA is capable of determining elemental composition of tissues, which are needed in brachytherapy with low energy (< 50 keV) photons and proton therapy. The algorithm provided quantitative monoenergetic images with beam hardening artifacts removed. Its convergence was fast, image sharpness expressed via the modulation transfer function was maintained, and image noise did not increase with the number of iterations.

I. INTRODUCTION

X-ray CT is the basis for dose calculations in radiotherapy. In external beam therapy with MV photon beams,

electron density is the quantity needed for accurate dose calculations because Compton scattering is the dominant interaction process at these high photon energies. With development of new applications for brachytherapy with low energy (< 50 keV) photons and proton therapy, information on electron densities is not sufficient. Knowledge of the elemental composition (concentrations of H, C, N, O etc) of the tissues is also needed [1]. This is because in brachytherapy with low energy photons, the photoelectric effect is an important interaction process

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that depends strongly on atomic number.

Until now, dose calculations for treatment planning in brachytherapy have been done assuming soft tissues to be equivalent to water [2]. This may lead to errors in absorbed doses to soft tissues of up to a factor of 2 using 20-30 keV photons as emitted from radioactive seeds of, e.g., ^{125}I and ^{103}Pd and miniature x-ray sources operated at 50 kV (Figure 3 in Ref. 1, based on data in Ref. 3). For accurate treatment planning the soft tissues need, in these instances, be known individually on a voxel by voxel basis [1]. Model based dose calculation algorithms (MBDCAs) taking into account patient anatomy [1] have recently been developed and implemented in commercially available treatment planning systems, viz., Electra's "On-centra Brachy" and Varian's "Brachy Vision". Accurate tools providing information on the elemental composition of the tissues is, however, still not available [1]. In radiotherapy with protons and heavier ions, mean excitation potentials (I -values) and nuclear cross sections for these particles depend on atomic number [4]. Significant errors in I -values increase range uncertainties and consequently the position of the Bragg peak [5]; relative concentrations of C and O are particularly important [6]. As in brachytherapy, there is need for accurate tools for determination of elemental compositions. A recent review [7] on dual energy CT in radiotherapy summarizes the needs and status for both modalities.

In contemporary CT scanners, beam hardening and scatter artifacts adversely affect the accuracy of quantitative CT (QCT). In principle, the artifacts could be removed by model-based iterative reconstruction (MBIR) methods [8], which include geometric modeling, physical modeling and prior object information modeling. For QCT, modeling of the poly-energetic x-ray spectrum and material composition is most important, but only few reconstruction algorithms described in scientific literature deal with both. For instance the iterative maximum-likelihood polychromatic algorithm for CT [9] and the MBIR algorithm for QCT [10] (a precursor to the algorithm presented in this article) modeled the poly-energetic x-ray spectrum and material decomposition of body tissues in single- and dual-energy CT, respectively. Iterative reconstruction algorithms implemented in commercially available CT scanners (e.g., ADMIRE, ASiR-V) implement some of the MBIR techniques (details have not been published in scientific literature), but they primarily focus on noise reduction so as to allow reduction of patient doses while maintaining (or improving) image quality for diagnostic purposes; they are not optimized for QCT.

Material composition of the imaged object can be modeled by material decomposition, i.e. a method determining fractions of pre-selected material components (bases) using projection-space or image-space data. In projection space, a decomposition to (i) photoelectric effect and Compton scattering components or (ii) two arbitrary material bases, e.g. water and bone, can be done inside a non-iterative image reconstruction algorithm in DECT

described by Alvarez and Macovsky [11]. The algorithm suppresses the beam hardening artifact, but the resulting CT values are biased since coherent scattering is not considered in the former case and any two bases cannot fully represent all body tissues in the latter case. The algorithm demands geometrically consistent raw data projections.

Several methods performing the material decomposition in image space have been developed. The material decomposition from inconsistent rays (MDIR) [12] is an iterative algorithm that can be used when geometrically consistent raw data projections are not available. Lower noise and bias than in the MDIR method can be achieved in the extended algebraic reconstruction technique (E-ART) [13] at the expense of longer computation time. The iterative reconstruction algorithm for polychromatic CT imaging [14] (here abbreviated as RAPCTI) can suppress beam hardening artifact in single-energy CT and, in case of DECT, also allows material decomposition to two material bases.

Material decomposition in image space performed on already reconstructed data was used in the following algorithms. A two-material decomposition was applied in single-energy CT [15] and a three-material decomposition in DECT. For instance DECT was used to quantify mass fractions of water, hydroxyapatite and aqueous iron nitrate [16]. The method was also applied for the determination of (i) iron content in liver composed of soft tissue, fat and iron (ii) bone mineral density in a trabecular bone composed of calcium hydroxyapatite, yellow- and red-marrow [17]. The three-material decomposition method in DECT was extended to a framework that also includes the two-material decomposition and tissue segmentation to quantify soft tissues in terms of their mass fractions of water, protein and lipid [18]. Another approach using image data from DECT is to determine electron densities and effective atomic numbers of the materials [19–21]. Additional mathematical models that link these quantities to elemental concentrations [6, 22] or I -values [23] have been developed. However, all the non-iterative image-space based methods cited above use data from commercially available CT scanners and are prone to inaccuracies due to biased CT numbers caused by beam hardening.

Today's radiation therapy requires quantitative information about tissue compositions, a need that current commercial image reconstruction algorithms do not satisfy. To address this problem the aim of this work was to develop and evaluate the MBIR dual-energy iterative reconstruction algorithm (DIRA), whose design goals are: (i) Conversion of polyenergetic reconstruction results to monoenergetic and thereby the elimination of beam hardening artifacts, and (ii) the decomposition of human tissues in doublets and triplets of base materials.

In this work a proof of concept is presented for the determination of material composition using the DIRA algorithm with simulated data calculated for anthropomorphic phantoms. As the accuracy and precision of ma-

terial decomposition depends on noise in projection data, the behavior of the algorithm is presented and evaluated for three different noise levels and an analysis of associated uncertainties is performed.

II. THEORY

A. Three-material decomposition in DECT

The system of equations in the three-material decomposition method (3MD) in DECT can be derived from (i) the summation rule

$$\mu_m(E) = \sum_{i=1}^3 w_i \mu_{m,i}(E), \quad (1)$$

where $\mu_m(E)$ is the mass attenuation coefficient of a mixture at photon energy E and $\mu_{m,i}(E)$ is the mass attenuation coefficient at the same energy E of the i th base material with the mass fraction w_i ($1 \leq i \leq 3$), (ii) the normalization condition $w_1 + w_2 + w_3 = 1$, and (iii) the formula for the mass density of a mixture

$$\frac{1}{\rho} = \sum_{i=1}^3 \frac{w_i}{\rho_i}, \quad (2)$$

where ρ and ρ_i are mass densities of the mixture and i th material, respectively. Formula (2) is valid when partial molar volumes of base materials are the same when the materials are standalone and in the mixture. Eqs. (1) and (2) and the normalization condition lead to a system of linear equations that can be written in the matrix form as

$$\mathbf{A}\mathbf{w} = \mathbf{b}, \quad (3)$$

where $\mathbf{b} = (0, 0, 1)^T$ is the right-hand side vector, $\mathbf{w} = (w_1, w_2, w_3)^T$ is the vector of unknown mass fractions and $\mathbf{A}$ is the system matrix. The superscript T denotes a matrix transpose; the vectors $\mathbf{b}$ and $\mathbf{w}$ are represented by 3×1 matrices. The elements of the system matrix are

$$A_{i,j} = \begin{cases} \frac{\mu(E_i)}{\rho_j} - \mu_{m,j}(E_i) & i = 1, 2 \\ 1 & i = 3 \end{cases}, \quad (4)$$

where $j = 1, 2, 3$ and $\mu = \mu_m \rho$ is the linear attenuation coefficient. The mass fractions can be obtained as

$$\mathbf{w} = \mathbf{A}^{-1}\mathbf{b}, \quad (5)$$

where $\mathbf{A}^{-1}$ is the inverse matrix of $\mathbf{A}$ in Eq. (4).

B. Two-material decomposition in DECT

In the two-material decomposition method (2MD) in DECT [18], the summation rule (1) and the normalization condition $w_1 + w_2 = 1$ lead to a system of equations

that can be written in the matrix form as

$$\begin{pmatrix} \mu_{m,1}(E_1) & \mu_{m,2}(E_1) & -\mu(E_1) \\ \mu_{m,1}(E_2) & \mu_{m,2}(E_2) & -\mu(E_2) \\ 1 & 1 & 0 \end{pmatrix} \begin{pmatrix} w_1 \\ w_2 \\ 1/\rho \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix}, \quad (6)$$

where the mass fractions w_1 and w_2 and the mass density ρ of the mixture are unknown, the linear attenuation coefficients $\mu(E_1)$ and $\mu(E_2)$ of the mixture are known. Eq. (6) can be solved as

$$\mathbf{x} = \mathbf{A}^{-1}\mathbf{b} \quad (7)$$

where $\mathbf{x} = (w_1, w_2, 1/\rho)^T$ is the unknown vector, $\mathbf{b} = (0, 0, 1)^T$ is the right-hand side vector, and $\mathbf{A}$ is the system matrix in Eq. (6).

C. DIRA

The model-based iterative image reconstruction algorithm DIRA uses CT projections obtained at two different tube voltages and automatic quantitative tissue classification for the generation of the reconstructed volume. The main idea is that polyenergetic projections measured by a CT scanner are converted to monoenergetic ones by adding a correction term to each measured projection. The correction terms are calculated by simulating monoenergetic and polyenergetic projections using the reconstructed volume for each of the used tube voltages. The algorithm is illustrated in Fig. 1.

Step 1: Measured polyenergetic projections for two tube voltages are obtained. At iteration 0 and step 2, classical water beam-hardening correction[24, p. 121] (WBHC) is performed, otherwise not. Step 3: Reconstruction with filtered backprojection (FBP) is performed and reconstructed images μ_1 and μ_2 are obtained. These are then automatically segmented into pre-defined tissues and organs at step 4. In the presented example, a threshold segmentation to soft and bone tissue combined with filling of bone cavities is used. The user is free to choose different segmentation methods. In step 5, classification into mass fractions of base materials is performed. For soft tissue, three-material decomposition (3MD) (Section IIA) is used and for bone tissue two-material decomposition (2MD) (Section IIB) is applied. Forward monoenergetic and polyenergetic projections are calculated in steps 6 and 7. The goal is that after some iterations, the calculated polyenergetic projections become almost equal to the measured polyenergetic projections. Then only the calculated monoenergetic projections contribute to the reconstructed μ -volumes. The filter functions W_0 , W_A and W_B are described in Supplementary material. The result of DIRA is the classified reconstructed volume (CRV) in step 8.

To formulate DIRA in mathematical terms, set

$$\boldsymbol{\mu} = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \quad \mathbf{P}_{\mathbf{M},\mathbf{U}} = \begin{pmatrix} P_{M,U_1} \\ P_{M,U_2} \end{pmatrix}, \quad (8)$$

FIG. 1. Data-flowchart of the dual-energy iterative reconstruction algorithm DIRA. P_{M,U_1} and P_{M,U_2} denote measured polyenergetic projections at tube voltages U_1 and U_2 , respectively. P_{U_1} and P_{E_1} denote simulated polyenergetic and monoenergetic projections at the tube voltage U_1 and effective energy E_1 (see section IID), respectively, and similarly for P_{U_2} and P_{E_2} . The linear attenuation coefficients μ_1 and μ_2 denote reconstructed images. W_0 , W_A , and W_B denote filter functions (windows).

for the reconstructed images and the measured projections (sinograms), respectively. Furthermore, denote the filtered backprojection operator $\mathcal{B}$, and the filtering operator $\mathcal{F}_{W_k}$, where $k = 0, A, B$ denotes different filter functions. Set

$$\mathcal{P}_U = \begin{pmatrix} \mathcal{P}_{U_1} \\ \mathcal{P}_{U_2} \end{pmatrix}, \quad \mathcal{P}_E = \begin{pmatrix} \mathcal{P}_{E_1} \\ \mathcal{P}_{E_2} \end{pmatrix}, \quad (9)$$

for the projection operator for polyenergetic projections and monoenergetic projections, respectively. These projection operators include the automatic tissue segmentation and classification. The linear attenuation coefficient $\mu^{(i+1)}$ obtained at the $(i+1)$ th iteration is

$$\begin{aligned} \mu^{(i+1)} = & \mathcal{B}\mathcal{F}_{W_A}\mathcal{F}_{W_B}(\mathbf{P}_{M,U}) - \mathcal{B}\mathcal{F}_{W_B}\mathcal{P}_U(\mu^{(i)}) \\ & + \mathcal{B}\mathcal{F}_{W_B}\mathcal{P}_E(\mu^{(i)}), \end{aligned} \quad (10)$$

The filter function W_0 contributes multiplicatively to the modulation transfer function (MTF) of the imaging system at iteration 0 of the algorithm, and the product $W_A \cdot W_B$ contributes multiplicatively to the MTF at iteration i . In the presented work, $W_A = 1$ for reasons discussed in Supplementary material.

Assume that $W_A = W_B = W_0 = 1$, i.e. disregard the filters. Eq. (10) then reduces to

$$\mu^{(i+1)} = \mathcal{B}(\mathbf{P}_{M,U}) - \mathcal{B}\mathcal{P}_U(\mu^{(i)}) + \mathcal{B}\mathcal{P}_E(\mu^{(i)}). \quad (11)$$

Ideally, the simulated polyenergetic projections $\mathcal{P}_U(\mu^{(i)})$ converge towards the measured projection $\mathbf{P}_{M,U}$. The $(i+1)$ th iteration then gives $\mu^{(i+1)} \approx \mathcal{B}\mathcal{P}_E(\mu^{(i)})$, which is the filtered backprojection result of the monoenergetic projections.

Eq. (11) can be rewritten to

$$\mu^{(i+1)} = \mathcal{B}(\mathbf{P}_{M,U}) - \mathcal{B}\mathcal{P}_U(\mu^{(i)}) + \mu^{(i)} - \mathcal{F}_{HP}(\mu^{(i)}) \quad (12)$$

where $\mathcal{F}_{HP}(\mu^{(i)}) = \mu^{(i)} - \mathcal{B}\mathcal{P}_E(\mu^{(i)})$ denotes the result of filtration with a high pass filter. The reason is that projection followed by backprojection, $\mathcal{B}\mathcal{P}_E$, serves as a low pass filter on the original function. Eq. (12) shows that the generation of monoenergetic projections followed by backprojection in DIRA serve as a regularization. The importance of regularization stems from the fact that non-regularized iterative methods tend to increase noise in reconstructed images, more information is in section V.

The polyenergetic spectra and the tissue classification in base materials complicate the proof of convergence of Eqs. (10) and (11). With no proof available, the applicability of the method is shown experimentally by realistic simulations.

D. Computation of projections in DIRA

For a polyenergetic spectrum, the x-ray beam intensity at the detector position is given by

$$I = \int_0^{E_{\max}} E N(E) \exp \left[- \int_L \mu(x, y, E) dl \right] dE, \quad (13)$$

where $EN(E)dE$ is the energy carried by $N(E)dE$ photons with energies in the interval $(E, E + dE)$, $\mu(x, y, E)$ is the linear attenuation coefficient of the object at position (x, y) for photons with energy E . The inner integration is performed over a straight line L through the object. For an unattenuated ray that does not intersect the object, we get

$$I_0 = \int_0^{E_{\max}} EN(E) dE. \quad (14)$$

Projection data is calculated by

$$P = \ln \left(\frac{I_0}{I} \right). \quad (15)$$

For a monoenergetic spectrum, P is equal to the line integral of the object function $\int_L \mu(x, y, E) dl$. For the sake of simplicity an ideal energy integrating detector is assumed. A generalization to a detector with a known energy-dependent efficiency is straightforward.

As mentioned above, the reconstructed object is segmented into tissues defined by the user, for instance bone and soft tissue. Each tissue is then decomposed using the 2MD or 3MD. For the sake of brevity, the 3MD is used in the following explanation, i.e each voxel $\mu(x, y, E)$ is classified as a mixture of three base materials with mass attenuation coefficients $\mu_{m,i}(E)$, $i = 1, 2, 3$ and mass fractions w_i corresponding to Eq. (1). A modification for the 2MD is straightforward. The Eq. (13) can be written with μ replaced with $\rho\mu_m$, where ρ is the density of the mixture. This density is not known and so an approximation defined by Eq. (2) was made. Using Eq. (1), Eq. (13) can be written as

$$I = \int_0^{E_{\max}} E N(E) \times \exp \left\{ - \int_L [\rho(x, y) \sum_{i=1}^3 \mu_{m,i}(E) w_i(x, y)] dl \right\} dE \quad (16)$$

$$= \int_0^{E_{\max}} E N(E) \times \exp \left[- \sum_{i=1}^3 \mu_i(E) \rho_i^{-1} \int_L \rho(x, y) w_i(x, y) dl \right] dE \quad (17)$$

$$= \int_0^{E_{\max}} E N(E) \exp \left[- \sum_{i=1}^3 \mu_i(E) l_i \right] dE, \quad (18)$$

where ρ_i and $\mu_i(E)$ are the mass density and linear attenuation coefficient, respectively, of the i th base material and

$$l_i = \rho_i^{-1} \int_L \rho(x, y) w_i(x, y) dl = \rho_i^{-1} \int_L \rho_{p,i}(x, y) dl \quad (19)$$

is the line integral of the partial mass density $\rho_{p,i}$ normalized per unit mass density ρ_i of the i th base material. (The partial mass density is the mass of the i th base material in a unit volume of the mixture.) Such line integrals are calculated with Joseph's method [25].

Eqs. (18) and (19) show that the calculation of line integrals can be performed on the three images of partial mass densities $\rho_{p,i}$. The influence of the X-ray spectrum and linear attenuation coefficients can be taken into account afterwards. The intensity spectrum of the source $E N(E)$, and the linear attenuation coefficients as functions of energy $\mu_i(E)$, can be re-sampled to a common grid E_k , $k = 0, \dots, K$. Then Eq. (18) can be computed

using the Simpson's formula

$$I \approx \frac{1}{2} \sum_{k=1}^{K-1} E_k N(E_k) \exp \left[- \sum_{i=1}^3 \mu_i(E_k) l_i \right] (E_{k+1} - E_{k-1}). \quad (20)$$

Finally, the polyenergetic projections are received by inserting I into (15). Direct computation of Eq. (17) is considerably faster than computation of Eq. (16). The corresponding time complexities (see Supplementary material) are $O(KN)$ and $O(K+N)$ for discretized formulas in Eqs. (16) and (17), respectively, where K is the number of energy bins and $N \times N$ is the size of the voxel array.

Monoenergetic projections for the energies E_j , $j = 1, 2$, are calculated as

$$P_{E_j} = \sum_{i=1}^3 \mu_i(E_j) l_i, \quad (21)$$

where the summation is done over all three base materials.

III. METHODS

A. The phantom

An anthropomorphic phantom was created by approximating three slices (slice numbers 111, 113 and 115) of the ICRP 110 voxel male phantom [26] with ellipses fitting the tissue structures, see Fig. 2. The approximation was done to overcome the limitation of the Drasim code [27], which cannot calculate CT projections of voxel phantoms. The prostate-containing slices demonstrate large variations in the shape and positions of pelvic bones, which cause strong beam hardening artifacts in conventional CT. The resulting mathematical model for slice B is shown in Fig. 3. Elemental composition and mass density of materials in the three slices (adipose tissue (49), muscle (29), pelvis spongiosa (14), femora spongiosa (9), mineral bone (2), prostate (46), and urinary bladder (41)) were taken from Ref. 26; the corresponding tissue numbers are given in parenthesis. Linear attenuation coefficients of the tissues are shown in Fig. 4.

B. CT scanner simulation

The scanner geometry is described in Supplementary material. The energy E_j , $j = 1, 2$, in Eq. (21), here referred to as the effective energy, was chosen as the energy for which the linear attenuation coefficient for water equals the energy fluence weighted mean linear attenuation coefficient for water. The weighting was done for the energy spectrum of photons emitted from the x-ray source. In this work, effective energies of 50 and

FIG. 2. A colormap of material numbers in transversal slices A (a), B (b) and C (c) of the pelvic region of the ICRP 110 voxel phantom. Ellipses approximating tissue boundaries were used to construct mathematical models of the slices.

FIG. 3. (a) Color-coding of the resulting mathematical model of slice B: adipose tissue (brown), muscle (red), pelvis spongiosa (green), femora spongiosa (blue), mineral bone (black), prostate (yellow). (b) Circular regions for statistical analysis in slice B: R_M = muscle (green), R_A = peripheral adipose tissue (red), R_C = central adipose tissue (yellow), R_F = femora spongiosa (blue).

FIG. 4. Position of the chosen lipid, protein, and water triplet in the linear attenuation diagram. The point for mineral bone (0.79 cm^{-1} , 0.39 cm^{-1}) is off the scale.

88 keV were used for the 80 kV and Sn140 kV source energy spectra, respectively. Other approaches are possible, the algorithm is not very sensitive to the settings of E_j , $j = 1, 2$.

Simulations were performed for three levels of quantum noise in reconstructed images. The level 2 corresponded to a typical noise in clinical CT images (see Supplementary material). In this case, tube loads for a single projection were set to 0.217 and 0.080 mAs for the low and high tube voltages, respectively, in Drasim. This corresponded to tube loads of $0.217 \cdot 1152 = 250$ mAs and $0.080 \cdot 1152 = 92.16$ mAs per full rotation of the gantry

for the two tube voltages. The level 1 corresponded to tube loads increased by a factor of 10 compared to the level 2. The level 0 corresponded to no quantum noise. The tube load was the same for all projections; tube current modulation was not simulated.

C. Tissue segmentation

The reconstructed image at 50 keV was segmented to outside air (pixels with $\mu < 19 \text{ m}^{-1}$), soft tissue (pixels with $19 \text{ m}^{-1} \leq \mu \leq 33 \text{ m}^{-1}$) and bone (pixels with $33 \text{ m}^{-1} < \mu$) using threshold segmentation. If these values are outside of reasonable limits, the computed segmentation masks may not be accurate. The computation of the linear attenuation coefficients is not, however, affected much by those inaccuracies in the segmentation. Pixels at tissue boundaries received special treatment to reduce the adverse effect of volume averaging on the material decomposition routines: (i) The air-soft tissue boundary pixels were assigned to air by setting the threshold value (19 m^{-1}) close to the LAC of lipid, see Fig. 4. (ii) The bone-soft tissue boundary pixels were assigned to bone by expanding (dilating) the bone regions by including an extra pixel around the borders. Moreover, bone cavities containing bone marrow were added to the bone regions using hole filling, see Fig. 3. This segmentation was performed at each iteration of DIRA.

D. Tissue classification

Air pixels were decomposed to the lipid and water doublet using the 2MD method. Resulting inaccuracies for pure air pixels had little effect on the calculation of forward projections because of the small mass density of air. On the other hand, mass density and material composition of pixels at the air-soft tissue boundary was realistically modeled. Soft tissues were decomposed to the lipid, protein and water (LPW) triplet using the 3MD method (section IIA). Bone tissues were decomposed to the mineral bone and bone marrow doublet using the 2MD method (section IIB). Elemental compositions of the doublet and triplet components are in Supplementary material. The decomposition was done for energies of 50 and 88 keV and the resulting mass fractions were

stored in the CRV.

E. Uncertainty analysis

1. Uncertainty of reconstructed linear attenuation coefficients

Linear attenuation coefficients $\mu_1(x, y)$ and $\mu_2(x, y)$ for effective energies E_1 and E_2 , respectively, were provided by DIRA for each of the four homogeneous circular regions (Fig. 3). Corresponding sample mean, $\bar{\mu}$, standard deviation, σ , and correlation coefficient, $r(\mu_1, \mu_2)$, were calculated using the Matlab functions `mean`, `std` and `corrcoef`, respectively. Error, $\epsilon(\bar{\mu})$, of the sample mean was calculated as $\epsilon(\bar{\mu}) = \bar{\mu} - \mu^t$, where μ^t is the true value calculated from the known elemental composition of the phantom (see Eq. 1). Relative error, $\delta(\bar{\mu})$, of the sample mean was calculated as

$$\delta(\bar{\mu}) = \epsilon(\bar{\mu})/\mu^t = (\bar{\mu} - \mu^t)/\mu^t, \quad (22)$$

In the computation of uncertainties in mass fractions (section III E 2), the sample standard deviation σ was used as the estimate of the standard uncertainty, $u(\mu)$, in the linear attenuation coefficient μ calculated by DIRA. Corresponding relative standard deviation, $u_r(\mu)$, was calculated as $u_r(\mu) = u(\mu)/\mu$. It should be noted that the uncertainty estimate based on σ does not include uncertainties arising from inaccuracies in material data and the summation rule. This should not be a problem in practical situations since the quantum noise and image artifacts (the contribution from σ) dominate the uncertainty. Histograms of μ_1 and μ_2 were plotted and inspected for each considered configuration.

2. Uncertainty in estimated mass fractions

Uncertainty in estimated mass fractions was determined in two ways, here denoted as methods A and B. Method A used the μ_1 and μ_2 of each pixel in the four circular regions to calculate mass fractions (for each such pixel) from Eqs. (5) and (7). Means, standard deviations, correlation coefficients errors, and relative errors for these mass fractions were calculated similarly as for the attenuation coefficients in section III E 1. Note that the method A resembled the purely statistical, type A evaluation of measurement uncertainty [28]. Method B used the type B evaluation of uncertainty as derived by GUM [28]. Means and standard deviations for μ_1 and μ_2 described in section III E 1 were used as input data in the method B (see Supplementary material for details). Uncertainties in mass fractions calculated using the methods A and B were compared.

F. Hardware and software

Simulations were performed on a PC with 82 GB RAM and $2 \times$ Intel Xeon X5650 CPU. Each 2.67 GHz CPU had 6 cores and hyper-threading was turned on. OpenMP version of DIRA 2015a [29] was executed under MATLAB 2014a.

IV. RESULTS

A. Linear attenuation coefficients

Reconstructed images at energies $E_1 = 50$ keV and $E_2 = 88$ keV for the slice B, three noise levels ($L = 0, 1, 2$, Section III B and Supplementary material) and the 8th iteration are shown in Fig. 5. The beam hardening artifact was suppressed in all images. Quality of this suppression was notably better for DIRA than for the filtered backprojection with classical water beam hardening correction, see Fig. 6, which shows the differences between the phantom image processed with a filter having the MTF of MTF_{DIRA} (an image produced by an ideal imaging system) and corresponding reconstructed images for 0th and 8th iterations.

Relative errors less than 0.4% were observed in the four circular regions depicted in Fig. 3, see Table I; the true values were 23.76 and 18.47 m^{-1} for muscle (region R_M), 20.19 and 16.59 m^{-1} for adipose tissue (regions R_A and R_C), and 28.69 and 20.23 m^{-1} for femora spongiosa (region R_F) at energies of 50 and 88 keV, respectively.

A small difference between reconstructed and true values was observed for the bones (Fig. 6). Visual inspection of the 50 keV images showed that the reconstructed value had improved from approximately 67.0 m^{-1} for the 0th iteration to approximately 78.9 m^{-1} for the 8th iteration while the true value for bone was 79.3 m^{-1} ; the corresponding relative error was reduced from 16% to 0.5%. The discrepancy between the result for the 8th iteration and the true value was most likely caused by differences in the implementation of line integral calculations in DIRA and Drasim; the same material cross section data were used in both codes. This discrepancy combined with aliasing is also most likely the cause of dark streaks in no noise images associated with long photon paths through compact bones (Fig. Supp-I for $L = 0$.)

Relative standard deviations of the reconstructed linear attenuation coefficients (and consequently the standard deviations of the reconstructed CT numbers) increased with increasing noise level in all four circular regions, see Table I. Note that DIRA did not amplify noise in reconstructed images; the noise was approximately the same for iterations 0 and 8.

The reconstructed linear attenuation coefficients μ_1 and μ_2 were correlated (Table I). The correlation was positive for no quantum noise and became negative for noise levels 1 and 2. Most likely, the positive correlation for $L = 0$ was caused by weak artifacts resulting

FIG. 5. Reconstructed images at photon energies $E_1 = 50$ keV and $E_2 = 88$ keV corresponding to tube voltages of 80 and 140 kV for slice B. Noise levels $L = 0, 1$, and 2 denote no noise, reduced noise, and a typical noise, respectively (Section III B). Eight iterations of DIRA were used.

FIG. 6. Difference (in m^{-1}) between the reconstructed μ -values at 50 keV and corresponding true μ -values (phantom image) filtered with the system transfer function for 0th (a) and 8th (b) iteration. Similarly for 88 keV (c,d). The scale is chosen to highlight differences in soft tissues

TABLE I. Relative error $\delta(\bar{\mu}_i)$ of average reconstructed linear attenuation coefficients $\bar{\mu}_i$, relative standard uncertainty $u_r(\mu_i)$ of the reconstructed linear attenuation coefficients μ_i , standard uncertainty $u(H_i)$ of the corresponding CT number at the effective energy E_i ($i = 1, 2$) for pixels in four circular regions R , three noise levels L and 8th iteration. The correlation coefficient $r(\mu_1, \mu_2)$ is also listed. Values are rescaled using the factor $\%_0 = 10^{-3}$.

R	L	$\delta(\bar{\mu}_1)$ (%)	$\delta(\bar{\mu}_2)$ (%)	$u_r(\mu_1)$ (%)	$u_r(\mu_2)$ (%)	$u(H_1)$	$u(H_2)$	$r(\mu_1, \mu_2)$
R_M	0	-1.01	-0.17	1.43	0.69	1	1	0.94
R_M	1	-0.84	0.24	11.27	6.77	12	7	-0.30
R_M	2	-1.96	1.89	29.76	23.24	31	24	-0.18
R_A	0	-0.48	-0.06	2.78	1.43	2	1	0.99
R_A	1	-0.26	0.43	7.47	5.84	7	5	-0.06
R_A	2	-2.39	1.57	21.19	16.77	19	16	-0.20
R_C	0	-1.18	-0.25	5.11	2.54	5	2	0.99
R_C	1	-1.05	0.74	17.12	10.67	15	10	-0.04
R_C	2	1.79	2.74	62.62	30.36	56	28	0.01
R_F	0	-1.27	-0.13	1.03	0.56	1	1	0.96
R_F	1	-0.68	0.63	13.10	7.35	17	8	-0.22
R_F	2	-2.78	1.54	44.88	24.09	57	28	-0.22

B. Mass fractions

from the aliasing, which were present in both μ_1 and μ_2 images. The overall effect of this correlation was, however, very small since the corresponding covariance was less than 8×10^{-3} (see Supplementary material). For $L = 1, 2$, the noise resulted in close to zero correlation coefficients between μ_1 and μ_2 for the 0th iteration. The correlation coefficient was a decreasing function of the number of iteration; the decrease stabilized between 3rd and 5th iteration to the (mostly) negative values of the 8th iteration listed in Table I.

The three-material decomposition of soft tissue to the (lipid, protein, water) triplet resulted in per-pixel mass fractions shown in Fig. 7 for all noise levels $L = 0, 1, 2$ and iteration 8; corresponding true values were $(-0.128, 0.128, 1.000)$ and $(0.701, 0.029, 0.270)$ for the muscle and adipose tissue, respectively. The negative mass fraction of -0.128 for lipid in the muscle tissue is related to the fact that muscle is outside the (lipid, protein, water) triangle in Fig. 4, see Section V and Ref. 18 for more information. Fig. 7 also demonstrates an im-

provement in accuracy of the mass fractions achieved by DIRA at iteration 8 compared to the classical water beam hardening correction (iteration 0).

The achieved accuracy is quantified in Table II, which lists errors $\epsilon(\bar{w}_1)$, $\epsilon(\bar{w}_2)$, and $\epsilon(\bar{w}_3)$ of average mass fractions of lipid, protein and water, respectively, in the soft tissue regions R_M , R_A and R_C for all noise levels. Also listed is the relative error $\delta(\bar{\rho})$ of average mass density, where the per-pixel mass density was calculated from Eq. (2) and the mass density of the phantom material was used as the true density.

Noise levels in resulting mass fractions and densities were described by standard uncertainties estimated from standard deviations of the per-pixel mass fractions w_i and mass density ρ , see Table II. As expected, these uncertainties were low for the noise level $L = 0$ (no quantum noise), where the variation was caused by small aliasing artifacts only. For the noise level $L = 1$ the uncertainty in mass fractions was lower than 0.36. For the noise level $L = 2$, however, the standard uncertainties were quite high, e.g. up to 1.2. In this case, individual pixel values were very unreliable and an averaging over a region was needed. The mass fractions and the mass density were highly correlated, for instance $r(w_1, w_3) \approx -1$, $r(w_1, w_2) > 0.93$ and $r(w_2, \rho) > 0.94$ for noise levels $L = 1, 2$. The high correlation was expected since the four output variables (w_1, w_2, w_3, ρ) were computed from only two input variables (μ_1, μ_2).

The two-material decomposition of the bone to the (compact bone, bone marrow) doublet was associated with errors, $\epsilon(\bar{w}_1)$ and $\epsilon(\bar{w}_2)$, of average mass fractions and the relative error, $\delta(\bar{\rho})$, of average mass density listed in Table III for the region R_F . Corresponding true values were (0.203, 0.797) for the mass fractions and 1.123 gcm^{-3} for the mass density. The latter was calculated from Eq. (6), it was not the mass density of the phantom. This choice was motivated by the fact that (i) the relative difference between the two densities was small (0.07%), and (ii) the other choice obscured the dependence of the mass density on the noise level. The per-pixel mass fractions w_1 and w_2 fulfill the normalization condition. As a consequence, $\bar{w}_1 + \bar{w}_2 = 1$, $\epsilon(\bar{w}_1) = -\epsilon(\bar{w}_2)$, $u(w_2) = u(w_1)$, and correlation coefficients are $r(w_1, w_2) = -1$ and $r(w_1, \rho) = -r(w_2, \rho)$, see Supplementary material.

The convergence speed of DIRA is demonstrated in Fig. 8, which for slice A and noise level $L = 2$ shows that the average mass fractions were stable after the 4th iteration and, in most cases, close to the true values. An exception was the central adipose region R_C for the noise level $L = 2$ in slice A for which a small bias was observed; this position was more affected by noise than the other regions, and noise may bias the linear attenuation coefficient [30].

1. Comparison of method A and method B

Standard uncertainties $u(w_1)$, $u(w_2)$ and $u(w_3)$ in per-pixel mass fractions of protein, lipid and water, respectively, determined using the method A (section III E 2) and presented in Table II for the regions R_M , R_A and R_C were compared to standard uncertainties determined using the method B. Relative differences between results of these two methods were lower than 1.5% for all cases. Similar comparison was performed for uncertainties in the mass fractions of compact bone and bone marrow for the femora spongiosa region R_F ; the relative differences were lower than 0.2%. These results indicate that method B can be used for a quick and sufficiently accurate estimate of uncertainties in mass fractions computed using the 2MD or 3MD methods.

V. DISCUSSION

DIRA belongs to the class of iterative filtered back-projection methods (IFBP) [12, 31] whose main advantage is the high convergence speed relative to other iterative methods. Their disadvantage compared to statistical methods such as the iterative maximum-likelihood polychromatic algorithm for CT [9] is worse noise suppression. Methods inspired by the (i) basis decomposition algorithm [11] by Alvarez and Macovski such as MDIR [12] and E-ART [13] or (ii) the RAPCTI algorithm [14] decompose the resulting images into two base materials. Such methods effectively suppress the beam hardening artifact. DIRA extends the material decomposition approach by allowing either the 2MD or the 3MD method in the iterative loop. More generally, DIRA provides a framework where prior information about the anatomy [32] can be used for the selection of tissue-specific or contrast media-specific doublets (2MD) and triplets (3MD). The successful use of 3MD on reconstructed DECT images has been reported [16, 33]. However, the benefits of using 3MD inside the iterative loop—such as the more accurate estimate of tissue composition—remain to be demonstrated. The drawback of 3MD is a slightly higher computational load as more forward projections must be computed. The principal component analysis of XCOM data showed that the intrinsic dimensionality of the LAC data (which is of interest in spectral CT) is four for low-Z elements ($Z=1-20$) when reasonable uncertainties in the data are assumed [34]. DECT has only two degrees of freedom. Nevertheless the assumption about the conservation of molar volumes (equation (2)) allows the determination of mass fractions of three base materials. Radiotherapy treatment planning could benefit from the additional information since, for instance, prostatic tumors contain prostate tissue and calcifications with differing amount of calcium, zinc and other elements [35, 36].

Conceptually, DIRA is similar to RAPCTI as both algorithms perform the material decomposition at each iteration and the newly obtained material composition is

FIG. 7. Mass fractions (in %) of lipid, protein and water after 0th (first row) and 8th iteration (remaining rows) for noise levels $L = 0, 1, 2$ in slice B.

TABLE II. Errors of average mass fractions of lipid $\epsilon(\bar{w}_1)$, protein $\epsilon(\bar{w}_2)$ and water $\epsilon(\bar{w}_3)$, and the relative error of average mass density of the mixture $\delta(\bar{\rho})$ for the regions R_M , R_A , R_C , noise levels $L = 0, 1, 2$ and 8th iteration. Also shown are standard uncertainties $u(w_i)$ and $u(\rho)$ in per-pixel mass fractions and mass density, respectively. All listed quantities were calculated using the method A. Values are rescaled using the factor $\% = 0.01$.

R	L	$\epsilon(\bar{w}_1)$ (%)	$\epsilon(\bar{w}_2)$ (%)	$\epsilon(\bar{w}_3)$ (%)	$\delta(\bar{\rho})$ (%)	$u(w_1)$ (%)	$u(w_2)$ (%)	$u(w_3)$ (%)	$u(\rho)$ (g cm^{-3})
R_M	0	1.04	0.44	-1.48	-0.33	1.08	0.32	1.36	0.05×10^{-2}
R_M	1	1.04	0.59	-1.63	-0.27	17.00	10.69	27.54	1.50×10^{-2}
R_M	2	2.50	1.65	-4.15	0.06	46.44	30.98	76.79	4.67×10^{-2}
R_A	0	0.46	0.21	-0.67	-0.08	1.76	0.24	1.96	0.10×10^{-2}
R_A	1	0.58	0.49	-1.07	-0.01	9.86	7.26	16.87	1.01×10^{-2}
R_A	2	3.17	2.19	-5.37	0.29	29.46	21.91	50.80	3.01×10^{-2}
R_C	0	1.07	0.42	-1.49	-0.07	3.31	0.49	3.75	0.17×10^{-2}
R_C	1	1.46	1.04	-2.50	0.08	21.08	14.39	34.97	1.89×10^{-2}
R_C	2	-2.94	-0.90	3.84	0.28	73.69	46.26	118.49	5.61×10^{-2}

used for the computation of the correction to the measured projections. DIRA, however, does not work with x-ray spectrum weighted linear attenuation coefficients; it works with linear attenuation coefficients at the effective energies E_1 and E_2 . Also, RAPCTI was primarily designed for single-energy CT and uses only one material

doublet in DECT.

The main application area of DIRA is QCT for radiotherapy, specifically the determination of elemental composition and mass densities of imaged tissues. This article focuses on the application of the 2MD and 3MD methods in an iterative reconstruction algorithm. Ele-

TABLE III. Errors of average mass fractions of mineral bone $\epsilon(\bar{w}_1)$ and bone marrow $\epsilon(\bar{w}_2)$, and relative error of average mass density of the mixture $\delta(\bar{\rho})$ for the region R_F , noise levels $L = 0, 1, 2$ and 8th iteration. Also shown are corresponding per-pixel standard uncertainties $u(w_1)$ and $u(\rho)$ and the correlation coefficient $r(w_1, \rho)$. Values are rescaled using the factor $\% = 0.01$.

L	$\epsilon(\bar{w}_1)$ (%)	$\epsilon(\bar{w}_2)$ (%)	$\delta(\bar{\rho})$ (%)	$u(w_1)$ (%)	$u(\rho)$ (g cm ⁻³)	$r(w_1, \rho)$
0	-0.183	0.183	0.01	0.08	0.05×10^{-2}	0.760
1	-0.187	0.187	0.09	2.64	1.16×10^{-2}	-0.833
2	-0.443	0.443	0.26	8.92	3.84×10^{-2}	-0.828

FIG. 8. Average mass fractions of lipid $\bar{w}_1$ (*), protein $\bar{w}_2$ (□) and water $\bar{w}_3$ (o) as functions of the iteration number for muscle in region R_M (a) and adipose tissue in region R_C (b) for noise level $L = 2$ and slice A. True values are plotted with horizontal solid lines.

mental mass fractions can be determined from the mass fractions of doublets and triplets using for instance the method described in Ref. 18. The use of several doublets and triplets as in the multimaterial decomposition [33] avoids negative mass fractions. Of interest is the accuracy of these estimates and their applicability in Monte Carlo codes for radiation transport and dose calculations. This topic, including a comparison with other methods for the estimation of elemental composition from DECT scans, is beyond the scope of this article.

A major challenge in the determination of mass fractions is the statistical noise. A moderate noise in projection data may result in bias and large noise in the mass fractions. A workaround is to increase the tube load as in the presented simulations. Though this is typically not a serious problem for patients undergoing a radiotherapy, a better solution is desired. Without regularization (i.e. setting $\mathcal{F}_{HP}(\mathbf{f}^{(i)}) = 0$ in Eq. (12)), experiments not reported here indicated that the noise increased with iterations. This was also concluded in Ref. 31. No regularization was used in Ref. 12. For better noise handling in the future, photon statistic modeling and regularization based on prior object knowledge [8] should be exploited for DIRA.

The number of iterations and stability of the algorithm also affect the accuracy of results. Fig. 8 and figures in Supplementary material show that the algorithm stabi-

lized after approximately 4 or 5 iterations. For safety reasons, results were reported for the 8th iteration. The computation of 1 iteration took approximately 1.3 s on the 12-core system; the total time of 20 s for 10 iterations was still acceptable for the clinical practice of radiation treatment planning.

The representation of object materials via doublets and triplets allows to speed up the calculation of forward projections. Ref. 8 claims that x-ray beams can be modeled polychromatic by dividing the spectrum into a number of energy bins and computing each interaction for each bin. It claims that the computational expense would be very high. The implementation in DIRA lowered the time complexity of the algorithm from $O(KN)$ to $O(K + N)$, where N and K are the numbers of voxels and energy bins, respectively, see Supplementary material. In our case $N = 512$ and $K = 100$.

The classical WBHC algorithm performed at step 0 reduces the number of iterations needed to achieve the same accuracy by about 2, e.g., from 7 to 5, (<http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-80964>) compared to a situation when the algorithm is not used. If needed, WBHC can be removed from DIRA or replaced with a different algorithm, e.g., the method by Alvarez and Macovski.

The robustness of the algorithm, i.e., its sensitivity to errors in input quantities like x-ray spectra, has not been systematically investigated in this work. The authors' experience is that the algorithm converges even for input values deviating from true values; the resulting linear attenuation coefficients will be accordingly biased.

In the present form DIRA has limitations: for instance, forward projections are calculated in axial scanning geometry only, scattered radiation is not simulated and an ideal detector array is used. Implementation of a realistic detector response function and scatter contributions to the projections in the iterative loop (Fig. 1) are principally straight-forward. Addition of scatter could be accomplished, e.g., by Monte Carlo simulations [37–39]. However, computational efforts will increase considerably. It was beyond the scope of this paper to deal with these problems before a proof-of-concept for the simpler case was verified. Another future development is to introduce helical scanning to overcome the limitation of using axial geometry only.

VI. SHORT SUMMARY AND CONCLUSIONS

The simulations showed that DIRA was capable of determining material composition of tissues, which is needed in brachytherapy with low energy (< 50 keV) photons and proton therapy. Compared to the filtered backprojection with classical water beam hardening correction, the accuracy of resulting mass fractions of base materials was notably improved, for instance from 1.2 to 1.0 for water in the R_C region, see Fig. 8. The algorithm provided quantitative monoenergetic images with beam

hardening artifacts removed. Its convergence was fast, image sharpness expressed via the modulation transfer function was maintained, and image noise did not increase with the number of iterations. The derived type B evaluation could be used for the determination of uncertainties in mass fractions from uncertainties in linear attenuation coefficients with errors less than 1.5%. Optimization of the forward projection computation algorithm by eliminating summations over all energy bins in the spectrum for each line integral notably reduced the computational expense of the physical modeling part of the algorithm.

SUPPLEMENTARY MATERIAL

The supplementary material describes the CT scanner geometry, composition of the material doublets and triplets, determination of MTF and filter functions, determination of noise levels and computational complexity of forward projections. It complements Figs. 5, 7, 8 and Tables II and III with figures and tables for every simulated configuration. Also presented are the probability density functions (PDFs) of reconstructed linear attenu-

ation coefficients.

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DISCLOSURE OF CONFLICTS OF INTEREST

The authors have no relevant conflicts of interest to disclose.

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Supplementary material to the article: A model-based iterative reconstruction algorithm DIRA using patient-specific tissue classification via DECT for improved quantitative CT in dose planning

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I. METHODS

A. Simulation of measured projections

Polyenergetic CT projections were calculated using the Drasim simulation code for a configuration resembling a typical DECT scanner; simulation parameters are described below.

X-ray spectra: The X-ray spectra were produced by Drasim for tube voltages of 80 and 140 kV. For 140 kV, an extra 0.4 mm of Sn was added. Zero focal spot size was used, bowtie filter was not simulated. Effective energies of these spectra were 50 and 88 keV (section A III B).

Gantry: The number of projections was 1152 for a full rotation of 360° . The source-to-origin distance was $d_{SO} = 595$ mm and the detector-to-origin distance was $d_{DO} = 500$ mm. An ideal detector measuring energy fluence was simulated. The full fan beam angle was approximately 50° and the number of detector elements (channels) was 736. Each detector element registered 10 sub-rays equidistantly distributed in the fan-direction. The quarter off-set [1, p. 43] was used. The detector element width in z-direction was $d_z = 1.8403$ mm. It corresponded to the beam width of $d_z \cdot d_{SO} / (d_{SO} + d_{DO}) = 1.8403 \cdot 595 / (595 + 500) = 1$ mm at the iso-center for an axial scan and to the slice thickness of 2 mm for a helical scan fully and without overlapping covering the imaged object.

Rebinning: Using cubic interpolation, the 3D projections were rebinned to 720 parallel projections in 2D covering a projection interval of 180° . The number of detector elements was 511 and the detector element size in the 2D geometry was 0.69 mm. This size also became the pixel size in the reconstructed images.

B. Composition of selected materials

Elemental compositions of the material doublet (mineral bone, bone marrow) and triplet (lipid, protein, water) used in this work are listed in Table I. Also shown is the material composition of prostate.

TABLE I. Elemental atomic compositions and mass densities, ρ , of doublet and triplet base materials used in this work.

Material	Elemental mass fraction (%)	ρ (g cm ⁻³)
bone marrow ^a	H 11.0, C 52.9, N 2.05, O 33.5, Na 0.05, P 0.05, S 0.15, Cl 0.15, K 0.1, Fe 0.05	1.005
mineral bone ^b	H 3.6, C 15.9, N 4.2, O 44.8, Na 0.3, Mg 0.2, P 9.4, S 0.3, Ca 21.3	1.920
lipid ^c	H 11.8, C 77.3, O 10.9	0.920
protein ^c	H 6.6, C 53.4, N 17.0, O 22.0, S 1.0	1.350
water	H 11.2, O 88.8	1.000
prostate ^b	H 10.4, C 23.1, N 2.8, O 62.7, Na 0.1, P 0.2, S 0.3, Cl 0.2, K 0.2	1.030

^a Calculated as a mixture of 50% red marrow and 50% yellow marrow (by mass) taken from Ref. 2.

^b From Ref. 3.

^c From Ref. 4.

II. DETERMINATION OF MTF AND FILTER FUNCTIONS

The modulation transfer function (MTF) describes the spatial frequency response of an imaging system. An MTF curve, e.g., a typical Siemens body kernel [5], starts at 1 at the spatial frequency 0 cm^{-1} , is followed by a small overshoot before declining down to 0 at 8 cm^{-1} . The overshoot close to zero frequency results in over- and undershoots close to edges in the image, which might improve the visibility of organs but are not desired for quantitative measurements. The bandwidth of the MTF cannot exceed the bandwidth of the image when iterative reconstruction is used. In our case, the size of the phantom was 35.2 cm in the lateral direction and 511×511 pixels were used. The pixel size of $35.2/511 = 0.069$ cm corresponds to the Nyquist frequency (bandwidth) of $f_n = 0.5/0.069 = 7.2464 \text{ cm}^{-1}$. To mimic a typical body kernel while avoiding the problems with over- and undershoots close to edges and keeping

the MTF bandwidth limited by the Nyquist frequency f_n a simple function of the form $\cos^n()$ was used:

$$\text{MTF}_{\text{DIRA}}(f) = \begin{cases} \cos^{2.1}\left(\frac{\pi}{2} \cdot \frac{f}{f_n}\right), & f < f_n, \\ 0, & \text{otherwise,} \end{cases} \quad (1)$$

The parameter $n = 2.1$ provided the best visual match between the MTF and the Siemens' typical body kernel; the maximum difference between the two curves was less than 0.1.

In simulations presented in this work, the MTF is influenced by: (i) the zero size of the X-ray focus, (ii) the size of the detector elements, (iii) the interpolation used during rebinning from fan-beam to parallel beam, (iv) the interpolation used during backprojection in FBP, (v) the interpolation used during projection generation with Joseph's method and (vi) the smoothing filter function $W(f)$. (In FBP the smoothing filter function is combined with the Ram-Lak filter, which is the ramp filter cut off at the bandwidth frequency.) We recall that in Drasim we set the focus size to 0 and used 10 subrays per detector-element to simulate the rectangular detector response.

The smoothing filters (windows) W_0 , W_A and W_B in DIRA were assumed to have the form $W() = \cos^m()$, where the parameter m was chosen so that the $\text{MTF}(f)$ of the imaging system matched the $\text{MTF}_{\text{DIRA}}(f)$ in Eq. (1) for a suitable mathematical phantom. The parameter m in filter W_0 was obtained for the 0th iteration and corresponding parameters for filters W_A and W_B were obtained for the 8th iteration. The MTF of the imaging system was determined as follows. A water-filled cylinder positioned in the iso-center was used as the mathematical phantom. In an axial plane, this phantom can be described as a circular disc $f(x, y)$, where x and y are coordinates in the 2D spatial domain. Its Fourier transform $F(u, v)$, where u and v are coordinates in the Fourier domain, is known in analytic form, see e.g. Ref. 6, p. 323. Polyenergetic projections of the cylindrical phantom were obtained using Drasim, rebinned and used as measured projections in DIRA. Let $g(x, y)$ be the reconstructed image. The transfer function, $H(u, v)$, of the imaging system was then given by the ratio of the Fourier transforms of the reconstructed image, $G(u, v)$, and the mathematical phantom, $F(u, v)$, as $H(u, v) = G(u, v)/F(u, v)$. For a shift-invariant imaging system, the MTF can be calculated as $\text{MTF}(f) = |H(u, v)|/H(0, 0)$, where $f = (u^2 + v^2)^{1/2}$ (Ref. 7, p. 311). In our case, $H(0, 0) = 1$ and $H(u, v)$ was a real and rotational symmetric function due to the symmetry of the CT-system. Thus the MTF could be estimated as $\text{MTF}(f) \approx H(u, 0)$. The best agreement for W_0 was achieved for $m = 1$, resulting in

$$W_{\text{DIRA}}(f) = \begin{cases} \cos^1\left(\frac{\pi}{2} \cdot \frac{f}{f_n}\right), & f < f_n, \\ 0, & \text{otherwise.} \end{cases} \quad (2)$$

The combination of W_A and W_B should result in W_{DIRA} , i.e., $W_A W_B = W_{\text{DIRA}}$. This work used filters $W_A = 1$ and $W_B = W_{\text{DIRA}}$, which suppressed the noise better than the filters $W_A = W_{\text{DIRA}}$ and $W_B = 1$. Other combinations were also tested, but none of them provided notably better results.

III. DETERMINATION OF NOISE LEVELS

To determine the typical noise in clinical CT images of the male pelvis, an analysis of selected images reconstructed with FBP was performed. The analysis showed that typical standard deviations of CT numbers were approximately 15 - 35 HU in homogeneous regions with adipose tissue and muscle. Corresponding CTDI_{vol} was 4 - 12 mGy for the 32 cm diameter phantom. To avoid comparing noise in such images to noise in images reconstructed by an iterative reconstruction algorithm that automatically reduces noise, only the 0th iteration was used in DIRA. It was found that the per-projection tube loads of 0.217 and 0.08 mAs for the low and high tube voltages, respectively, resulted in standard deviations of 16 - 31 HU for the R_M and R_A regions (see Table A-I), which were similar to the standard deviations in the clinical images. Simulation setups with these and tenfold increased tube loads are referred to as noise levels $L = 2$ and $L = 1$, respectively, in this work. The setup with no simulated noise is denoted as $L = 0$.

IV. UNCERTAINTY OF COMPUTED MASS FRACTIONS

Uncertainty in the computed mass fractions depends on many factors, for instance the accuracy of the image reconstruction algorithm, accuracy of the tabulated cross sections as functions of energy, the accuracy of the independent atom approximation, and the accuracy of the formula for density of the mixture (Eq. (A2)). In clinical practice, the dominating factor is typically the quantum noise affecting the detector signal. For low photon intensities, the electronic noise may further reduce the signal-to-noise ratio by 30 to 50% [8, p. 49]. While the former factors are mostly deterministic and can, in principle, be corrected for, the quantum and electronic noise are random in nature

and typically determine the precision of the calculated mass fractions. In this section, a simple model is presented for the calculation of uncertainties in mass fractions w_i , $1 \leq i \leq 3$, from uncertainties in linear attenuation coefficients $\mu(E_1)$ and $\mu(E_2)$ at effective photon energies E_1 and E_2 , respectively, calculated by the reconstruction algorithm. For clarity, these linear attenuation coefficients are denoted as $\mu_1 \equiv \mu(E_1)$ and $\mu_2 \equiv \mu(E_2)$. Consider the measurement model $w_i = f_i(\mu_1, \mu_2)$, where the model function f_i is given by Eq. (A5). The standard uncertainty $u(w_i)$ in w_i can be estimated by [9]

$$u^2(w_i) = \left(\frac{\partial f_i}{\partial \mu_1} \right)^2 u^2(\mu_1) + \left(\frac{\partial f_i}{\partial \mu_2} \right)^2 u^2(\mu_2) + 2 \frac{\partial f_i}{\partial \mu_1} \frac{\partial f_i}{\partial \mu_2} u(\mu_1) u(\mu_2) r(\mu_1, \mu_2), \quad (3)$$

where $u(\mu_j)$ is the standard uncertainty in μ_j and $r(\mu_1, \mu_2)$ is the correlation coefficient between μ_1 and μ_2 . The sensitivity coefficients $\partial f / \partial \mu_j = (\partial f_1 / \partial \mu_j, \partial f_2 / \partial \mu_j, \partial f_3 / \partial \mu_j)^T$ can be calculated as

$$\frac{\partial f}{\partial \mu_j} = \frac{\partial(A^{-1}b)}{\partial \mu_j} = \frac{\partial A^{-1}}{\partial \mu_j} b = -A^{-1} \frac{\partial A}{\partial \mu_j} A^{-1} b, \quad (4)$$

where the matrix A and the vector b have the same meaning as in Eq. (A3), and A^{-1} is the inverse matrix of A . The formula

$$\frac{\partial A^{-1}}{\partial \mu_j} = -A^{-1} \frac{\partial A}{\partial \mu_j} A^{-1} \quad (5)$$

used in Eq. (4) allows the calculation of partial derivatives $\partial A^{-1} / \partial \mu_j$, which are difficult to express directly, through partial derivatives $\partial A / \partial \mu_j$. Eq. (5) can be derived from the relation $I = A^{-1}A$, where I is the identity (unit) matrix, by multiplying the following equation by A^{-1} from the right-hand side:

$$O = \frac{\partial I}{\partial \mu_j} = \frac{\partial(A^{-1}A)}{\partial \mu_j} = \frac{\partial A^{-1}}{\partial \mu_j} A + A^{-1} \frac{\partial A}{\partial \mu_j}. \quad (6)$$

In (6), O is the zero matrix.

The partial derivatives $\partial A / \partial \mu_j$ can be calculated directly from Eq. (A3) as

$$\frac{\partial A}{\partial \mu_1} = \begin{pmatrix} \rho_1^{-1} & \rho_2^{-1} & \rho_3^{-1} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad \frac{\partial A}{\partial \mu_2} = \begin{pmatrix} 0 & 0 & 0 \\ \rho_1^{-1} & \rho_2^{-1} & \rho_3^{-1} \\ 0 & 0 & 0 \end{pmatrix}, \quad (7)$$

For the 2MD method, the uncertainties $u(w_1)$, $u(w_2)$ and $u(\rho^{-1})$ can be calculated from Eq. (3) using the functional relation in Eq. (A7). The sensitivity coefficients can be calculated from Eq. (4), where

$$\frac{\partial A}{\partial \mu_1} = \begin{pmatrix} 0 & 0 & -1 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad \frac{\partial A}{\partial \mu_2} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & -1 \\ 0 & 0 & 0 \end{pmatrix}. \quad (8)$$

The uncertainty $u(\rho)$ can be estimated as [9] $u(\rho) = \rho^2 u(\rho^{-1})$.

V. COVARIANCE BETWEEN MASS FRACTIONS

There is an association between mass fractions computed using the three material decomposition. Consider that the linear attenuation coefficient μ_1 measured with the CT scanner at the effective photon energy E_1 has a distribution with the expectation $E(\mu_1)$ and variance $V(\mu_1)$. Corresponding quantities for the linear attenuation coefficient μ_2 measured at E_2 are $E(\mu_2)$ and $V(\mu_2)$.

The covariance between the mass fractions w_i and w_j , which are now considered as functions of random variables μ_1 and μ_2 , can be estimated using the same approach as in Ref. 9. The functional relation $w_i = f_i(\mu_1, \mu_2)$ given by Eq. (A5) is linearized using the Taylor series. The approximate mass fraction $\hat{w}_i$ is then

$$\hat{w}_i = f_i(E(\mu_1), E(\mu_2)) + \frac{\partial f_i}{\partial \mu_1} (\mu_1 - E(\mu_1)) + \frac{\partial f_i}{\partial \mu_2} (\mu_2 - E(\mu_2)), \quad (9)$$

where the partial derivatives are evaluated at the point $(E(\mu_1), E(\mu_2))$. The covariance can be calculated from the definition

$$C(\hat{w}_i, \hat{w}_j) \equiv E[(\hat{w}_i - E(\hat{w}_i))(\hat{w}_j - E(\hat{w}_j))] \quad (10)$$

by substituting $\hat{w}_i$ in Eq. (9) to (10) and realizing that $E(\hat{w}_i) = f_i(E(\mu_1), E(\mu_2))$ and $C(\mu_2, \mu_1) = C(\mu_1, \mu_2)$:

$$C(\hat{w}_i, \hat{w}_j) = \frac{\partial f_i}{\partial \mu_1} \frac{\partial f_j}{\partial \mu_1} V(\mu_1) + \frac{\partial f_i}{\partial \mu_2} \frac{\partial f_j}{\partial \mu_2} V(\mu_2) + \left(\frac{\partial f_i}{\partial \mu_1} \frac{\partial f_j}{\partial \mu_2} + \frac{\partial f_i}{\partial \mu_2} \frac{\partial f_j}{\partial \mu_1} \right) C(\mu_1, \mu_2) \quad (11)$$

Note that Eq. (3) follows from Eq. (11) since $u^2(w_i) = V(w_i) = C(w_i, w_i)$ for $1 \leq i \leq 3$ and $u^2(\mu_j) = V(\mu_j)$ for $1 \leq j \leq 2$.

For the 2MD, the normalization condition $w_1 + w_2 = 1$ associates the mass fractions w_1 and w_2 so that $C(w_1, w_2) = C(w_1, 1 - w_1) = -C(w_1, w_1) = -V(w_1) = -V(w_2)$. The correlation coefficient is then

$$r(w_1, w_2) \equiv \frac{C(w_1, w_2)}{[V(w_1)V(w_2)]^{1/2}} = -1. \quad (12)$$

and $r(w_2, \rho) = r(1 - w_1, \rho) = -r(w_1, \rho)$.

VI. TIME COMPLEXITY OF FORWARD PROJECTIONS

Time complexity of an algorithm can be quantified by the number of performed elementary operations. Of special interest is the asymptotic behavior of algorithms, when certain parameters approach infinity. In this case the time complexity is commonly described by the big-O (ordo) notation. For instance the time complexity of the order N , denoted as $O(N)$, means that the number of elementary operations is proportional to the parameter N .

Suppose that a slice of the voxel array has the size of $N \times N$ (e.g. 512×512) and the number of energy bins in the x-ray spectrum is K (e.g. 100). The number of operations performed in a discretized version of Eq. (A18) (see Eq. (A20)) is proportional to K assuming that the integrals l_i have been pre-calculated. Since their calculation requires a number of operations that is proportional to N , the total time complexity is $O(K + N)$.

On the other hand, the number of operations performed in a discretized version of the expression $\exp[\dots]$ in Eq. (A16) is proportional to KN , thus the complexity is $O(KN)$. The number of operations performed in the discretized remaining part of the formula is proportional to K . The total time complexity is thus $O(K + KN)$, which is the same as $O(KN)$.

VII. RESULTS

Figs. 1 and 2 show reconstructed linear attenuation coefficients at 50 and 88 keV, respectively for the 0th (classical water beam hardening correction) and 8th iteration of DIRA. They complement Fig. A-5 in the article.

Figs. 4–9 show normalized probability density functions (PDFs) of reconstructed linear attenuation coefficients in muscle, adipose tissue, femora spongiosa and pelvis spongiosa regions for all pixels (except those close to the edges) and iterations 0 and 8; the regions were defined by manually created masks shown in Fig. 3. The PDFs show that DIRA reduced the bias while the statistical noise (the width of the peaks for noise levels $L = 1, 2$) remained approximately the same.

Figs. 11–13 show calculated mass fractions for slices A–C; they complement Fig. A-7 in the article. The soft tissue was separated by automatic segmentation in the iterative loop of DIRA; Fig. 10 shows masks of all segmented tissues.

Figs. 15–17 demonstrate the convergence speed of DIRA by showing average mass fractions in the four circular regions (Fig. 14) as functions of the number of iterations. They complement Fig. A-8 in the article.

Table II complements Table A-I in the article; it contains information on all three slices A, B and C. It also lists the covariance between linear attenuation coefficients μ_1 and μ_2 . Tables III and IV complement Table A-II, and Tables VI and VII complement Table A-III; they contain information on all three slices. Table V shows that calculated mass fractions and mass densities were highly correlated.

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FIG. 1. Reconstructed slices A, B and C for effective photon energy of $E_1 = 50$ keV corresponding to the tube voltage of 80 kV, noise levels $L = 0, 1, 2$, and iterations $I = 0, 8$.

FIG. 2. Same as Fig. 1 for $E_2 = 88$ keV corresponding to the tube voltage of 140 kV.

FIG. 3. Manually created masks defining muscle, adipose tissue, femora spongiosa and pelvis spongiosa regions. These masks were used to select pixels for histograms in Figs. 4–9. We recall that these masks were derived from regions defining the phantom by erosion and dilation so that border pixels (plotted as white regions) are not included.

FIG. 4. Normalized probability density function of reconstructed linear attenuation coefficients μ at 50 keV in the muscle, adipose tissue, femora spongiosa and pelvis spongiosa regions of slice A for iterations 0 (blue) and 8 (green) and noise level $L = 0$ (left column), $L = 1$ (middle column) and $L = 2$ (right column). True values are plotted as a vertical line (red).

FIG. 5. Same as Fig. 4 for slice A and μ at 88 keV.

FIG. 6. Same as Fig. 4 for slice B and μ at 50 keV.

FIG. 7. Same as Fig. 4 for slice B and μ at 88 keV.

FIG. 8. Same as Fig. 4 for slice C and μ at 50 keV.

FIG. 9. Same as Fig. 4 for slice C and μ at 88 keV.

FIG. 10. Masks determined by DIRA for slices A (top row), B (middle row) and C (bottom row) for the 8th iteration and noise level $L = 0$. The masks were produced by automatic segmentation of the μ -images to outside air ($i\text{Doublet}=1$), bone ($i\text{Doublet}=2$) and soft tissue ($i\text{Triplet}=1$). We recall that the outside air was decomposed to the (lipid, water) doublet, bone was decomposed to the (compact bone, bone marrow) doublet and the soft tissue was decomposed to the (lipid, protein, water) triplet. The main purpose of the outside air doublet was to reduce partial volume artifacts at the soft tissue - outside air border. The masks were recalculated at each iteration of DIRA.

FIG. 11. Mass fractions of lipid, protein and water for noise levels $L = 0, 1, 2$, iterations $I = 0, 8$, and slice A.

FIG. 12. Same as Fig. 11 for slice B.

FIG. 13. Same as Fig. 11 for slice C.

FIG. 14. Circular regions of interest: R_M (red) in muscle, R_A (green) in adipose tissue, R_C (blue) in adipose tissue and R_F (magenta) in femora spongiosa for slices A, B and C.

FIG. 15. Mass fractions of lipid w_1 (*), protein w_2 (□) and water w_3 (○) as functions of the iteration number for muscle in region R_M and adipose tissue in regions R_A and R_C . Mass fractions of compact bone w_1 (*) and bone marrow w_2 (□) and mass density relative to water ρ/ρ_w (○) for femora spongiosa in region R_F . True values are plotted with horizontal solid lines. Noise level $L = 0, 1, 2$ and slice A were used.

$L = 0$

 $L = 1$

 $L = 2$

FIG. 16. Same as Fig. 16 for slice B.

$L = 0$

 $L = 1$

 $L = 2$

FIG. 17. Same as Fig. 16 for slice C.

TABLE II. Relative error $\delta(\bar{\mu}_i)$ of average reconstructed linear attenuation coefficients $\bar{\mu}_i$, relative standard uncertainty $u_r(\mu_i)$ of the reconstructed linear attenuation coefficients μ_i , standard uncertainty $u(H_i)$ of the corresponding CT number at the effective energy E_i ($i = 1, 2$) for pixels in four circular regions R , three noise levels L , three slices S and 8th iteration. The correlation coefficient $r(\mu_1, \mu_2)$ and covariance $C(\mu_1, \mu_2)$ are also listed. Values are rescaled using the factor $\%_0 = 10^{-3}$.

S	R	L	$\delta(\bar{\mu}_1)$ (%)	$\delta(\bar{\mu}_2)$ (%)	$u_r(\mu_1)$ (%)	$u_r(\mu_2)$ (%)	$u(H_1)$	$u(H_2)$	$r(\mu_1, \mu_2)$	$C(\mu_1, \mu_2)$ (cm^{-2})
A	R_M	0	-0.93	-0.13	1.40	0.69	1	1	0.96	0.41×10^{-3}
A	R_M	1	-1.29	0.68	11.80	6.21	12	6	-0.09	-2.97×10^{-3}
A	R_M	2	-2.05	1.01	32.05	20.94	33	22	-0.05	-16.02×10^{-3}
A	R_A	0	-0.23	-0.00	3.75	1.90	3	2	0.99	2.37×10^{-3}
A	R_A	1	0.27	0.43	8.00	5.55	7	5	0.02	0.27×10^{-3}
A	R_A	2	1.87	0.10	21.70	17.32	19	16	-0.19	-24.41×10^{-3}
A	R_C	0	-0.53	-0.17	4.13	2.00	4	2	0.99	2.76×10^{-3}
A	R_C	1	-0.68	0.32	17.51	9.63	16	9	-0.14	-8.01×10^{-3}
A	R_C	2	3.56	0.89	56.38	28.47	50	27	-0.18	-99.34×10^{-3}
A	R_F	0	-1.57	-0.22	0.94	0.50	1	1	0.96	0.27×10^{-3}
A	R_F	1	-2.50	0.27	12.95	6.79	16	8	0.00	0.03×10^{-3}
A	R_F	2	-1.34	2.65	43.57	24.28	55	28	-0.01	-5.48×10^{-3}
B	R_M	0	-1.01	-0.17	1.43	0.69	1	1	0.94	0.41×10^{-3}
B	R_M	1	-0.84	0.24	11.27	6.77	12	7	-0.30	-10.22×10^{-3}
B	R_M	2	-1.96	1.89	29.76	23.24	31	24	-0.18	-55.15×10^{-3}
B	R_A	0	-0.48	-0.06	2.78	1.43	2	1	0.99	1.32×10^{-3}
B	R_A	1	-0.26	0.43	7.47	5.84	7	5	-0.06	-0.88×10^{-3}
B	R_A	2	-2.39	1.57	21.19	16.77	19	16	-0.20	-23.78×10^{-3}
B	R_C	0	-1.18	-0.25	5.11	2.54	5	2	0.99	4.33×10^{-3}
B	R_C	1	-1.05	0.74	17.12	10.67	15	10	-0.04	-2.27×10^{-3}
B	R_C	2	1.79	2.74	62.62	30.36	56	28	0.01	4.83×10^{-3}
B	R_F	0	-1.27	-0.13	1.03	0.56	1	1	0.96	0.33×10^{-3}
B	R_F	1	-0.68	0.63	13.10	7.35	17	8	-0.22	-12.57×10^{-3}
B	R_F	2	-2.78	1.54	44.88	24.09	57	28	-0.22	-135.34×10^{-3}
C	R_M	0	-0.74	-0.11	2.65	1.31	3	1	0.97	1.48×10^{-3}
C	R_M	1	-0.42	0.47	10.35	8.37	11	9	-0.21	-7.88×10^{-3}
C	R_M	2	-0.86	2.47	32.02	21.37	33	22	-0.15	-45.26×10^{-3}
C	R_A	0	-0.17	0.01	3.74	1.93	3	2	0.99	2.41×10^{-3}
C	R_A	1	-0.45	0.67	7.72	5.99	7	6	-0.04	-0.61×10^{-3}
C	R_A	2	0.24	0.23	22.40	18.18	20	17	-0.30	-40.64×10^{-3}
C	R_C	0	-0.25	-0.10	6.99	3.44	6	3	1.00	8.06×10^{-3}
C	R_C	1	0.81	0.52	18.24	9.92	16	9	0.07	4.08×10^{-3}
C	R_C	2	-3.75	2.30	52.61	31.95	47	30	-0.30	-167.37×10^{-3}
C	R_F	0	-2.30	-0.32	2.07	1.09	3	1	0.96	1.25×10^{-3}
C	R_F	1	-1.84	0.67	13.99	9.46	18	11	-0.11	-8.30×10^{-3}
C	R_F	2	-4.48	2.12	44.71	28.63	56	33	-0.15	-112.83×10^{-3}

TABLE III. Errors of average mass fractions of lipid $\epsilon(\bar{w}_1)$, protein $\epsilon(\bar{w}_2)$ and water $\epsilon(\bar{w}_3)$, and the relative error of average mass density of the mixture $\delta(\bar{\rho})$ for slices S , regions R , noise levels L and 8th iteration. Also shown are standard uncertainties $u(w_i)$ and $u(\rho)$ in mass fractions and mass density, respectively.

S	R	L	$\epsilon(\bar{w}_1)$ (%)	$\epsilon(\bar{w}_2)$ (%)	$\epsilon(\bar{w}_3)$ (%)	$\delta(\bar{\rho})$ (%)	$u(w_1)$ (%)	$u(w_2)$ (%)	$u(w_3)$ (%)	$u(\rho)$ (g cm ⁻³)
A	R_M	0	0.98	0.42	-1.41	-0.33	1.01	0.27	1.25	0.05×10^{-2}
A	R_M	1	2.09	1.31	-3.40	-0.17	16.02	9.61	25.42	1.32×10^{-2}
A	R_M	2	2.01	1.11	-3.13	-0.08	45.10	28.53	72.89	4.17×10^{-2}
A	R_A	0	0.24	0.12	-0.37	-0.08	2.40	0.37	2.71	0.13×10^{-2}
A	R_A	1	0.00	0.19	-0.20	-0.03	9.89	6.96	16.58	0.95×10^{-2}
A	R_A	2	-2.80	-1.68	4.48	-0.17	30.88	22.98	53.27	3.10×10^{-2}
A	R_C	0	0.42	0.13	-0.55	-0.09	2.73	0.45	3.13	0.13×10^{-2}
A	R_C	1	0.67	0.43	-1.10	-0.00	21.81	14.49	35.91	1.83×10^{-2}
A	R_C	2	-6.66	-3.77	10.43	-0.12	71.45	46.40	116.79	5.62×10^{-2}
B	R_M	0	1.04	0.44	-1.48	-0.33	1.08	0.32	1.36	0.05×10^{-2}
B	R_M	1	1.04	0.59	-1.63	-0.27	17.00	10.69	27.54	1.50×10^{-2}
B	R_M	2	2.50	1.65	-4.15	0.06	46.44	30.98	76.79	4.67×10^{-2}
B	R_A	0	0.46	0.21	-0.67	-0.08	1.76	0.24	1.96	0.10×10^{-2}
B	R_A	1	0.58	0.49	-1.07	-0.01	9.86	7.26	16.87	1.01×10^{-2}
B	R_A	2	3.17	2.19	-5.37	0.29	29.46	21.91	50.80	3.01×10^{-2}
B	R_C	0	1.07	0.42	-1.49	-0.07	3.31	0.49	3.75	0.17×10^{-2}
B	R_C	1	1.46	1.04	-2.50	0.08	21.08	14.39	34.97	1.89×10^{-2}
B	R_C	2	-2.94	-0.90	3.84	0.28	73.69	46.26	118.49	5.61×10^{-2}
C	R_M	0	0.78	0.34	-1.11	-0.34	1.89	0.47	2.30	0.10×10^{-2}
C	R_M	1	0.76	0.53	-1.29	-0.26	16.54	11.12	27.45	1.68×10^{-2}
C	R_M	2	1.89	1.69	-3.58	0.10	47.19	30.13	76.68	4.39×10^{-2}
C	R_A	0	0.20	0.11	-0.30	-0.08	2.36	0.30	2.61	0.13×10^{-2}
C	R_A	1	0.99	0.83	-1.82	0.04	10.07	7.39	17.20	1.03×10^{-2}
C	R_A	2	-1.08	-0.76	1.84	-0.07	32.97	24.64	57.09	3.34×10^{-2}
C	R_C	0	0.19	0.04	-0.23	-0.10	4.55	0.64	5.15	0.22×10^{-2}
C	R_C	1	-0.71	-0.18	0.89	-0.04	21.10	13.62	34.20	1.73×10^{-2}
C	R_C	2	2.05	1.25	-3.30	0.47	70.38	48.66	118.05	6.23×10^{-2}

TABLE IV. Relative errors of average mass fractions of lipid $\delta(\bar{w}_1)$, protein $\delta(\bar{w}_2)$ and water $\delta(\bar{w}_3)$ and corresponding average mass fractions $\bar{w}_1$, $\bar{w}_2$ and $\bar{w}_3$ for slices S , regions R , noise levels L and 8th iteration.

S	R	L	$\bar{w}_1$	$\delta(\bar{w}_1)$ (%)	$\bar{w}_2$	$\delta(\bar{w}_2)$ (%)	$\bar{w}_3$	$\delta(\bar{w}_3)$ (%)
A	R_M	0	-0.119	-7.6	0.132	3.3	0.987	-1.4
A	R_M	1	-0.107	-16.3	0.141	10.3	0.967	-3.4
A	R_M	2	-0.108	-15.7	0.139	8.7	0.970	-3.1
A	R_A	0	0.704	0.3	0.030	4.3	0.267	-1.4
A	R_A	1	0.701	0.0	0.030	6.8	0.268	-0.7
A	R_A	2	0.673	-4.0	0.012	-59.0	0.315	16.6
A	R_C	0	0.705	0.6	0.030	4.5	0.265	-2.0
A	R_C	1	0.708	1.0	0.033	15.0	0.259	-4.1
A	R_C	2	0.635	-9.5	-0.009	-132.3	0.375	38.6
B	R_M	0	-0.118	-8.1	0.132	3.4	0.986	-1.5
B	R_M	1	-0.118	-8.1	0.133	4.6	0.985	-1.6
B	R_M	2	-0.103	-19.4	0.144	13.0	0.959	-4.1
B	R_A	0	0.706	0.7	0.031	7.3	0.264	-2.5
B	R_A	1	0.707	0.8	0.033	17.3	0.260	-4.0
B	R_A	2	0.733	4.5	0.050	77.1	0.217	-19.9
B	R_C	0	0.712	1.5	0.033	14.9	0.255	-5.5
B	R_C	1	0.716	2.1	0.039	36.5	0.245	-9.2
B	R_C	2	0.672	-4.2	0.019	-31.6	0.309	14.2
C	R_M	0	-0.121	-6.1	0.131	2.6	0.990	-1.1
C	R_M	1	-0.121	-5.9	0.133	4.2	0.988	-1.3
C	R_M	2	-0.109	-14.7	0.144	13.2	0.965	-3.6
C	R_A	0	0.703	0.3	0.030	3.7	0.267	-1.1
C	R_A	1	0.711	1.4	0.037	29.1	0.252	-6.7
C	R_A	2	0.690	-1.5	0.021	-26.6	0.289	6.8
C	R_C	0	0.703	0.3	0.029	1.5	0.268	-0.9
C	R_C	1	0.694	-1.0	0.027	-6.3	0.279	3.3
C	R_C	2	0.722	2.9	0.041	43.9	0.237	-12.2

TABLE V. Correlation coefficients between variables. Mass fractions of lipid, protein and water are denoted w_1 , w_2 and w_3 , respectively. Calculated mass density of the mixture is denoted ρ .

S	R	L	$r(w_1, w_2)$	$r(w_1, w_3)$	$r(w_2, w_3)$	$r(w_1, \rho)$	$r(w_2, \rho)$	$r(w_3, \rho)$
A	R_M	0	0.836	-0.993	-0.895	-0.615	-0.081	0.517
A	R_M	1	0.967	-0.995	-0.987	0.846	0.954	-0.894
A	R_M	2	0.958	-0.994	-0.984	0.832	0.955	-0.888
A	R_A	0	0.786	-0.996	-0.836	-0.912	-0.463	0.874
A	R_A	1	0.933	-0.989	-0.977	0.786	0.956	-0.870
A	R_A	2	0.955	-0.992	-0.985	0.863	0.973	-0.920
A	R_C	0	0.902	-0.998	-0.927	-0.936	-0.693	0.913
A	R_C	1	0.956	-0.993	-0.984	0.838	0.962	-0.897
A	R_C	2	0.962	-0.994	-0.986	0.850	0.960	-0.901
B	R_M	0	0.847	-0.992	-0.907	-0.468	0.074	0.354
B	R_M	1	0.976	-0.996	-0.991	0.898	0.972	-0.932
B	R_M	2	0.966	-0.995	-0.988	0.873	0.968	-0.918
B	R_A	0	0.801	-0.997	-0.843	-0.939	-0.545	0.911
B	R_A	1	0.941	-0.989	-0.980	0.820	0.965	-0.895
B	R_A	2	0.954	-0.992	-0.985	0.862	0.973	-0.920
B	R_C	0	0.880	-0.998	-0.908	-0.946	-0.678	0.924
B	R_C	1	0.942	-0.990	-0.979	0.803	0.956	-0.878
B	R_C	2	0.949	-0.992	-0.981	0.792	0.942	-0.860
C	R_M	0	0.841	-0.994	-0.896	-0.680	-0.176	0.594
C	R_M	1	0.968	-0.995	-0.989	0.881	0.971	-0.924
C	R_M	2	0.966	-0.995	-0.987	0.859	0.962	-0.907
C	R_A	0	0.819	-0.998	-0.855	-0.954	-0.610	0.932
C	R_A	1	0.938	-0.989	-0.979	0.813	0.964	-0.890
C	R_A	2	0.963	-0.993	-0.988	0.886	0.977	-0.933
C	R_C	0	0.930	-0.999	-0.946	-0.969	-0.810	0.956
C	R_C	1	0.936	-0.990	-0.976	0.766	0.943	-0.848
C	R_C	2	0.965	-0.994	-0.988	0.876	0.969	-0.922

TABLE VI. Errors of average mass fractions of mineral bone $\epsilon(\bar{w}_1)$ and bone marrow $\epsilon(\bar{w}_2)$, and relative error of average mass density of the mixture $\delta(\bar{\rho})$ for the slice S , region R_F , noise levels L and 8th iteration. Also shown are corresponding standard uncertainties $u(w_1)$, $u(w_2)$ and $u(\rho)$ and the correlation coefficient $r(w_1, \rho)$.

S	L	$\epsilon(\bar{w}_1)$ (%)	$\epsilon(\bar{w}_2)$ (%)	$\delta(\bar{\rho})$ (%)	$u(w_1)$ (%)	$u(\rho)$ (g cm ⁻³)	$r(w_1, \rho)$
A	0	-0.219	0.219	0.01	0.08	0.05×10^{-2}	0.735
A	1	-0.431	0.431	0.10	2.34	1.01×10^{-2}	-0.746
A	2	-0.447	0.447	0.36	8.02	3.62×10^{-2}	-0.753
B	0	-0.183	0.183	0.01	0.08	0.05×10^{-2}	0.760
B	1	-0.187	0.187	0.09	2.64	1.16×10^{-2}	-0.833
B	2	-0.443	0.443	0.26	8.92	3.84×10^{-2}	-0.828
C	0	-0.318	0.318	0.02	0.17	0.10×10^{-2}	0.739
C	1	-0.374	0.374	0.13	2.85	1.42×10^{-2}	-0.808
C	2	-0.770	0.770	0.37	9.18	4.37×10^{-2}	-0.816

TABLE VII. Relative errors $\delta(\bar{w}_1)$ and $\delta(\bar{w}_2)$ of average mass fractions $\bar{w}_1$ and $\bar{w}_2$ of mineral bone and bone marrow, respectively, for the slice S , region R_F , noise levels L and 8th iteration.

S	L	$\bar{w}_1$	$\delta(\bar{w}_1)$ (%)	$\bar{w}_2$	$\delta(\bar{w}_2)$ (%)
A	0	0.201	-1.1	0.799	0.3
A	1	0.199	-2.1	0.801	0.5
A	2	0.198	-2.2	0.802	0.6
B	0	0.201	-0.9	0.799	0.2
B	1	0.201	-0.9	0.799	0.2
B	2	0.198	-2.2	0.802	0.6
C	0	0.200	-1.6	0.800	0.4
C	1	0.199	-1.8	0.801	0.5
C	2	0.195	-3.8	0.805	1.0